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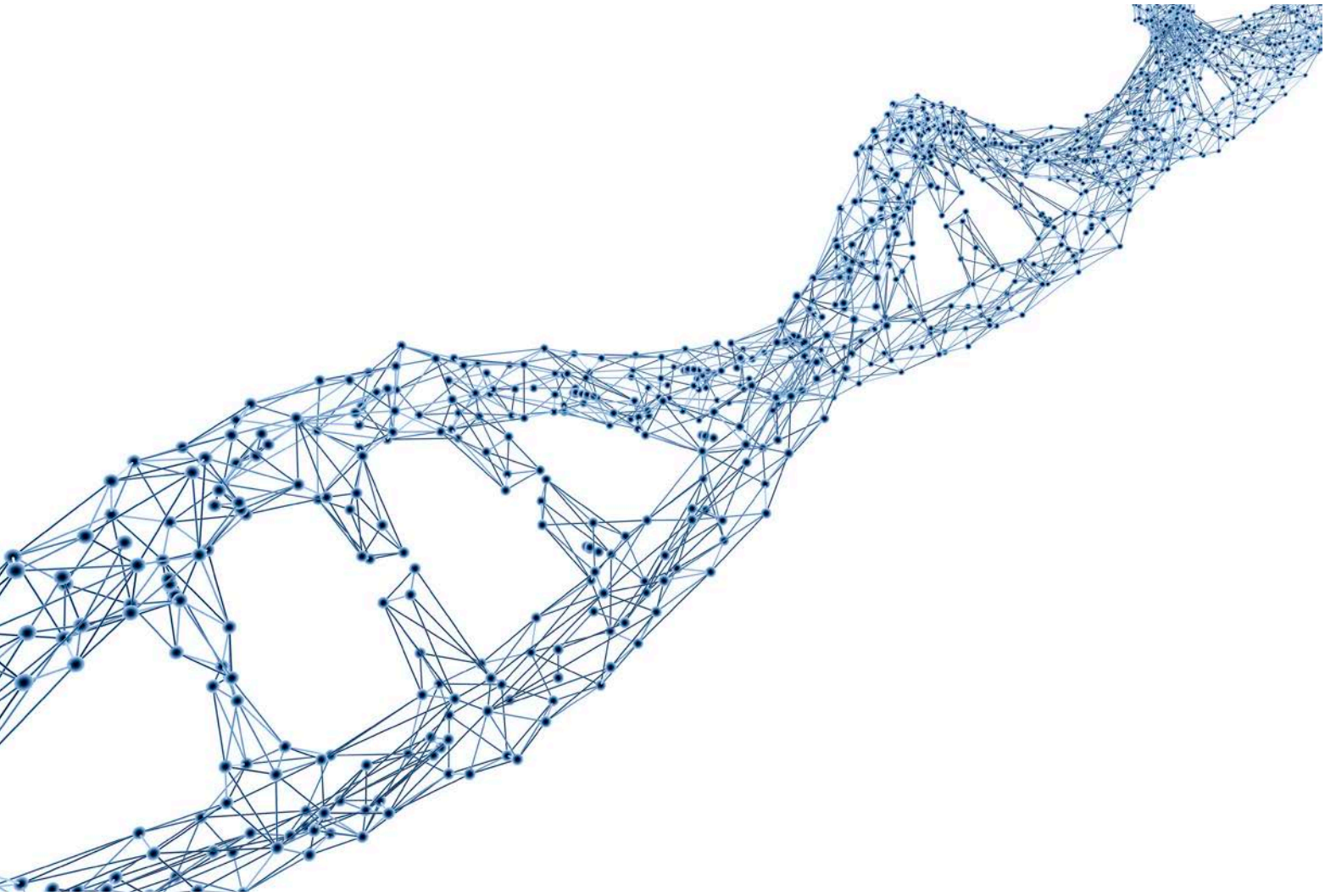

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WHITEPAPER

Top five risks facing your small biopharma clients

• API • BIOLOGICS • VIRAL VECTOR SERVICES • EARLY & LATE PHASE DEVELOPMENT • CLINICAL TRIAL SOLUTIONS • LOGISTICS SERVICES • COMMERCIAL MANUFACTURING

patheon

Abstract

Biopharma firms function in a risky development environment with compressed timelines and budget constraints. Companies often overlook critical factors which could delay or suspend efforts down the road. Consultants should help clients understand five key risks in order to avoid costly problems and maximize financial returns during the development process.

Drug development is an expensive proposition. Discovery and preclinical work are estimated to cost $318 million, with an additional $800 million to $1.1 billion required to advance a molecule from first-in-human testing to market approval[1-2]. For small biopharmaceutical innovators, steep development costs are compounded by the fact that large molecules are becoming increasingly complex and serious clinical or manufacturing problems may not surface until late in the process. Identifying these risks early on and choosing the right CDMO partner will ensure these risks are diminished, while financial returns remain. Learn how Thermo Fisher Scientific has the solution and is the right partner, every time.

Introduction

For small biopharmaceutical innovators, steep development costs are compounded by the fact that large molecules are becoming increasingly complex and serious clinical or manufacturing problems may not surface until late in the process. Building upon this risk, events such as mergers, acquisitions, restructurings, political uncertainty and even public criticism can all have a huge effect on a small company's stock and monetary resources.

With a limited amount of money at their disposal for generating clinical data, biopharma firms are often waiting for the perfect moment to excute and move products quickly through development. This creates a situation where highly compressed process development timelines lead companies to overlook critical factors that could delay—or even suspend—efforts down the road.

In this article, we identify some important risks that consultants should put on the radars of their small biopharma clients. Doing so, along with choosing the right outsourcing partner, will ensure their risks—not their financial returns—are diminished.

1. Planning for tech transfer

The events-driven culture of a small biopharma affects everything from the amount of process data a firm collects to its options for early-stage manufacturing.

In that regard, condensed timelines and limited financial resources usually drive small biopharmaceutical companies to select smaller CDMOs that have immediate capacity. As the molecule matures, and additional capacity and clinical development are needed, innovators often move to a larger CDMO with late-stage development experience and commercial capacity.

The transfer of data, specs and detailed knowledge about a process from an innovator to another party—or from CDMO to CDMO—is extremely common in the biopharmaceutical lifecycle. Unfortunately, it is also very common for companies inexperienced in chemistry, manufacturing and controls (CMC) to underestimate the time and effort a proper tech transfer requires.

At Thermo Fisher Scientific, a typical tech transfer takes approximately six to nine months. Most companies require much longer to move from a kick-off call to starting final production. One way we can save time during this process is with single-use bioreactors, which allow for more efficient tech transfers while eliminating cross-contamination concerns.

A six-month transfer process often comes as an unwelcome surprise to young biopharmas looking for a 60-day turnaround time. Such a fast timeline is virtually impossible. Even if a customer has a fully prepared tech transfer package that aligns with our requirements, the process will still take about four months to complete, and even that timeline is pushing it.

Time is needed to ensure the right facility fit, proper risk assessments of the facility fit and bench-scale work to either modify the process or to demonstrate comparability between the new and old equipment and small-and larger-scale production processes.

Moreover, some files and data can be shared digitally, but eventually, you need to schedule additional time for information to be delivered in person. We've also seen poor planning cause the loss of historical data or process development reports during tech transfer, which not only extends deadlines but also results in duplicated efforts.

A CDMO-to-CDMO transfer can be especially messy in this regard when the two parties are reluctant to work together. Innovators are then forced to take whatever information they can secure from the smaller CDMO and work backward, filling in the gaps with the new CDMO.

Contrast the uncertainties involved in moving from a small-scale to large-scale CDMO with the stability of using just one manufacturer capable of working on the development of a large molecule through to commercialization. At Thermo Fisher, we've found that the use of a single project manager and integrated quality systems eliminates potential hand-off challenges and provides enhanced communication, stronger CMC filing and time savings of 14–20 weeks.

2. Limited regulatory experience

Virtual biopharmas often do not have a regulatory expert on staff due to financial constraints and, therefore, may have a limited understanding of the data required to proceed into first-in-human testing. Even if a compound is years away from first-in-human studies, biopharmas cannot wait to collect the data needed for a successful Investigational New Drug (IND) filing.

The FDA requires evidence that a proposed human clinical study is safe, based on prior animal studies. All too often, new innovators have the mistaken impression that they can slide into first-in-human testing with a fairly anemic portfolio of data, often lacking in areas like media screens, drug stability, operating parameters and justification for their decisions. Not long ago, it was not uncommon to see the CMC section of an IND run a maximum of 32 pages; today, we see CMC portions that are 180 pages or more.

Without a regulatory expert on staff, such changes in FDA's requirements may go unnoticed until an IND filing is rejected by the agency due to missing information. Regulatory guidelines clearly lay out the expectation that developers should be doing process development work from the get-go—not wait until later stages.

Innovators should have good designs of experiments, proper data to support operating ranges, alert and action limits and a validated scale-down model that bridges into process performance qualification (PPQ) work. In a nutshell, they must make an early commitment to continuous process improvement and validation, and follow through with sufficient data.

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The amount and quality of data collected during product characterization studies will be connected to FDA's assessment of risks for commercial manufacturing processes and product safety as a whole. Many times, smaller companies do not have a clear understanding of this overarching architecture for process development.

Gone are the days of a standard three-run validation requirement. The data collected throughout the process will feed into the number of validation runs the agency wants to see.

Unlike small molecules, validation data for a biopharmaceutical must be submitted up front in an IND filing so that FDA can evaluate the process development Inadequately preparing today for tomorrow's regulatory filings becomes especially problematic as assets approach later development stages.

Over the past decade, big pharma companies have made an effort to de-risk by waiting to purchase new molecules until Phase III. If a virtual company does not complete adequate process development work in early phases, it must generate this data during late-stage development when it should be working on a PPQ strategy.

We are also seeing this issue come to bear in the rush to market for biosimilars.When companies file a Biologics License Application (BLA) without sufficient CMC data, FDA will likely issue a complete response letter and prohibit them from moving forward. It could take years for firms to go back and create a better risk profile. We expect that FDA will continue to make its filing requirements stricter as time goes on, especially for biosimilars.

3. Unclear product profile

It is essential for innovators to establish a target product profile to ensure formulation work is effective and focused. A typical document will contain the route of administration, dosage form and amount, indications, product specifications and other key attributes. Formulation scientists can cross-check these clear objectives as they proceed to ensure their work is on target.

When a product profile is unclear, drug formulation work can suffer as clients may uncover problems very late in the commercialization process. It is not uncommon for firms to move a sub-optimal formulation into early clinical stages with the expectation that it can be optimized as the program moves through development.

Making changes to the formulation isn't a problem if given enough time. However, challenges surface when significant upstream development is needed and it is discovered late in the development timelines.

Consider this example: a small biopharma is working on a therapeutic molecule it expects to be given at a physician's office with a syringe and vial. As the first batches are delivered, the company realizes the drug is competing in an environment where self-administration is prevalent, accepted and expected. Transforming the presentation into an autoinjector will be critical to the product's success on the market, but such a major change can have a huge impact on the development timeline.

A drug delivered with an autoinjector will have additional constraints as part of its target product profile when compared to a drug in a vial. Most autoinjectors can only deliver about 1 mL of fluid or less, and it must have the proper viscosity to avoid performance failure. If the existing formulation does not meet these requirements, the company can suddenly face a reformulation challenge that results in stability issues. In addition, it's possible that the original specification will not support the new formulation, meaning the company must backtrack to allow for tighter specifications.

The medical device requirements for an autoinjector are very complex. Studies must demonstrate that people can inject the product themselves, that it is user friendly, and that it is appropriate for the intended patient population —i.e., an arthritic geriatric patient can use the device if it is an arthritis formula. In-human use studies can be substantial, have very specific requirements—e.g., a system for collecting user feedback or having separate shipping validation assessments—and take two to three years to complete. These fine points are not always well understood.

A less obvious formulation issue may arise when the dose is increased significantly during clinical development. Since the dose is not typically finalized until after Phase II, using a range that includes all possible dosages during planning is important. If the plan is to address the increased dose by further concentrating the product during the drug product stage of manufacturing, this may require careful examination of the drug substance specifications. If tighter specifications are necessary, the current drug substance manufacturing process may not be capable of meeting the new specifications.

4. Changes in clinical product demand

Small biopharma companies often only manufacture product when they have clinical demand, and they typically choose a small bioreactor size for financial reasons.

The problem with this situation is that if companies underestimate their needs—purchasing a 500-L bioreactor when they end up needing a 2,000-L bioreactor—it brings significant risks to the commercialization process.

Clinical demand can quickly increase when clinical trial recruitment goes better than expected or, surprisingly, when it goes poorly. To draw additional study participants, companies may need to open additional clinical trial sites, which requires additional supply. Also, some drug developers are surprised by the amount of drug required for non-clinical needs such as stability studies, viral clearance studies, characterization work and formulation development.

Securing another batch to fill the gaps is rarely an easy task due to limited manufacturing capacity in the biopharmaceutical realm and the need for board approval. Companies might get lucky and locate immediately available supply, but it is much more common for capacity to be sold out for up to a year in advance. Indeed, finding a CDMO with midscale expertise in biopharmaceutical manufacturing is often difficult.

From our perspective, customers would be better served discussing their clinical demand with a qualified CDMO and tapping into their expertise for determining the proper amount to meet all their needs and having the flexible solutions required to fulfill additional capacity in the future.

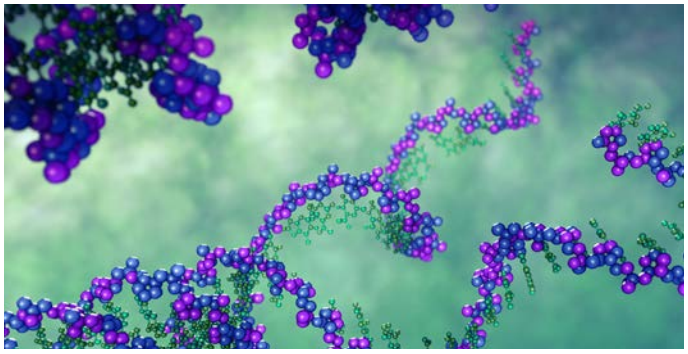
This situation is not unlike the critical need for determining adequate supply once a product is on the market. If companies underestimate commercial supply, patients cannot get the medications they need; and if firms over-manufacture, expensive supply is wasted.

Therefore, it is key to partner with a CDMO that offers flexible solutions that allow you to plan how to respond to your capacity needs in the future.

5. Limited CMC resources

Many small virtual biopharma companies have roots in clinical research with MDs and PhDs at the helm. While they are well versed in clinical research, they often don't have CMC experience and hiring a CMC specialist is rarely in the budget.

In the early stages, firms can typically keep CMC off the commercialization critical path timeline. As the program progresses, however, the volume of CMC work ramps up sharply and can create a bottleneck. Some companies simply delay this work until they reach Phase III and are heading to filing. However, the amount of process development and process characterization work required to gain approval can quickly stall any forward movement in this direction. In short, if you do not understand the requirements and you file anyway, you are setting yourself up for failure.



The answer for many firms is to rely on consultants to fill this gap in CMC knowledge. If firms hire a knowledgeable consultant, he or she can be a great resource, particularly if that person has worked at a big biopharma or big pharma company and has a full breadth of experience in both the manufacturing and the analytical segments.

If firms choose not to invest in someone with CMC experience, the biopharma team may learn late in the game that the time and effort required to go back and generate the CMC information required for filing will take years. Assessing these five risks, and addressing them at the appropriate time in the development lifecycle, will keep CMC on the critical path.

About us

Thermo Fisher Scientific provides industry-leading pharma services solutions for drug development, clinical trial logistics and commercial manufacturing to customers through our Patheon brand. With more than 65 locations around the world, we provide integrated, end-to-end capabilities across all phases of development, including API, biologics, viral vectors, cGMP plasmids, formulation, clinical trials solutions, logistics services and commercial manufacturing and packaging. We give pharma and biotech companies of all sizes instant access to a global network of facilities and technical experts across the Americas, Europe, Asia and Australia. Our global leadership is built on a reputation for scientific and technical excellence. We offer integrated drug development and clinical services tailored to fit your drug development journey through our Quick to Care™ program. As a leading pharma services provider, we deliver unrivaled quality, reliability and compliance. Together with our customers, we're rapidly turning pharmaceutical possibilities into realities.

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