ThermoFisher SCIENTIFIC

THERE MAY BE DRAGONS

MAPPING 7 NEW & EMERGING PHARMA DEVELOPMENT RISKS

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

patheon

This eBook about unexpected challenges in development for new and emerging pharma companies employs a visual theme of antique maps. Before the Age of Enlightenment (1685-1815), mapmakers such as Giuseppe Rosaccio and Abraham Ortelius filled their maps with richly imagined details including the strange sea monsters and serpents many assumed still lurked in uncharted waters. In 1503 a globe included the words Hic Sunt Dracones, or Here Are Dragons. Since then, variations of the phrase have been used to refer to unpleasant surprises that upend the best-laid plans. In pharmaceutical development, risks are all around but can be mitigated with good planning and experienced partners.

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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.

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.

The Seven Seas of Risk

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

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.

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.

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?

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:

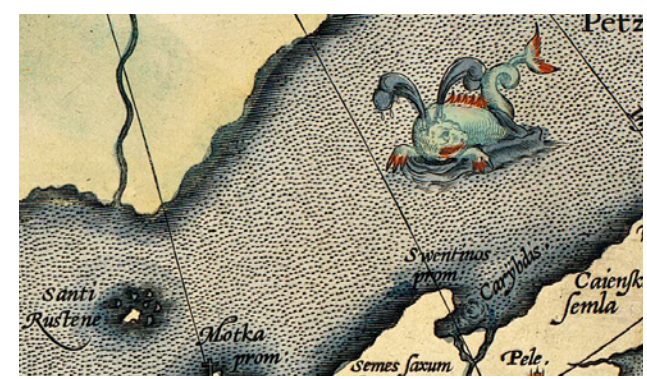
- A commercial-focused CDMO may insist on a tablet for your formulation when a powder would be adequate. You can end up spending a lot more money than you need to.
- Commercial quality standards are likely to be higher than you need for pre-Phase I work while the necessary flexibility for the same kind 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.

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.

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?

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 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.

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?

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

With unwavering commitment to service, science and process engineering, Thermo Fisher Scientific is powered by people with an exceptional commitment to quality, deeply instilled ethics of personal responsibility and unrivaled expertise.

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 55 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.

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Published 03/21

ThermoFisher SCIENTIFIC