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Growing Your Biopharma: Ten Questions You're Likely to Face from Investors—And How to Respond to Them

Developing a Method for Success Through Partnerships

There May Be Dragons: Mapping 7 New & Emerging Pharma Development Risks

Balancing Internal Focus Against External Capabilities

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Growing Your Biopharma: Ten Questions You're Likely to Face from Investors—And How to Respond to Them

INTRODUCTION

There are many important considerations to address in building your new drug program. Without a doubt, one of the most critical is funding to get you to your next milestone. As you grapple with funding issues, it can be useful to consider the point of view of a potential investor.

Why? Because investors are betting on you to manage development effectively and to move quickly. In assembling this guide, we asked investment veterans and biopharma executives what questions they ask (and have been asked) when both parties sit down together. Answer these questions well and your potential investors are that much more likely to support your company's vision.

We've also included a few "red flags" that you should avoid. Sometimes knowing what gives potential funders pause is just as important as knowing what they are likely to ask.

BUSINESS MODEL AND STRATEGY QUESTIONS

1. What's your hypothesis?

Why are they asking this question?

To secure funding for your new or emerging pharma company, it's critical that you articulate your core idea. If you can describe your company's strategy succinctly, investors will be able to make a clearer call on whether your hypothesis has merit. You may only have limited information at this point in your evolution, but you need to make your potential investors excited about investigating further.

Why is it relevant and important?

Investors are asking themselves two questions when they sit down with you: Is this a scientific bet worth making, and is there a market for it? The more specific you can be about your company's core idea and why it has a ready market, the more likely you are to find funders that can get behind the idea.

Red Flag: No elevator pitch

Pharma and biotech investors regularly attend conferences where they hear pitches from dozens of aspiring companies in short, timed presentations. These are often referred to as "speed dating" sessions. If you are unable to articulate in one or two sentences why your treatment or technology is important and why it will matter, you will inspire doubt rather than confidence. Most investors aren't scientists, so if you can't simply and clearly articulate the benefits your company will bring to the world, they are likely to pass. Best advice? Nail your 15-second elevator speech before you approach investors.

What's the best way to respond?

Be clear and concise. Write out a response and memorize it. If your hypothesis is that a particular antibody works in such a way that it may address a rare disease, for example, state this in as few words as possible.

2. What's your business strategy?

Why are they asking this question?

Venture capital and large pharma companies are accountable to their investors and shareholders and need to know how quickly they can see a return on their investment. They understand that most of their investments may not pan out, so they want to "fail fast" and move to the next promising company, if that's appropriate. They also will tend to fund one major milestone at a time for your company and want to know how you plan to get there.

Why is it relevant and important?

It's critical for any investor to know what their risks are over a prescribed time frame. If it will take $5 million to get to a yes/no answer based on your hypothesis, your investor will want to know how your plan of action breaks out and how quickly you can achieve results.

What's the best way to respond?

Expect to provide details about not just your current strategy but also your strategy over the next three to five years—including your strategy for an exit scenario. Investors find it helpful to hear strategy in bite-size pieces so they can get excited about a stepwise investment.

For example, you may plan to take an asset, move it to the clinic and sell it to a pharma company or other acquiring entity based on how it works in progressively larger human populations. On the other hand, you may plan to build a sustainable, integrated biopharma company and move to an IPO. Or you may plan to partner with a large pharma for a commercial launch. All three directions are legitimate—the point is to make sure that you clearly articulate your envisioned future.

Red Flag: Unrealistic timeline or budget

Although they may not be scientists themselves, most investors employ scientific experts and rely on consultants to provide them with counsel on candidates they are considering for funding. Confidence is essential to making a good impression, and investors realize that companies tend to present best-case scenarios for timing, but too much confidence about when you will be ready for the clinic can backfire.

Since you're likely to be in the company of business experts, it's best to stress what you know and admit what you don't. Budgets to get you to clinic that underestimate costs such as specialty ingredients, API formulation, viral vector production or manufacturing redundancies may get you into hot water. In the same way, spending too much up front on space, equipment and expensive staff can raise warning flags.

TEAM AND COMPETITION QUESTIONS

3. Who are your founders and management team?

Why are they asking this question?

Although most investors will have researched this topic in advance, they will want to hear in your own words about your track record, how successful the members of your leadership have been in their careers and how they are executing in your new company. It's unlikely that you're a public company with a board of directors at this stage, but investors still want to understand who your key opinion leaders (KOLs) are: Who is guiding you on your journey? How will they help you stay on course if your program has issues, or if it succeeds? Investors are also looking for consistency in what they hear. A lead investor from a large pharmaceutical company was once quoted as saying, "When you're interviewing, ask the same question of everyone. You want to make sure you're getting the same answer."

Why is it relevant and important?

It's essential that your investors believe you have the right team in place, including operational expertise, insightful scientific minds, entrepreneurial business leadership and, increasingly, CMC know-how. Depending on the investor's funding model, they may also want to determine your openness to working with them to pull together a more complete team, often complementing your existing scientific expertise with business acumen. This may include a CEO suggested by the investor or VC firm.

What's the best way to respond?

Stress the successes you and your team members have had in the past, because funders believe that success breeds more success. Also remember to point out the strength of

Red Flag: Too much ego

As a successful academic researcher, you may have an MD-PhD and have served as principal investigator of a prestigious lab. You may have discovered a molecule and formed your own company. You may have headed up an entire therapeutic area at a large pharma company. In short, you may be accustomed to being seen as the smartest person in the room. A confident ego can inspire funders to see and share your vision, but an arrogant ego does not sit well with many venture funders, especially if you haven't been back on the bench in 15 years.

Investors are looking for scrappy entrepreneurs who know how to get things done and ideally have a track record of doing so. On the other hand, investors will turn a wary eye on start-ups that claim they can do everything themselves with little help from outside partners. New generations of biotech VC firms focus more on a collaborative, hand-in-hand company development and creation process. Reputable firms also are committed to helping you succeed because your therapy or medicine could save lives. Arrogance does not mix well with these settings. A good strategy is to focus on humility.

your network, both scientific and financial. It increases an investor's comfort level to know that they won't be the sole party who might have to invest more money down the line because you haven't secured other investors.

An investor would much prefer to hear, "I don't know the answer to that, but I know it's important, and here's how I'm thinking about it."

4. What's your competition?

Why are they asking this question?

Every funder wants reassurance that you're not simply copying an idea that's already in the market. And even if many competitors are working in your area, funders want to know what your advantage is in meeting these competitive headwinds. For example: What are the key differentiators about your product—durability, efficacy, dosing or something else? Why will your program be clinically meaningful in ways that others aren't?

Why is it relevant and important?

If ten companies have the same hypothesis and approach to a problem, it will dilute the value of your company if your competitors are further along. Investors want to make educated decisions.

What's the best way to respond?

Before you ask for funding, conduct the most thorough competitive audit you can. If someone is pursuing your hypothesis already, be prepared to describe what's unique about your approach. Take the time to conduct your due diligence and be prepared to defend your unique qualities, be they therapeutic modality, use (and redundant supply) of raw materials, CMC requirements, scale-up process or anything else that presents your company as a sound scientific and business investment.

Red Flag: "We have no competition"

Some innovators feel that their innovation is novel or a one-of-a-kind solution. Unless this therapy is a gene therapy and there is no other innovator working on this specific indication, there is competition.

INFRASTRUCTURE AND PARTNERSHIP QUESTIONS

5. How much are you investing in infrastructure?

Why are they asking this question?

Much of what you need to do in drug discovery research can now be outsourced, so if you plan to purchase a significant amount of equipment or hire large numbers of scientific staff to answer your business's core go/no-go question, that strategy is likely to be challenged by an investor.

Why is it relevant and important?

Investors are looking for new and emerging companies to run lean, without the infrastructure baggage of legacy organizations that may have spawned or inspired them. Just as the CRO industry grew up to complement—and in many cases replace—pharma companies' conducting their own trials, the CDMO industry offers a more financially and scientifically favorable model for new and emerging drug development and manufacturing. If you are making in-house infrastructure a priority beyond a base level of internal infrastructure and expertise to evaluate data and track progress, you may need to make a very strong case for the value this will deliver.

And don't forget: With a reputable CDMO, your team will act as an extension of your company, not as a "set it and forget it" capability that you never see.

What's the best way to respond?

Be honest and make a strong case for why you must maintain in-house control over certain elements of your discovery and development program. If you think you can take risk off the table by having an integrated CDMO as part of your strategy, consider this approach.

Red Flag: Too much focus on efficiency, not enough on innovation

Striving for higher efficiencies and eliminating costs in areas such as engineering probably have utility in large, mature organizations, but do not tend to drive value in new and emerging biotechs. If you come out of a large organization with a cost-saving culture and make claims about driving efficiency in a start-up, it will sound upside-down to investors. No one wants to be the VP of CMC who has to approach their board and say, "I thought I was going to save $500,000, but now the program is six months behind."

6. What's your development and manufacturing strategy, and who are your partners?

Why are they asking this question?

Especially in high-complexity areas like cell and gene therapy, funders will want to understand your strategy in clinical development based on the high cash burn rate and the supply chain capacity you'll need in order to produce a reliable supply of product. CMC skills are increasingly important as well, because most investors understand that excellent clinical data on its own is not sufficient to scale manufacturing of your product and get it approved by regulatory agencies. Characterizing and understanding your process and product quality are essential.

Investors know that most small companies have neither the size nor the resources to develop and manufacture their own drugs, so they also need to know what your outsourcing strategy is. Large-molecule drugs are more difficult and expensive to manufacture than small, so having a strong manufacturing relationship with a respected CDMO that brings a strong track record can make a difference with funders. It stands to reason that investors will be more likely to approve of CDMOs with which they've had positive relationships in the past.

Why is it relevant and important?
Funders want to know that you will be following a proven path to a commercially realized product. New and emerging companies need credible, high-quality partners that will not only perform development and manufacturing work, but also help interpret the results of pathology reports and DMPK studies. Good partners also anticipate the downstream impacts from upstream development and manufacturing decisions and can help you present your data package to regulatory bodies like the FDA as they want to see it.

What's the best way to respond?
Do the math. If you'll need 15,000 square feet of manufacturing capacity to make enough of your product to realize its revenue potential, make sure that you've checked your numbers. Investors want you to demonstrate that you understand your supply chain requirements, regardless of how you plan to address them: internal build, outsourcing or a hybrid strategy.

Choose your CDMO partners carefully based on a set of key factors affecting performance outcomes. Be ready to share with investors why you've made your decisions, based on:

- **Track record**
  - Has the company taken a product and commercialized it?
- **Quality processes**
  - Is there any risk associated with choosing this company?
  - Might it have inspection issues based on past programs?
  - Has it previously had FDA actions?
  - How has it performed in pre-license inspections?
- **Reputation**
  - Is it a recognized company or relatively unknown?

Think about the best way to convey that you're focused on the most efficient path

Red Flag: Overclaiming or "getting out over your skis"

Having confidence and conviction in settled science is good. Conveying the same level of confidence in areas where you're out of your depth is not. For example, if you haven't really built out your CMC strategy, you're better off acknowledging it than trying to talk your way through it. If you start to claim that "We're really going to think out of the box on CMC and do this differently" or "Yes, we can make the product; don't worry about that," expect some raised eyebrows. VC investors don't expect a molecular biologist to have all the answers. The important thing is to be capable of engaging with other people who do have this expertise.

to the next milestone, but that you're also looking to make key foundational investments that will set you up for success faster in the next phase. This is a difficult balance to strike, so work out the response with your team and your partners before pitching to an investor.

7. Are you working with one CDMO or many?

Why are they asking this question?

Every investor wants to future-proof their investment as much as possible. If your company has contracts with multiple CMOs or CDMOs for drug substance, drug product, clinical trial and other services, it's likely that each new team will be restarting at each step.

Why is it relevant and important?

Investors would prefer that you remain focused on reaching the next milestone rather than on educating new vendors and managing multiple relationships, especially if new and existing vendors compete with each other.

What's the best way to respond?

Keep in mind that as a new and emerging biopharma, you have to move fast with a limited amount of budget and resources to get to first-in-human trials followed by proof of concept. If you currently have multiple partners working on your program, this can be seen as adding risk to your program, so put together a strong argument for why this isn't the case. You might also consider collecting proposals from larger, integrated CDMOs with which you'll spend less time negotiating terms, overseeing day-to-day details or transferring processes between partners.

Red Flag: Scattered focus

Investors would prefer that you stay focused on science and development rather than acting as program manager for multiple CDMO relationships. Partnering with multiple CDMOs potentially adds risks and delays as well. If your attention appears spread across too many outsourced partners, expect to be asked why you haven't considered a larger, integrated partner that can handle program oversight on your behalf.

8. How are you thinking about the data package you'll be submitting to regulators?

Why are they asking this question?

Although it may seem to be a downstream consideration, many cell and gene therapy start-ups are surprised by how quickly their Phase I results lead to requests from the FDA to submit for accelerated designations. With the FDA predicting that it will be approving 10 to 20 cell and gene therapy products a year by 2025,1 it's important to think about the regulatory submission earlier.

Why is it relevant and important?

A strong, high-quality data package is key to a fast, successful regulatory submission. When you work with a single integrated CDMO, information and learnings are shared across the teams focused on your program. If your asset is split among multiple CMOs or CDMOs, investors may have to invest time and money in helping to pull the data package together. Investors do not consider this a good use of their precious resources.

What's the best way to respond?
Before you pitch to an investor, talk to some experts about what the best route to a clean, integrated data package will be for you. If working with a single integrated CDMO is part of the solution, incorporate this into your planning process.

RISK MITIGATION AND PROBLEM-SOLVING QUESTIONS

9. What will you do when problems occur?

Why are they asking this question?
Investors are unlikely to ask you about responding to highly specific problems if you are pre-IND. With a question like this, the investors are likely trying to determine how you think about approaching a problem or creating a Plan B, both of which are important considerations to establish confidence. Given the current global pandemic, new considerations also arise. For example, if you can't visit your CDMO in Europe due to travel restrictions, how will you ensure that quality stays high enough?

Why is it relevant and important?
Problems and challenges are part of the nature of the biopharma business, so investors want to get inside your thought process. From their perspective, they also want to avoid getting pulled in to contribute more money (and even more important, more time) to get your program across the finish line.

What's the best way to respond?
Think in advance about different categories of problems your program might face and how you'd work to mitigate them. For example, you might consider building in manufacturing redundancy if manufacturing falls on the critical path for your R&D program. You might also consider a manufacturing partner that has a proven ability to identify the root cause of manufacturing process deviations and a broad network that can be called on to get you back on track. When the question comes, it's ideal to be able to say, "The CDMO we want to work with is the best fit for our product. It has the ability to expand capacity. It can leverage a broad network. We can leverage its resources here for distribution. It has strong regulatory experience. And given all this, our CDMO can help us manage any problem that may arise."

10. How are you positioning yourself for the next step in your program?

Why are they asking this question?
Drug development presents many options for a young biopharma company, including the partners you've chosen and the decisions they may lead you to make. For example, what is the development route you'll choose for your API, if you are pursuing a small-molecule drug?

Why is it relevant and important?
Investors want to know that you've taken off the table every risk that you can control for today. In the API example above, you may choose purity over yield in your formulation instead of fully characterizing your molecule and investigating formulation and solubility. This can be a shortsighted decision in terms

of next steps if it compromises downstream bioavailability and increases cost. If your CDMO combines drug substance and drug product capabilities under the same roof, however, this is much less likely to happen.

What's the best way to respond?
Make sure that you have explored the downstream implications of your development decisions as well as the foresight of your potential partners. Investors will be impressed that you have thought through these issues before you sit down together.

CONCLUSION

Obviously, there is a lot to think about when it comes to making a case to investors. Get the answers to the basic questions before you pitch, and you'll have a greater chance of succeeding:

- What is my concept?
- What could it be good for?
- How much will it cost to get to an answer?
- How can I make developing and manufacturing my drug as fast and successful as possible?

Also ensure that you are working with a CDMO partner that has the right skills and experience, gives you the right level of attention and project management, integrates as many steps of development and manufacturing as possible, is clear about how you'll work together, and can help you think strategically about commercial supply. Some investors will be more willing to give you a higher valuation and provide more capital if you can show you've thought seriously about manufacturing issues. Once you have, you'll be a lot closer to the funding and positive patient impact you envision.

"When you're interviewing, ask the same question to everyone. You want to make sure you're getting the same answer."
— Lead investor, large pharmaceutical company

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Funding Flavors

Seed money:

Friends and family money to get your idea off the ground

Series A:

VC funding to launch your company, ideally to get you to the discovery finish line and into the clinic

Series B:

VC funding to move your programs through clinical testing for safety, efficacy and large-scale patient efficacy

Mezzanine funding:

An additional level of VC funding to make up for a budget shortfall or to fund extra necessary research to reach your goal

IPO:

Public funding to bring your company to the world of investors at large

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Developing a Method for Success Through Partnerships

By Felicity Thomas

Outsourcing method development offers multiple benefits to companies, including access to experience and expertise, streamlined costs, and development time efficiencies

The market for outsourced pharmaceutical and biotechnology services is expected to experience healthy growth and is forecast to reach $91.4 billion by 2028 (1). Factors influencing this market swell include rising pressure on drug prices, increasing drug development costs, higher rates of failure, regulatory hurdles, and deficient internal capabilities of sponsor companies, all leading to an increased demand for outsourced solutions (1).

Method development is an evident area where pharma companies can gain an economic benefit from outsourced services, particularly when there are limited to no capabilities for these services in-house. As an integral facet of drug development, optimization and selection of the most appropriate methods can help save on costs and reduce development times.

“The importance of method development cannot be understated,” says Emma Leishman, manager, Advanced Analytics, Avomeen. “Methods are the backbone of being able to answer scientific

questions. Advancements in technology, as well as tighter regulatory needs, are driving methods that are more targeted, efficient, and sensitive. Spending time on method development upfront will build a solid foundation for validation and subsequent sample testing."

Factors for consideration

"Method development and evolution of a drug product are continuous processes that progress in parallel with one another," explains Alex Wheeler, senior technician at Wickham Laboratories. "It can be assumed that as the life cycle of a drug product progresses, overall knowledge of the drug product increases as should the robustness of the analytical tests that are being performed."

Any analytical tests that are due to be performed must relate to the type of drug being developed and are required to comply to any regulatory requirements, continues Wheeler. "During method development, full transparency of the procedure performed is imperative so that when the information is presented to the relevant market authority, it is clear, accurate, and concisely conveys what has been done," he says. "Investing in robust analytical tests to be established during the method development process will help to ensure that costs are kept down during the further stages of the drug development program."

Factors for consideration in method development are dependent upon the molecules being developed, agrees Vincent Thibon, technical development lead, RSSL. "For developing methods for small molecules, the analytical method should be developed by looking into the factors such as pH, ionic strength, mobile phase composition, sample preparation, column technology, type of detection, [liquid chromatography–mass spectrometry] LC–MS compatibility, robustness, speed of [quality control] QC, length of time required for stability indication, cost effectiveness, and whether the method is easy to run," he states. "For developing methods for large, protein-based molecules, the method should be developed by looking into factors such as sample preparation, sensitivity of technique, time to achieve results, complexity of method, and so on."

A structured method development procedure is vital to ensure the intended methods are fit for the phase of drug product development, they provide the data required for product development support, and they can be validated to the correct product phase following industry guidelines, such as those from the International Council for Harmonisation (ICH), for the release of the product to clinic or market, asserts Amanda Curson, head of Analytical Development, Tredegar, PCI Pharma Services. "The method should be well developed at the start with the view of having a long lifecycle without major changes," she says. "Redevelopment later can be time consuming and have an impact on regulatory submissions."

For Jerry Mizell, senior director, Analytical Services, Metrics Contract Services, developing a 'QC ready' method is the most critical aspect in the method

development process. “Having a method QC ready implies that it is very robust, [and the] rigorous challenging of the method will also establish a stability indication to ensure the quality of API or drug product over time,” he comments.

“Throughout development, methodologies are challenged with stressed and design-of-experiment samples to demonstrate performance. Design space creation is also used to determine the range of chromatographic performance and cover multiple formulation compositions for the product,” Mizell continues. “This approach sets a project up for success if there are future changes to the drug product as the developed method will be suitable for use.”

Outsourced offerings and benefits

“Outsourcing method development can give a drug developer access to a more experienced or advanced skill base with minimal delay than it is able to access internally,” highlights Anders Mörtberg, analytical chemist at Recipharm. “As a dedicated specialist in method development, the outsourcing partner can provide dedicated expertise to deliver a much higher quality service than a developer may be able to achieve alone.”

It is fundamental that an outsourcing partner has solid insight into regulatory guidelines and expectations, in addition to being able to provide access to industry-standard separation equipment, Mörtberg notes. “Access to structure elucidation techniques for impurity identification is also advisable in an outsourced partner, as this is often necessary in method development,” he states. “Resources to provide computer-aided method development is desirable, as this can help the partner provide guidance on reducing labor and laboratory costs for method development.”

The three ‘E’s’—equipment, experience, and expertise—are important aspects for consideration when seeking an outsourcing partner for method development services, confirms Leishman. “Equipment should be up-to-date and able to meet dynamic regulatory needs. A wide range of equipment is a plus, since the most suitable instrumentation can be applied, and many methods can be developed at the same time,” she says. “Experience of the company and their scientists is a strong indicator of future success. Ideally, the company has experience with similar analytes and matrixes. Aside from the scientific experience, having regulatory experience with method development and validation minimizes risk.”

Choosing an outsourcing partner with a broad range of expertise, which is somewhat dependent on experience, and scientists on staff who are subject matter experts is advisable, Leishman continues. “Method development sometimes requires a creative approach, [therefore] adequate expertise can ensure that even the most challenging methods are successfully developed in a timely manner,” she emphasizes.

DEVELOPING A METHOD FOR SUCCESS THROUGH PARTNERSHIPS

A desirable outsourcing partner should be able to offer a range of modern, but widely available equipment and should have an experienced technical team with vast method development experience and knowledge, concurs Rebecca Coutts, general manager, Tredegar, PCI Pharma Services. "A company can benefit by working with an outsourced services team that has in-depth knowledge and experience with a range of dosage forms, particularly with dosage forms that can sometimes prove to be more troublesome for method development, such as ointments, creams, suspensions, or very low-dose potent products," she says. "Using an outsourcing lab that has previous experience on method development, validation, and quality assurance specialist support will ensure the client is guided through the process required to ensure the method is ready for use to release clinical product, and for stability testing."

For Mizell, development experience represents the most critical capability of a potential outsourcing partner. "Development chemists are not created overnight as it is a learning process that takes time—and there's no substitute for that," he asserts. "Knowledge is built upon with every successful development project, especially where technical challenges must be overcome."

In terms of instrumentation capabilities, Mizell agrees that an outsourcing partner with multiple means of detections in-house, such as diode array, ultraviolet–visible, charged aerosol detection, and LC–MS, are beneficial. "Environmental chambers are also great to have for stressed studies," he adds.

"Some outsourcing partners can also provide training programs to assist in clients' learning of regulatory requirements, which would be particularly useful to smaller start-up companies," confirms Thibon.

Oftentimes, contract research organizations (CROs) are employed for method development due to the wealth of knowledge they can offer in specific aspects of analytical tests relevant to the drug development and approval process, comments Wheeler. "An established CRO will operate facilities that are purpose built for analytical testing, maintained to a high standard, often utilize the most cutting-edge technologies, and already have validated and compliant in-house procedures," he says.

Single versus multiple provider

Whether a single provider or multiple providers of outsourced services are used is dependent on the project and its specific requirements, specifies Curson. "For example, it may be possible for most of the method development to be carried out by one provider; however, there may be individual specialized analysis required, such as X-Ray powder diffraction, particle size analysis or Franz cell analysis, which is more unique and may require a specialized provider to perform method development for one aspect of the analysis," she explains.

DEVELOPING A METHOD FOR SUCCESS THROUGH PARTNERSHIPS

It is beneficial to choose a main provider of services—one that can perform the majority of the method development and validation and outsource any specialized aspects of the analysis to a partner laboratory when required—adds Curson. "The main provider would have overall responsibility for the project requirements with one or two outsourced specialized aspects undertaken by a lab with more specific specialized technical experience or available equipment required for the individual analysis," she says.

According to Thibon, a clear advantage of using a single provider is the fact that all communication between the client and provider can be streamlined, which can mean that a good relationship can be built. "If using multiple providers, then the key thing is that all providers communicate clearly and on time and are willing to collaborate to achieve the goal," he notes. "Regulations ensure that methods are consistent across providers, but using a single provider for all method development requirements could introduce efficiencies and reduce costs overall."

"Using multiple providers will add complexity and may result in reduced efficiency due to coordination losses," stresses Mörtberg, who highly recommends opting for a single supplier that is capable of providing all required resources for a project, wherever possible.

A single point of contact is undoubtedly advantageous, as it can allow for easier access to the specific project manager at the CRO, timelines are generally clearer and more consistent, and all the information is presented in the same style, concurs Wheeler. "However, there are some risks as well such as the potential for a greater impact on the stages/phases of testing if an issue should arise," he says.

"By using multiple providers, it could be possible for multiple aspects and stages of testing to be performed concurrently if working with strict timelines, but this would generally require more internal coordination on the part of the client in such cases," states Wheeler.

"A different approach is to use one provider to coordinate a multi-site study, therefore coordinating all testing, tracking of timelines, and compilation of results," continues Louise Rigden, technical documentation officer at Wickham Laboratories. "This [approach] means the client still only deals with one point of contact for any information required and results can be reported in a consistent fashion."

If a single provider has all the necessary equipment and expertise, then that approach can be ideal for a client, comments Leishman. There are time and cost efficiencies that

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can be gained through the use of a single provider, such as employing one sample preparation technique for multiple methods or employing a singular outsourcing lab to do an entire stability program, and in some instances, volume discounts for work can be applied, she adds.

"By reducing the number of outsourcing partners, a stronger relationship can be established with the single provider," Leishman says. "However, a niche application or a method that needs a state-of-the-art instrument may benefit from a specialist provider."

Mizell believes that selecting a single contract development and manufacturing organization (CDMO) that can provide all the required development needs provides a multitude of benefits. Not only does it ensure effective communication between the client and provider but can also lead to reduced meeting frequency and eliminates the need to ship API and/or drug product from site to site for different development activities, he asserts.

"When working with a single CDMO that a sponsor has established a working partnership with, they can have greater confidence that the development being performed will meet all project requirements and timelines," Mizell summarizes.

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There May Be Dragons: Mapping 7 New & Emerging Pharma Development Risks

INTRODUCTION

You've made incredible strides in forming a viable pharma or biopharma company with a mission to help transform the lives of patients. But as you move deeper into development, complexity will arise that involves much more than just your molecule.

You have to think about things like technology tranfers, shipping and logistics, not to mention comparator drugs and ancillaries such as needles, glucometers and IV sets. Then there are also increasingly complicated regulatory expectations across countries.

Large pharma companies often have the staff and experience to manage and move drug products and ancillaries within and across borders, but new and emerging companies tend to run lean and be scientifically focused. As a result, you may not have the resources or expertise to coordinate development programs across multiple sites, geographies or vendors.

The Seven Seas of Risk

1. Scale
2. Expertise
3. Supply Chain
4. Management
5. Quality
6. Technology Transfer
7. Liability

On paper, it's easy to draw a streamlined process leading to clinical development success—but with complex modern molecules you're likely to encounter unexpected risks and challenges along the way that may threaten the resilience of your plan.

This eBook is designed to help you map seven key risk areas in drug development and clinical services—and build a plan to overcome them.

1. SCALE RISK

Assumptions you may make:

I should contract with smaller CDMOs more scaled to my size because I'm less likely to get lost in the shuffle.

Potential risk:

Using multiple CDMOs of smaller size is no guarantee of success, especially as program conditions change.

Smaller pharmas may end up choosing one or several smaller CDMOs because these companies sell them on high-touch, personalized service that they may claim large CDMOs can't deliver. However, using multiple CDMOs of smaller scale can reveal several areas of risk.

Your small pharma company may not know what questions to ask, and buy into a smooth marketing pitch from a smaller CDMO that can't back up its claims or scale to meet your needs.

Small-scale CDMOs are often set up to take their contract work from Point A to Point B, and may not anticipate issues or problems beyond what they are executing. And if a smaller CDMO in your network wins a contract with a large pharma, you may become a second-level priority to them as they quickly scale their resources to the new client. Moreover, small pharma companies may not know what questions to ask, and buy into a smooth marketing pitch from a smaller CDMO that can't back up its claims or scale to meet their needs.

Another element some companies may forget is that small, unaddressed problems early in development tend to scale up as the drug product does. This can lead to costly delays, or in rare cases that halt production entirely at Phase III. Smaller CDMOs rarely have the foresight to think this far downstream.

Key questions for planning

- Do the vendors I'm evaluating present risk because of an inability to scale, transactional relationships, or difficulty shifting resources if the scope or focus of my program changes?
- Could the full technical and scientific know-how I need be retained and accessible in a single CDMO, or do I have to assemble and manage it myself?
- Can my CDMO manage the supply chain risks and challenges in the face of a pandemic if my molecule is not directly related to it?

Finally, some small companies favor single-point contracting through contract research organizations for their supply chain activities. Although CROs are valuable for research, they may not be well suited for logistics. You may lose time dealing with issues because the CRO is a go-between rather than an expert in clinical supplies, and may subcontract work further, which multiplies your risk.

2. EXPERTISE RISK

Assumptions you may make:
Specialty CDMOs can give me what I need to get to my next milestone.

Potential risk:
Specialty CDMOs may not have the skill sets to focus on what you'll need for the next several milestones.

Smaller pharma companies may choose CDMO partners for the skills they need today rather than focusing on what they are also likely to need downstream. This can be a risky decision. For example, if the performance of your API in tablet form during trials isn't as good as expected, you'll need the ability to try different approaches, such as spray drying or milling, while still in the drug substance stage. If your CDMO can't offer a broad range of formulation options, you may be putting yourself at risk for delay and additional cost. The same may apply if your CDMO's limitations make it difficult to reformulate your dose for niche audiences such as pediatric patients.

If your CDMO runs up against a challenge on a program with a specific site, they should have enough expertise from another part of their company to help address it. The same holds true for alternate sites if the work has to be transferred. However, if a CDMO you chose for early development is more focused on commercial-phase development, you could quickly see misalignments cropping up between your early-phase goals and the ability of the CDMO to meet them.

Some considerations:

- A commercial-focused CDMO may insist on a tablet for your formulation when a powder would be adequate. You can end up spending a lot more money than you need to.
- Commercial quality standards are likely to be higher than you need for pre-Phase I work while the necessary flexibility for the same kind of work is less likely to be offered.
- Your CDMO should have an understanding of IND Phase I expectations from the FDA or the EMA, and be able to apply the right level of phase-specific qualification. If your CDMO is too commercially focused, they could require many extra steps that might add months to your program.

Broad expertise can help you address considerations before they become problems or delays. For example, have you thought about how your injectable is going to be used in the clinic? Is it a transfusion treatment or is it subcutaneous? If the latter, it will have to be developed as a high-concentration formulation. And will you need

different needle types, which may be in short supply because of a pandemic, for adult and pediatric patients?

As drug repurposing continues to grow in momentum, it's also important to consider working with a broad-capability CDMO now so that repurposing is easier—two, five or even twenty years into the future. Repurposing drugs with a larger CDMO, especially the one that initially developed it, saves time and additional investment.

Key questions for planning

- Does my partner have expertise across multiple development areas to help problem-solve downstream before we get there?
- Will my partner's good intentions be undermined by a lack of breadth across drug substance, product, regulatory, planning or scheduling?

3. SUPPLY CHAIN RISK

Assumptions you may make:

Any CDMO can plug me into a regional or global supply chain based on existing networks.

Potential risk:

Without constant oversight, critical gaps can appear in any supply chain.

Supply chains take on greater importance as global dynamics shift, especially if you need to scale up beyond the original reach of your supply chain; e.g., from Europe to North America or Japan. When you factor in the impact of the COVID-19 pandemic on global supply chains, the risk only intensifies. Not only are countries rethinking their clinical supply sourcing strategies and considering the repatriation of some drugs, but COVID vaccines and therapies are consuming production capacity, raw materials and components. Regardless of scenario, delay is something no one can accept with our just-in-time supply chains. Supply chain disruption can lead to patients not receiving the medicine their lives depend on, longer timelines to meet enrollment targets, or other openings for your competition.

Another question many new and emerging pharma companies don't ask: Does our CDMO have a mechanism in place to transition our supply chain from development to commercial? For example, does it have a safety stock of our drug substance that the drug product sites can pull if something happens downstream, so we don't have any interrupted supply? Working with one supply chain team reduces the risk because they have continuous visibility to the supply chain. It's up to you as the customer to decide what your safety stock level is if you're managing it yourself.

Key questions for planning

- Is my supply chain an integrated chain or just a series of independent parts?
- Can my vendors help me plan for shipping and logistics issues even if I'm just moving into drug product?
- Would it make sense to consolidate drug and ancillary planning so both are at sites for start-up in the right quantities so we can keep moving quickly?

Although all CDMOs may have instances in their history of shipping a product to the wrong place or attaching the wrong label, this risk is amplified with each new vendor you add to your drug development network. This also can happen if you use a CRO to manage your supply chain, which may in turn subcontract services where it has no expertise. If you're aware of this risk, you may find yourself overstocking to mitigate the risk in advance, which can incur unwarranted expenses.

4. MANAGEMENT RISK

Assumptions you may make:

Stringing together multiple best-of-breed CDMOs just requires some dedicated management from our team.

Potential risk:

Small pharma companies are typically unprepared for the substantial amount of time involved in managing multiple contract vendors.

Many large pharmas can afford a staffing model that can support a "string-of-pearls" multi-CDMO program, but new and emerging pharmas who try to follow the same path or manage the process themselves may be opening themselves up to significant risk. As many new pharmas have discovered, even something as seemingly simple as obtaining placebo doses is far more complicated and time-consuming than placing an order on a website and waiting for your materials to arrive.

Small pharma companies are typically unprepared for the amount of time involved in managing multiple contract vendors. Weekly or even daily meetings with each vendor mean that you are managing direct communications as well as back-and-forth communications between vendors. This can quickly become overwhelming. If your drug substance and drug product or drug product and packaging teams aren't communicating because they're in separate companies, you may miss vital information that can impact your downstream success. Multiply this by number of vendors and it expands quickly.

For example, imagine that you hit a development lag in your program. If you are managing your CDMOs yourself, you will be accountable for the fees and suffer the schedule consequences for moving out a deadline such as a batch slot. With an integrated CDMO, the onus is on them to make these scheduling changes.

It's also helpful in mitigating risk to be able to connect analytics and development teams, and to allow drug substance teams who have developed your formulation to transmit this knowledge downstream to the drug product

Key questions for planning

- Can I generate clear line of sight across drug development phases if I'm managing multiple vendors?
- Will the CDMO choices I'm making add value to our asset in the event of a sale, or decrease that value?
- Would a potential acquisition partner be impressed enough with our CDMO to keep the work with them versus transferring it out?

site. This is especially important if something in your formulation triggers a question; e.g., sterile formulation related to lyophilization, or what your drug substance team looked at when they did their matrix of formulations. With separate vendors for each, this rarely happens efficiently.

5. QUALITY RISK

Assumptions you may make:

CDMOs are more or less the same, and most will deliver the quality I need to get us to clinical trials.

Potential risk:

There is often a wide gap between claims made by smaller CDMOs and what they can actually deliver.

For example, does your partner know what's needed for your NDA? Can they do the right amount of work to support a proper submission? Do they have a good history with the FDA and EMA? If not, you risk having to "switch horses" later in the race to NDA.

All CDMOs claim to perform their work with impeccable, cGMP quality, but not all share the same reputation for credibility and detail orientation.

If your CDMO does possess regulatory expertise across its sites, it may have pre-constructed schedules around cost and time expectations to file for an IND, a BLA or an NDA. Integrated regulatory teams can collaborate between sites to execute this work by helping to draft Module 3 aspects of the FDA's Common Technical Document (CTD), which concerns manufacturing process and control information. This can save you time and money.

And let's face it: if your data package for submission isn't robust, it will require rework and hence cost increases that you'll end up owning. Can your CDMO provide the details of how they handle this process?

A counterfeit comparator or ancillary that does not meet local country requirements can be the show stopper to site initiation, or even worse, disrupt patient dosing in an active trial.

Key questions for planning

- Do the CDMOs I'm considering have commercial vendor approval for any medicines, as well as proof of regulatory expertise?
- If there's a quality problem that stops my trial midstream, how will this vendor respond?

6. TECHNOLOGY TRANSFER RISK

Assumptions you may make:

Tech transfer is table stakes. That should be every CDMO's specialty.

Potential risk:

Overlooking the subtleties of tech transfer can cripple your schedule or sap the value of your molecule.

In a tech transfer, an integrated CDMO can qualify assays from drug substance to drug product ahead of time, thereby enabling a fast transition to manufacturing on the drug

product side. With two separate (and likely competing) CDMOs, the risks and costs are higher because the analytical teams are unlikely to be communicating. Assay information required for transfer would go to the pharma company, which would then have to transfer that information on to the other CDMO. Transferring or re-creating and re-qualifying methods is another risk you will have to bear.

Some new and emerging pharma companies don't realize that simply transferring files is not the real technology transfer. The bench-level touch, feel and know-how of the transfer are often lost when multiple CDMOs are involved.

As you move into Phase II and Phase III trials, drug product assays will still need to be transferred to the next vendors in your network, because the FDA places more responsibility on the drug product site to release their own material. Some new and emerging pharma companies don't realize that simply transferring files is not the real technology transfer. The bench-level touch, feel and know-how of the transfer are often lost when multiple CDMOs are involved.

Aligning on equipment being used at drug substance versus drug product sites is critical as well. You face a much lower risk if there is a direct flow of assays, instrumentation and institutional knowledge across sites. Mismatches in timing from sites based on disconnects in how schedules will work together are more common than you may think. Even if the schedule milestones are six months away, it's essential to ensure that all parties are aligned. With multiple vendors this level of coordination rarely happens. Risk mitigation ahead of time is a powerful antidote to future problems.

Key questions for planning

- What can go wrong in a tech transfer, and are we prepared for that risk?

7. LIABILITY RISK

Assumptions you may make:

Contracting out to several CDMOs spreads my liability rather than focusing it all on me.

Potential risk:

Every contact point between vendors is a potential liability exposure.

If you think about it, each point where a transfer happens between vendors is a potential financial liability exposure. And with many vendors defining their services at a high level, there could be more handoff gaps than you expect, especially around logistics. For example, if an investigational medical product (IMP) is manufactured by one CDMO and packaged by another, but that IMP drug is unpacked and manipulated without proper tracing, your company may be left to manage the liability fallout between the two CDMOs.

Moreover, the vendors you contract to may be competitors of each other, and rarely engage in end-to-end collaborative problem-solving on your behalf. They may be more focused on winning additional pieces of the

business away from other vendors, and may not act in your best interests, making it very difficult to determine accountability and assess liability.

If you are managing a separate drug substance partner, the liability is yours as soon as the drug substance shipment arrives at the loading dock at its destination. An integrated CDMO is in a better position to help you manage liability if anything goes amiss in the supply chain between drug substance and drug product sites. The same is true if you have separate drug product and packaging vendors. With a single integrated CDMO to help you manage potential risk, clinical supply teams can focus on their jobs rather than chain of custody, integrity and control issues.

And a truly integrated CDMO can start problem-solving much earlier on in the process, in some cases even before the problem ever occurs. For example, an end-to-end CDMO can identify potential stockout months before it occurs in the clinic. Communication back to the drug product sites can activate batches to address this issue and avoid it altogether because they are integrated with production.

A final consideration: many small CDMOs may not have the bankroll or financial strength to pay out for lost or damaged drugs, which can quickly mount to seven figures or more.

If you are managing a separate drug substance partner, the liability is yours as soon as the drug substance shipment arrives at the loading dock at its destination.

Key questions for planning

- Am I prepared for the consequences if details fall through the cracks between smaller CDMOs?
- Do we have the financial strength to pay out for lost or damaged materials if our vendors can't?

CONCLUSION

As a new or emerging pharma, every minute counts—but so does every employee's time and expertise. When dealing with multiple small CDMOs, even seasoned project managers can become frazzled by the oceans of detail they are required to manage and the questions they're expected to know to ask. To slay—or better yet, avoid—the "dragons" of risk, your company will be better served by working with a CDMO that has the scale, expertise and scope of services that free your time to focus on the business of discovery and transforming patient lives.

ABOUT US

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ThermoFisher SCIENTIFIC

Balancing Internal Focus Against External Capabilities

By Chris Spivey

Demand for outsourced services of technical R&D activities is increasing

In pharmaceutical science several divergent paths typically exhibit clear validity. Decisions often boil down to embracing instead of eschewing risk, to accelerate as the only priority, or to trust a partner rather than emphasize self-reliance. Each molecule, each company or research group possessing that molecule, has an assortment of strengths and weakness to guard against or to leverage. Multiple factors weigh in the balance when deciding how best to move forward, and increasingly the route chosen is to outsource research, development, and manufacturing.

The global contract development and manufacturing organization (CDMO) industry, averaging across several market research firm estimates, is currently valued around $100 billion (1). In part, this growth is shaped through direct regulatory influences suggesting, if not demanding, that a drug have multiple sites of manufacture to spread the risk for supply chain planning. Above regulations, companies also seek to reduce the complexity of their operations internally, and to reallocate internal resources most effectively.

BALANCING INTERNAL FOCUS AGAINST EXTERNAL CAPABILITIES

Rising demands

According to Hanns-Christian Mahler, CEO and board member of ten23 health—a new CDMO that offers development, manufacturing, and testing services for injectables—there are a variety of reasons as to why demand for outsourced services of technical R&D activities is increasing. "[Reasons] include a potential lack of internal asset(s) for a given technology and/or specific requirement," he says. "For example, the building and operating costs of a sterile fill/finish facility are significant. If a pharma company would not have sufficient molecules in a portfolio that would benefit from being manufactured in that facility, the costs could be quite prohibitive, and outsourcing is surely much more cost efficient."

There could also be instances where a pharma or biotech company has an asset but does not necessarily have the required technology or features, Mahler continues. For smaller companies, in particular, he adds, there may not be internal knowledge or industry and scientific expertise available. "Hence, specialized providers, such as ten23 health, may provide significant advantages for [such companies], contributing to faster development timelines whilst minimizing and derisking any R&D obstacles that can be anticipated by the Experts," Mahler states. "Finally, even in existence of internal assets and internal experts, there may be insufficient capacity in house."

Focusing somewhat on internal capacities and the fact that the outside economic environment is encouraging. Ramesh Subramanian, chief commercial officer, Aragen, believes it is a buoyant time for R&D outsourcing at the moment. He specifies that this buoyancy can be attributed primarily to three reasons, "increased fund flowing into [the R&D outsourcing] space, a high number of targets in the pipeline, and renewed interest in pharma R&D due to the COVID-19 pandemic."

"In fact, as a direct consequence of this better funding environment, we are seeing increasing number of biotechs pursuing their research programs with renewed vigour," Subramanian adds. "In the past, those companies that were quite conservative in advancing their discovery programs are now focusing on advancing their assets quickly through the development continuum to reach the proof-of-concept milestone. With this shift, we see more biotechs approaching us for more end-to-end integrated solution offerings, from discovery through to Phase IIb—where their assets get them better valuations. Venture capitalists are also open to a longer-term view on development and willing to take risks for such potential upsides from valuation of successful programs. For Big Pharma, outsourcing of all but core activity is the de rigour approach to achieve fastest development timelines."

Sy Pretorius, MD, president, Clinical Development, and chief medical officer at Parexel, points to the need to focus on and build a lasting relationship when partnering. "To meet complex industry challenges, successful outsourcing partnerships are essential," he asserts. "This is necessitated by

increasing pressures to reduce the cost of drug development and to bring therapies to market sooner. Rather than purely transactional in nature, these partnerships should be truly collaborative. Strong relationships can foster innovation beyond contractual obligations and typically leads to higher levels of staff engagement and better quality. The reason for continued demand for outsourced services can be attributed to a variety of factors including a burgeoning drug pipeline, record levels of funding, lack of in-house resources or expertise, and increased operational complexities."

Many different shades

"Outsourcing happens in many different shades," notes Mahler. "Outsourcing can include full technical programs including drug substance and drug product, it can include only specific studies. It could be only for early-stages of a program or the opposite, just for the commercialization stage. In the end, the outsourcing model needs to fit to the needs of the pharma and biotech company, their own expertise and knowledge base and their preference on either working with the most qualified outsourcing partners for specific studies, versus the preference on working with just one partner."

Subramanian reflects that the focus of Big Pharma has now shifted to ensure they can retain their core activities in-house. "[Big Pharma's] definition of core has become a lot smaller as they look to CDMOs to be their R&D engines. We are seeing these emerging trends in R&D outsourcing," he says. "Pharma/biotechs are looking for more integrated discovery service offerings to leverage on the efficiencies and synergies of chemistry and biology offerings from one service provider/co-location of these capabilities. In the outsourcing of development services, pharma/biotech companies still prefer to have the final drug substance being manufactured closer to their locations in the United States/ European Union. Given the greater demand for access to capacities, a large number of these biotechs leverage the capacities/ expertise available in Asia to execute the initial steps and the final steps in US/EU."

The range of relationships is large, encompassing full-service outsourcing (FSO) to functional provider (FSP) type arrangements, Pretorius states. "Likewise, these [relationships] range from tactical/ per study outsourcing to more strategic programmatic outsourcing," he notes. "Landing on the right outsourcing model requires an assessment of each individual organization's needs. Functional service provision continues to be a core outsourcing model allowing the vendor to provide embedded teams that support sponsors for specific services and work directly with their client's systems and infrastructure. In other instances, a hybrid, more limited scope might work best".

Decisions often boil down to embracing instead of eschewing risk...

Contract, Development, Action! Analyzing Recent Events in Outsourcing

The actions taken by contract development and manufacturing organizations (CDMOs) and contract research organizations (CROs), large or small, provide insight into the greater state of the biopharmaceutical industry. Recent news surrounding CDMOs prioritizing mRNA services and full-service integration may provide one such inisght.

Full-service integration

Piramal Pharma Limited (PPL) increased its stake in Yapan Bio, an India-based biologics manufacturer, with an investment of approximately $13.7 million, which was announceed in December of 2021. Yapan Bio works with various complex biologics, including current good manufacturing practice (CGMP)-compliant manufacturing of vaccines and biotherapeutics. This includes high-containment classes up to biosafety level-2, recombinant vaccines, both RNA and DNA vaccines, gene therapies, monoclonal antibodies, and therapeutic proteins.

According to a company press release, PPL made this move in an effort to augment their antibody-drug conjugation capabilities. Peter DeYoung, CEO of Pharma Solutions at PPL, noted in the press release that biologics (and their accompanying development services) are the fastest growing segments of the CDMO business. Integrating biologics into their offerings allows CDMOs to provide a full suite of services, including development, manufacturing, conjugation, and fill/finish (1).

This news touches on a key trend among CDMOs: the desire to provide an all-encompassing service. For instance, in June of 2021, three companies—Protagen Protein Services, BioAnalytix, and GeneWerk—agreed to a merger. In January of 2022, the newly formed company, ProtoGene, announced that they would supply "advanced, integrated, and complete protein and gene analytic services for biological therapeutics and cell and gene therapy platforms" (2).

Other CDMOS, such as the recently formed ten23 health, have also allocated resources toward providing an integrated offering (3). Still other CDMOs that have existing end-to-end service capabilities, such as Curia (4) and WuXi Biologics (5), are making it a point to highlight the end-to-end service aspect of their business structure. Industry demands are putting pressure on CDMOs for more comprehensive services.

The increase in demand can be attributed to various factors, such as the COVID-19 pandemic, which caused severe supply chain disruptions. These disruptions highlighted the idea that working with a full-service company for pharmaceutical needs may be more prudent. But independent of "why", the "what" of this trend may be showing how successful CDMOs will need to operate in the future.

The shift toward mRNA

Merck KGaA announced in January that they would spend $780 million to acquire Exelead, an Indianapolis-based CDMO specializing in complex injectable formulations. These include both lipid nanoparticle (LNP)-based drug delivery technology, as well as fill/finish capabilities.

According to Belén Garijo, CEO of Merck KGaA, Exelead was purchased because of the company's complementary abilities as it concerns messenger RNA (mRNA) delivery services. mRNA therapies have received a well-documented boom in interest following the release of mRNA-based vaccines for the SARS-CoV-2 virus. In a press release detailing the acquisition, Garijo stated that Merck felt that the acquisition would allow the company to pounce on this fast-growing market for mRNA therapies (6).

Merck's $780 million move may foreshadow an increased prominence on mRNA in the industry. In addition to Merck's acquisition, industry powerhouses such as Lonza (7) and Samsung Biologics (8) have both ramped up their presence in mRNA over the course of the past year, suggesting a strong trend toward mRNA. CDMOs are being rewarded for putting significant sums of money into mRNA, an indication that mRNA delivery mechanisms will likely continue to grow in prominence in the biopharmaceutical space.

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—Grant Playter

COVID-19 impact

Pretorius observes that the pandemic forced industry to reexamine how research studies are designed and conducted, while also demanding record-breaking speed of innovation. "As a result, digital medicine was embraced in ways never seen previously. Decentralized clinical trials (DCTs) became embedded in the overall clinical development ecosystem and part of the new norm in how we operate," he emphasizes. "At Parexel, DCTs are now being woven into 80% of Phase II/III trials and 100% of real-world evidence new trial proposals include DCT elements."

However, Pretorius cautions this movement is not without obstacle. "A challenge is the lack of industry-wide data standards and how best to manage more and more data from disparate and diverse sources across multiple platforms while ensuring quality," he says.

Mahler adds that downstream manufacturing and the supply chain were affected by the pandemic. "The significant demand in vaccine manufacture also led to significant demand in primary packaging and disposables," he stresses. "This has an impact on the globally available outsourcing capacity for any kind of (sterile) product development and manufacturing, which certainly has become smaller given the capacity need for vaccine manufacturing, and the shortage in supplies of raw materials poses some specific challenges and risks for supply chain planning and inventory."

When contemplating the pandemic, Subramanian specifies that, on a global scale there has been an obvious impact on resources, with CDMOs required to prioritize COVID-19 targets and vaccines—an aspect that will continue onto the future as new variants of the virus continue to develop. "Geo-diversity has also been on the rise, and if innovators are too reliant on China, Europe, or India, they will look to rebalancing their spread. However, the net result is that India has been the biggest beneficiary—as there was more reliance on China previously," he says.

"The other interesting impact of COVID-19 has been the development further down the chain from the messenger RNA (mRNA) vaccines," Subramanian continues. "So, there is much greater interest now in areas like oligonucleotide discovery and development, and even peptides—areas that Aragen is investing in due to increasing demand. In terms of mRNA vaccines, we are also seeing innovators look for smaller aspects of its production from lipids to linkers—basically they look for anything that can increase speed and deliver customer value."

Beyond the pandemic

Looking beyond the pandemic, Subramanian expects that industry will see a continuation in oncology as a leading therapeutic area of interest, although he adds that there

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has also been a rapid uptick in demand for central nervous system (CNS) targets. "Almost all Big Pharma is involved in oncology, so on the development side, we see a similar make up in CDMOs and of course in technologies like HP," he says. "CNS is interesting, as there have been several high-profile failures. So, innovators are looking for partners to advance several candidates simultaneously to increase their chances of success."

For Mahler, other potential trends that will likely impact outsourcing of R&D services are the diverse therapeutic modalities and APIs being investigated. "For example, in the category of therapeutic proteins, we see increasingly complex formats," he says. "We also see a huge variety of indications and administration routes, including the challenging intravitreal and subcutaneously administered products."

Additionally, the trend for self-administration is broadening out to areas such as oncology, where devices are typically required (i.e., an increasing trend towards drug/device combination products), Mahler notes. "Of course, these [trends] bring specific challenges related to the product design, manufacture, and testing," he adds.

Pretorius returns focus to DCTs. "Given the rapid speed of adoption and the evolving vendor and regulatory landscape, [contract research organizations] CROs are particularly well-placed to deploy DCT strategies because of the breadth of experience obtained across multiple sponsors," he empathizes. "Some CROs have been active in the space for more than a decade enabling them to leverage significant learnings and expertise."

Looking toward another burgeoning area, cell and gene therapy, Pretorius lauds the availability of new technologies, which are allowing industry to see the potential of such innovative therapies. "For patients, [cell and gene therapy] provides promising options with potentially less toxicity," he says. "We are seeing significant interest and investment in this area beyond treatment for oncology."

Parting thoughts

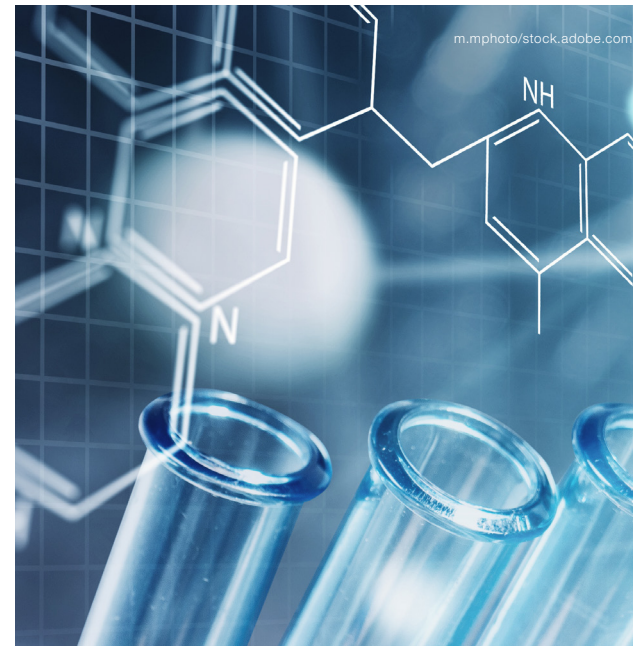
As parting thoughts, Mahler expresses his belief that "outsourcing and the development and commercialization of medicines in general should be more a 'system thinking' approach. Companies or outsourcing services may be getting so specific about one given part of the product, that the interconnectivity and dependency of all the components of a drug product are being forgotten: a sterile product can only be reliably and reproducibly manufactured if the formulation, primary packaging, and processing parameters are wisely chosen in its entity."

Furthermore, Mahler stresses the importance of focusing on 'people'—patients and employees—as well as the planet. "We, at ten23 health, hence embed considerations of fairness and sustainability in all we do. There is only one Planet," he adds.

BALANCING INTERNAL FOCUS AGAINST EXTERNAL CAPABILITIES

Pretorius also points to the larger operating system, observing that outsourcing can also prove beneficial in the area of regulatory operations through aiding with submissions, product registration, tracking agency interactions, and so on. "This [service] requires working in tandem with partner internal regulatory teams and carefully defining roles and responsibilities to assure alignment," he says. "At Parexel, our regulatory outsourcing teams consist of former regulators from FDA, European Medicines Agency, National Medical Products Administration, among others with specialized knowledge and first-hand experiences of regulatory expectations."

While there is much to weigh and evaluate, the uptick in outsourcing appears well founded on benefits and advantages. This has led to what might be termed a 'run' on available scheduled slots within CMOs and CDMOs. Currently, not only must one place a large cash down payment but also the requesting company must now face wait times of around 12 months to get their place in the que. However, in this case good things take time, and time taken pays dividends at the (pun intended) finish line.

Reference

1. PWC, *Current Trends and Strategic Options in the Pharma CDMO Market*, PriceWatershoueCoopers, November 2019.