ARTICLE

ADARE PHARMA SOLUTIONS

Streamline Early-Stage Development to Reach the Clinic Faster

It can be easy to overlook the importance of early-stage pharmaceutical product development, viewing it as a series of checklist tasks slowing progression toward clinical trials. Rather, early-stage development is critical to establish a solid foundation for those trials.

Success at this point in development means constructing a clear quality target product profile (QTPP) to drive positive proof of concept (PoC) results, all while considering scalability at each step to minimize development challenges downstream.

Sponsor companies can ease the transition from preclinical research into clinical trials by preparing for early-stage development well in advance, though the actual timeline depends on numerous factors (e.g., drug complexity, therapeutic area, and regulatory requirements relevant to the dosage form). CDMOs, meanwhile, must always be prepared to advance clients' early-stage projects. With that in mind, Adare leverages its product development expertise to expedite the early-stage development for PoC studies.

Key Early-Stage Considerations

Preclinical studies are critical during early-stage drug development and typically involve animal studies to assess the drug candidate's safety profile, pharmacokinetics (PK), and pharmacodynamics (PD). In addition to hinting at potential risks, these studies also inform dose range and initial efficacy. Many early-stage drugs exhibit various issues (e.g., solubility, permeability, bioavailability, stability, polymorphism, etc.), jeopardizing the outcome of these critical preclinical studies.

For this reason and others, sponsors must focus on preformulation and formulation development during the preclinical stage, even if the preclinical formulation is a seemingly simple solution or powder in a capsule. Essentially, early-stage formulation development should have a phase-appropriate quality target product profile (QTPP), and a simple formulation with a scalable process should be developed to avoid any challenges during late-stage development. Also, the formulators should be cognizant of regulatory compliance, as use of any unapproved or new excipient, use of excipient in higher-than-approved quantity, non-reproducible processes, etc., may delay regulatory approval.

This is one reason why a firm regulatory strategy — and a CDMO partner capable of guiding clients through that strategy — are the third vital element of early-stage development. Crafting such a strategy is not as problematic for pharmaceutical companies boasting product development experience; they generally are clear on what must be accomplished during early-stage development, the necessary resources, and their intended regulatory pathway. But inexperienced organizations and academic spinoffs often encounter difficulties.

For example, they may not understand the importance of pre-formation activities: solubility, pH, polymorphic form, etc. Consider that a first-time sponsor may present an API to its CDMO in solid form, claiming it is soluble. However, has that solubility been tested in gastric pH? Is it soluble enough to achieve the required therapeutic concentration?

The sponsor may not understand the crystal nature of its drug: the drug may be able to exist in different polymorphic forms, and one may exhibit greater stability than the others.

Misunderstanding the minimum API volumes necessary to complete any given process also is common, as is erroneously believing that positive results in animal testing all but guarantee regulatory approval.

It warrants mention here that PoC can easily be conflated with early-stage development. In fact, PoC is a development element supported by early-stage development, whose aim is to produce initial evidence supporting the hypothesis that the drug works or has the potential to produce the desired therapeutic effect. While Phase 1 development sets out to prove safety/PK/PD in humans, it does not establish efficacy. PoC begins in earnest in Phase 2.

Fortunately, regulatory bodies generally are enthusiastic collaborators. Too often, they are viewed as an adversary, rather than a source of deep expertise to support pharma sponsors. Constant communication with regulators during early-stage development clarifies their minimum expectation (e.g., relevant to evidentiary burden potential approval pathways). A sponsor that approaches its CDMO partner(s) with this information in-hand helps its projects move forward more expeditiously.

Third, early-stage development provides clarity and alignment between partners on project nature, milestones, timeline, deliverables, etc. In short, it prepares them to work together well when the stakes are highest. It also provides the sponsor an opportunity to tap its CDMO partner for information about trends and new technologies relevant to its development and regulatory strategy. For example, a sponsor may not be aware of the utility provided by flexible dose technologies (e.g., Minitabs™, which provide the flexibility of multiparticulate dosage forms, or Adaptdose™, which provides the ability to combine multiple active ingredients and/or release profiles in a single capsule) that can be used from early dose-ranging studies to commercial production.

Productive Early-Stage Development is Ceaseless

Early-stage development is a continuous process and must be repeated for every project, regardless of the molecule's complexity or the delivery system. It also is an iterative process: as new data and insights are generated from preclinical studies, early clinical trials, and other research activities, adjustments and modifications to the product's formulation, dosage, delivery method, or target population may be necessary. This allows for optimization and improvement of the product based on emerging knowledge.

These changes can occur for a number of reasons, from more efficient formulation/use of API and a speedier manufacturing process to risk mitigation and regulatory agency concern. Continuous monitoring and evaluation of product performance allow for ongoing risk assessment and management. For example, what issues were encountered during Phase 1? How did study or product design change based on those challenges?

Regulators are fond of the term "baby steps" — indicating they wish to see a step-by-step approach that provides a robust and evolving body of evidence throughout the development process. A continuous and iterative approach ensures the regulatory requirements for safety, efficacy, and quality are met at each stage. Again, constant communication with the agency ensures its feedback can guide those steps in a positive direction. Sometimes, early-phase development can feel long and inefficient, but the process smooths as the project moves forward, strategies for formulation and manufacturing become more complete, and advances in scientific understanding or technology become applicable.

Notably, cost-cutting, greater efficacy, and improved efficiency are not the only critical parameters. The healthcare landscape is subject to changes in disease prevalence, treatment paradigms, and patient needs. Continuous product development allows developers to adapt to evolving market dynamics and patient requirements, as well as align their products with up-to-date medical knowledge, emerging therapies, and changing treatment standards, ensuring relevance and competitiveness in the market.

Final Thoughts

Early-stage development comprises an engagement between sponsors, their CDMO partner(s), and regulatory authorities. Regulatory agencies provide recommendations on project elements including preclinical testing, clinical trial design, safety monitoring, and data submission. Sponsors generally are responsible for designing and conducting preclinical/clinical studies: protocol, endpoints, population, etc. A CDMO partner can be invaluable toward helping the sponsor achieve those aims, as few organizations retain full-time, in-house expertise capable of making those critical decisions.

However, not every CDMO can provide the services needed to shorten the timeline to the clinical trial phase. Adare has the product development expertise, platform technologies, and integrated range of services to help companies reach the clinic faster to generate PoC data. Seasoned development scientists and technical experts working on the bench and manufacturing floor can provide technical insight to our customers, with scale-up always in mind, even during early-stage activities. This iterative approach fosters flexibility, adaptability, and innovation, leading to more effective and commercially viable products.

In particular, Adare's expertise in pediatric medicine is a benefit to our clients, as such knowledge and experience can be difficult to find. Regulators require a pediatric friendly formulation for most drug products — a demand regularly overlooked in the race to market — and Adare excels in the two key requirements for pediatrics: taste-masking and easy-to-swallow formulations.

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ADARE® PHARMA SOLUTIONS

Adare Pharma Solutions is a global technology-driven CDMO providing end-to-end integrated services, from product development through commercial manufacturing and packaging, with small molecule expertise focusing on oral dosage forms for the pharmaceutical industry. Adare's specialized technology platforms provide taste-masking, customized release, solubility enhancement, and patient-centric dosing solutions. With a proven history in drug delivery, Adare has developed and manufactured more than 65 products sold by customers in more than 100 countries globally.