Two Steps Forward, One Step Back: The Dance Toward IND Submission In Early Development

Innovation across the pharmaceutical industry has given way to a wide range of novel modalities, opening up new possibilities in patient care. Despite the industry's evolving landscape, the success rate for drug candidates during early development continues to sit at only 10%.[1]

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This number is even lower when taking into consideration drug candidates that fail during the preclinical stage.[1] Thus, while drug discovery and development are already inherently risky, these numbers mean the risk-versus-reward trade-off is even more unpredictable. The good news, though, is that when you understand the pitfalls that can impede early development, the associated risks can be effectively managed, ultimately driving your program and your organization toward long-term commercial success.

In a recent roundtable discussion, a panel of product development experts with diverse perspectives examined the blind spots that can plague an early development strategy, as well as which considerations must be accounted for when navigating the path toward an IND submission.

Accommodating Constricted Timelines In A New Era Of Drug Development

Pre-pandemic, speed to market ranked as one of the highest business drivers among pharmaceutical companies. However, a recent report by CRB Group shows the industry now ranks speed to market as its top priority.[2] Derek Koops, VP and General Manager of Cambrex's Longmont, CO, site – who has an extensive background in product development, project management, and leadership at industry-leading CDMOs – has seen the impact the pandemic has had on expectations during early drug development. "Timelines have always been paramount in product development, where you want to get your product either to the next stage as quickly as possible or, if it is going to fail, you want it to fail early before investing a tremendous amount of effort into that project," explains Koops. "What we're seeing now, though, is an exacerbation of that pressure on timelines with our sponsors as we come out of the pandemic."

Koops outlines two primary reasons for this change. The first is the increased cost of capital as the cost of borrowing has gone up, which has customers focused on moving forward as quickly as possible while using fewer resources to extend their cash runway to the next funding milestone as much as possible.

About Cambrex

Cambrex is a leading global contract development and manufacturing organization (CDMO) that provides drug substance, drug product, and analytical services across the entire drug lifecycle.

With over 40 years of experience and a growing team of over 2,400 experts servicing global clients from North America and Europe, Cambrex is a trusted partner in branded and generic markets for API and finished dosage form development and manufacturing.

The other is the result of the pandemic exposing the vulnerabilities of the pharmaceutical supply chain, leading to a fervent effort to book time and/or materials with industry suppliers, which can impact the entire lifecycle of development if things go awry. One example Koops points to is the limited availability of laboratories to conduct toxicology studies. "Sponsors are often booking these time slots [for tox studies] even before they secure work with us, so when the project starts at our site, there is already a hard date [for the tox study] and a firm commitment that GLP materials will be provided for it," he says. Even minor delays in the delivery of those materials can create significant setbacks to a sponsor's timeline should a tox study slot be missed and need to return to the long queue to be rescheduled. "So, while the focus on timelines isn't necessarily new to product development, they are certainly more critical to successful product development than we've seen in the past."

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James Graham
Research Fellow, Drug Substance and Process Chemistry R&D, Cambrex Longmont

James Graham, Research Fellow for drug substance and process chemistry at Cambrex with 25 years of experience in pharmaceutical discovery and development, says the expectation for shorter timelines adds further complexity to the learning process that inherently accompanies early development. "It's important to understand that, at this very early stage of development, we are learning new things about your compound every single day, so we find ourselves in a 'take two steps forward, one step back' situation. Science never goes perfectly without any setbacks or hiccups," he explains. "In my group, we're looking at how to transform a medicinal chemistry synthesis route into a fully scalable manufacturing process, and we're trying to do this in a way that helps the client deliver on these constricted timelines. That takes some patience and understanding until we reach the point where we are setting up other downstream groups to have that success." Jason Gregersen, Director of Formulation, R&D, and Drug Product Operations at Cambrex who has overseen numerous regulatory filings and lifecycle management programs, explains the key to accommodating any timeline is flexibility. "Many of the challenges my team faces relate to the quantity of drug substance," says Gregersen. "And if the quantity is limited, we have to make sure to use it sparingly. We're also always learning about what dosage form and strengths are needed, so we just need to be as flexible as we can as the project continues to evolve."

Accounting for the unexpected in your project plan, including the timeline, is crucial in drug development, but especially in the early stages when so much is unknown about the molecule and its unique needs. Tracy Milburn, Director of Analytical Services at Cambrex, has experience spanning from early-stage development through commercial product manufacturing and says not taking this into consideration is a common mistake she sees companies make, particularly as it relates to analytical development. "The analytical team has to keep up with those changes both on the process chemistry side as well as on the product development side, and I think there is a tendency to believe that once the analytics are done, it's done. However, every change in process or dose increase or decrease needs to be re-vetted to make sure the methods continue to be scientifically sound," she explains. "Sponsors often neglect to include that work in their timeline, but any change in the process or manufacturer of the materials will cause some sort of delay."

A Phase-Appropriate Approach To Facilitate Early Development

With the industry as a whole at the cutting edge of research, there has been rapid growth in many areas of the market.[3] As a result, the FDA is reporting a significant increase in original investigational new drug (IND) submissions.[4] However, with this uptick in IND submissions is also a growing number of IND holds, with the most commonly cited reasons related to chemistry, manufacturing, and controls (CMC); safety/efficacy; and toxicity.[5] The fallout of these holds can be far-reaching, especially during Phase I research when any interruptions or delays can be especially damaging to your timeline.

Cambrex's Longmont, CO, site, where the panel of experts work together on an extensive portfolio of early development projects for small molecules ranging from preclinical to Phase IIa, represents a true integration of drug substance and drug product development. In addition to drug substance and drug product development and manufacturing capabilities,

the Longmont facility also includes pre-formulation capabilities and a full analytical suite of services. With these groups co-located in one facility rather than distributed across multiple sites, they are able to collaborate when issues arise and make informed decisions together. This also allows them to efficiently execute a phase-appropriate approach to early development that facilitates the transition to late-stage development, which can help improve the chances of success of your IND submission.

"As we move through process chemistry, we're designing a manufacturing process that is fit-for-purpose and phase-appropriate, meaning if you're filing an IND for your first Phase I studies, there is usually a smaller amount required for the deliverable," explains Graham. "So, we have to develop a process that can deliver those quantities under GMP conditions and within the specifications determined by the client." For the earliest phases, a fully optimized process isn't necessary but could be developed in the background as a program moves through development. As Graham explains, it's okay to not have all of the answers up front. "There are certain ones you have to have [for your IND] and focusing on only those in the early stages allows you to meet your timelines and deliverables at each phase." While many clients may want to have optimization done early to avoid having to make changes later, Gregersen explains the team has found this isn't necessary, especially with the breadth of capabilities at the Longmont site. "A lot of times, it comes down to just needing enough to get into the clinic and into a stability program, so our batch sizes might be only 10,000 units but as it progresses, we can always scale up and do larger batch sizes."

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Milburn stresses that overall, it's important to keep in mind that there is no perfect IND submission, especially when it comes to analytics. "Every time you increase the ize or make any change, such as to a solvent, you're going to have to look at everything all over again," she explains. "So, you have to strike a balance between what you need to do now and what you need to do going forward to make sure that everybody is in alignment with the strategy, especially if you're partnering with a CDMO." Working in a dedicated early development facility can also help address some of the gray areas that come up during development. "In my experience in other combined facilities, one of the challenges is that late-phase quality standards are sometimes applied to early-phase development work," says Koops. "For example, there are things that are perfectly acceptable in early development [that aren't in late-stage development], such as using qualified rather than validated analytical methods or by primarily doing ID testing on excipients. Instead, combined facilities tend to apply the most stringent quality standards across the site, which makes it difficult to be fast and flexible."

Early Development Calls On Flexibility And Proximity

Flexibility is often necessary to deal with issues that arise during early-phase development work, and this skillset has helped the team resolve a wide range of issues at the Longmont facility. For example, in a recent project, the team was moving a molecule through process chemistry optimization and preparing for GMP production of drug substance. During this time, they identified an unknown polymorph in the final step of the demonstration batch, which required characterization before they could move forward. With all of the groups co-located in the same facility, Graham explains that what could have taken several weeks to do was resolved within days through quick collaboration and by eliminating transit of the material between facilities. "All of our instrumentation and systems are optimized for addressing common problems that pop up, allowing us to pivot in an instant to start working on problems immediately," he says. "That's a major benefit that our clients and the people on the line experience as they develop their compound in our facility."

Gregersen cited another issue where flexibility and proximity were crucial to maintaining a client's timeline. "At our site, we typically produce a small-scale pilot first and then go into a GMP drug product batch after setting parameters. However, because the drug substance synthetic process is frequently developed in parallel, a risk-based decision is sometimes made to use API from development batches for the pilot drug product batch. The GMP API is then used for the GMP drug product batch to reduce the overall

timeline. This can create risk, though, as any difference in the API between the two batches may impact on the performance of the drug product," explains Gregersen. "For one project, we followed this approach and encountered dissolution issues with the clinical batch that were not observed with the pilot batch. It was determined that this was due to a significant difference in particle size between the lots of API used for each batch. However, because of our on-site material characterization and micronization capabilities, we were able to quicky identify and address this by characterizing the target particle size in our lab with Tracy's team and then adding in a micronization step into our drug product batch record to correct the particle size of the API. As a result, we were able to produce clinical drug product material with suitable dissolution characteristics within several weeks. If the micronization had to be performed off site with a chain of custody and material release requirements for GMP, it would have resulted in a delay that could have lasted months."

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Milburn stresses that the need to make quick decisions in real time is particularly necessary during analytical development where the unexpected often occurs. Thus, the co-location of the other development teams is crucial. This was demonstrated in an instance outlined by Milburn, where the residue on ignition (ROI) content of the material, which is typically less than 2%, showed a value of 10% upon release to GMP manufacturing. An ROI level this high would cause an assay to fail, due to a high level of impurities; nevertheless, the combined capabilities and close proximity of the other groups allowed for quick resolution on site. "Using our in-depth impurity profile screening via mass spectrometry, we were able to quickly pinpoint why that value coming out was high, which was related to a wash step in the process," explains Milburn. "We were able to harvest the material from [ROI] testing, get it into our material characterization lab, and then give the information back to the process chemistry team to look at and see what they could do to clean it up, all within a week." She adds that being able to just walk down the hallway to get that done versus relying on outside testing offers not just quick resolution for the process and the client, but also valuable insight for other projects. "It's a learning experience for everybody, and it gives us things to look out for as we're doing different development projects."

The ability to streamline communication is what makes this "one-stop shop" approach so effective. The various teams can quickly discuss issues as they arise and then not only resolve them, but also update the client, who is finding out about the problem as well as the solution at the same time. And, as Graham explains, it is these conversations that can be the key differentiator when trying to stay ahead of your competitors in the race to market. "If time really is your enemy, then you need to find ways everywhere you can to remove unproductive time, and that's often in the margins and in the handoffs between groups. So, if that's your approach, you must be cognizant of that and prepare for it."

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