Product Quality in the Balance

Managing Risk for Long-Term Success in Outsourced Operations

Cheryl Scott

Commercializing biopharmaceutical products requires navigating an increasingly complex and interconnected ecosystem in which strategic manufacturing decisions can determine market success or failure. Outsourced development and manufacturing increasingly dominates that landscape, where adoption of single-use systems (SUS) and evolving quality paradigms have transformed how companies approach scale-up and commercial readiness. The COVID-19 pandemic exposed critical vulnerabilities in supply chains and regulatory frameworks that many organizations had overlooked before. Today's biomanufacturers must balance cost efficiency with operational resilience, rethink old quality systems, and develop sophisticated risk-management strategies. Success will come from moving beyond traditional zero-risk mentalities toward pragmatic approaches that prioritize patient safety while maintaining the agility needed in competitive global markets.

This spring, I spoke with two industry experts about how those trends are affecting biopharmaceutical companies as they seek to commercialize their products. Lisa Cozza and Scott Myers are principals with Tunnell Consulting, which specializes in advising such companies through decisions related to product quality, regulatory compliance, early clinical studies, technical problems in manufacturing, and contract relationships.

Collaboration and communication are key to outsourcing success. (HTTPS://WWW.WUXIBIOLOGICS.COM)

Making Strategic Decisions

The line from early development to commercial manufacturing is rarely a straight one. Many companies end up changing contract development and manufacturing organizations (CDMOs) and/or switch manufacturing platforms during scale-up. A change "is not a given, but it happens," Cozza explained. "Maybe a third [of developers] will switch over. The CDMO they choose to get to first-in-patient might be a small, inexpensive CDMO, and it can't do phase 3 and commercial development. Companies should go into [outsourcing] knowing they will have to change sites."

"I've seen a number of clients manufacturing at one site or one company then having trouble trying to manufacture at a second one," Myers remarked. And he said that cell/gene therapies (CGTs) present particular scaling challenges that differ significantly from traditional biologics, especially when working with adherent-dependent cells. "If they need to increase volumes, it might not be an option. There might not be a scale for it."

Market-demand forecasting is an inevitable layer of complexity that companies must include in their manufacturing strategies. And sustainability of supply is a two-way street: for raw materials coming in and final products going out.

Proactive Risk Management: Many biomanufacturers and drug developers tend to delay contingency planning until problems materialize. Despite warnings from experts and partners about potential risks, some companies postpone difficult decisions about backup strategies and alternative approaches until it's too late.

Cozza described a common organizational dynamic. "Functional groups will be more rigid in the name of regulatory rigor, but [that becomes] a form of bureaucracy. One person says, 'It's my job to make sure that the filing is good.' Instead of allowing others to find ways to do that better, faster, and cheaper, they might find ways to make their little empire as complex as possible so that no one else can do it." However, after COVID-19 and the associated material-availability crisis, many organizations have made improvements here.

"That's the outcome of a zero-risk mentality," Myers said. The pharmaceutical industry has always been cautious about innovations that need justification and explanation to regulators. No one wants to be the first to try something, and it's often the large companies with the means to do so that become early adopters.

Cozza agreed that small, early stage companies can panic at the thought of taking such leaps. "The big lesson learned was not to be overly descriptive in filings." Providing extraneous details early in development can lead to unnecessary restrictions on future operations, and early consideration of commercial-scale requirements can prevent costly late-stage changes. And yet, many young companies focus primarily on near-term development milestones.

Quality Responsibilities and Economics: Meanwhile, the outsourcing landscape is undergoing transformation in how both sponsors and manufacturers approach quality assurance and control (QA/QC). Cozza said that CDMOs face a fundamental challenge in balancing comprehensive service offerings with profitability. "They have a very tight margin and need to improve

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continuously to reduce costs and improve profits for all activities they do for their clients," she explained. Although QA/QC testing services can generate "pretty good" returns, the reality is more complex when accounting for the full cost structure. "What is often unaccounted for are errors, rework, out-of-specification results — all those things will happen, and the write-ups, corrective and preventive actions (CAPAs), and audits are costs that have to be absorbed by the CDMO." Becoming aware of such unplanned costs with the burden of maintaining full-time laboratory employees, she said, has prompted some strategic reassessment of the "one-stop–shop" model that dominated outsourcing in the 2000s and 2010s.

Cozza advocated for a nuanced strategy that distinguishes between routine and specialized testing. "If I were designing a CDMO today, I would probably still have everything that you need for in-process controls, to enable completion of a batch in house." That includes basic testing for endotoxins, identity, and so on that are essential for batch completion. However, for more complex characterization and nuanced final release testing, she recommends developing strong relationships with professional contract-testing laboratories. The critical caveat, she emphasized, is establishing robust service-level agreements. "One of the things you lose control of when you outsource is time," Cozza warned, noting that without proper agreements, external laboratories might delay results while clients urgently need them to release a batch to the clinic.

When it comes to outsourcing QA functions themselves, Cozza drew a firm line. Although certain activities (e.g., supplier audits) can be outsourced effectively to consultants or third parties, she insisted that core QA functions should remain internal. "Batch release has to be internal because you're looking at deviations, investigations, and change controls, and those are very site-based. You want to ensure you control the narrative as a CDMO."

Document control presents another practical limitation, she said, citing as examples standard operating procedures (SOPs), technical documents, protocols, and batch records. "The ability to get those has to be at site. You don't want your printer to be miles away." Many companies still use paper-based documentation even today.

From a regulatory standpoint, sponsors remain ultimately accountable for everything. But Cozza said that agencies are increasingly holding contract manufacturers accountable as well. "If they don't have meeting minutes saying, 'We tried to get the client to agree to this work based on our experience, and they didn't want it,' then a CDMO could be held liable."

Rethinking the Quality Mindset: Some other aspects of outsourcing are becoming outdated as well. Cozza described quality

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departments in older companies as operating "like the police force with intimidation tactics to have people do things how QA sees fit" or implementing "endless bureaucratic procedures" with low return on investment. She advocates for a risk-based approach instead, asking clients, "What's your return on doing this? What's the risk? What's the worst that can happen if you don't do it? Can it wait until phase 3?"

She even challenged the fear-driven mentality concerning US Food and Drug Administration (FDA) inspections, arguing that "there's nothing wrong with a 483, as long as the items on it are minor." The FDA form 483 ("Notice of Inspectional Observations") is intended to notify company managers at the conclusion of an inspection about observed conditions that could violate regulations. It communicates specific deficiencies in manufacturing, quality systems, and documentation to encourage immediate corrective actions. Thus, Cozza views form-483 observations as potential business-improvement opportunities. "The agency sees the best of the best and the worst of the worst. If you're working off a 1980s system, they're going to call you out on it. They're going to say, 'You can improve this, right?' And that's not the end of the world; it's a good thing."

A risk-management approach focuses resources on critical issues that could affect product quality while resisting the pursuit of perfection especially in areas that have no patient impact. Her general advice to companies is pragmatic: "Don't go for 100%; go for 85–90% and put the criticality and spend where they belong."

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Human Elements: Some virtual pharmaceutical companies operate with as few as four people. "You have a finance person, a businessperson, a scientist, and a legal person," said Cozza, "and all they do is manage the contract partners who execute the plans." Such a model presents clear challenges, particularly when naive sponsors lack manufacturing or regulatory knowledge and expertise. She described a situation of bench scientists "trying to use manufacturing as a laboratory," making constant mid-process changes, even at late stage. "I tell everybody on the project teams to document, document, document because that is a train-wreck waiting to happen. And the CDMO [staff] needs to demonstrate that they did all they could to persuade the client" to do the right thing.

Relationships between CDMOs and inexperienced clients require careful management, and most large CDMOs can be selective about who they work with. Cozza noted that although some such companies are "in need of business," clients can be "fired" just as much as service providers can.

Throughout our discussion, both Cozza and Myers emphasized

the often-overlooked human factors in outsourced manufacturing. "It's behaviorally driven," she said. "'How am I going to do what you're asking me to do? I have human beings, and they have to take steps, attach hoses, turn valves. . .'" She contrasted that with the data-driven mindset of many scientists working at laboratory scale.

That disconnect becomes particularly apparent in working with SUS at large scale. Simply handling large bags and their associated connections can be unwieldy. Although disposables offer often-touted flexibility, Cozza noted that for producing multiple batches per year at 4000-L scales and above, "it's probably cheaper to use stainless steel. You can't reuse those bags, and they cost millions in passed-through expenses over time."

With or without specific SOPs, major operations can be waylaid by the simplest actions such as unfolding something while taking it out of a box. Many early single-use systems failed due to basic problems such as seals breaking at fold lines when bags were unpacked.

Supply-Chain Vulnerabilities

The shift from traditional multiuse stainless-steel systems toward disposable components represents one of the most significant changes in biologics manufacturing in the 21st century. The enclosed nature of SUS has revolutionized facility design, enabling biomanufacturers to rethink traditional cleanroom requirements and spatial configurations. The advent of fully enclosed systems has enabled revolutionary approaches to facility design and multiproduct operations for CDMOs as well, providing significant benefits in capital efficiency and operational agility. And single-use bioreactors have evolved to accommodate scales up to 4000–5000 L; cost–benefit considerations become increasingly complex at such volumes, however.

"Although disposables dramatically reduce contamination risks and eliminate the need for cleaning validation," Cozza explained, "they do come with a substantial trade-off: bill-of-materials costs that run two to four times higher than those of comparable stainless steel systems." Users must weigh those economic considerations when planning for future commercial operations.

The COVID-19 pandemic served as a stark reminder of the vulnerabilities inherent to modern biopharmaceutical supply chains. Shortages of disposable bags, filters, tubing assemblies, and other critical components created severe bottlenecks that rippled through the industry, forcing companies to confront the risks of the single-source dependencies they had created for themselves.

Reflecting on lessons learned, Cozza notes, "I was on a materials task force during the pandemic, and it was awful. What everyone learned the hard way was that we had put too much detail into our regulatory filings. The ability to maneuver under those difficult situations was daunting and time-consuming. We had to file to the agencies to request the silliest things: 'Can I replace a like-for-like bag if the tubing that's attached to it is six feet instead of two feet long?'"

Such experiences drove a fundamental shift in how companies approach supply-chain resilience. "When you rely on these critical raw materials, then you have to have a second source," Cozza emphasized. "You really do need second-sourcing considerations."

And that introduces its own complexities. Myers pointed out the burden of associated validation efforts. "You have to take batches and test for leachables and extractables. Where are they getting the plastics from? Are those the same globally? If you're purchasing from a major supplier, is the manufacturing and all the componentry the same in Europe or Asia as it is in the United States?"

He provided context on contingency planning from pandemic experience as well, recalling a European CDMO whose bag manufacturer's capacity was constrained. "So it became true project management about when you can get that bag or these bags, maybe not even a whole pallet of bags. 'Can I get just one or two?' Then it was down to distribution. If you had a relationship with your bag manufacturer, then you had to discuss how to distribute things to multiple sites, and so on."

As Cozza advised, companies must consider such potentialities as they strategize toward commercialization. "What you can do in a filing is describe the materials of construction, the purpose, and the general build of something without getting to the level of its specific manufacturer. Or if it's critical that you list the manufacturer, then you definitely should have two."

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A Balancing Act

The biopharmaceutical manufacturing landscape continues to evolve rapidly, driven by technological innovation, market dynamics, and lessons learned from recent challenges. Success in this environment requires a sophisticated understanding of the trade-offs between different manufacturing approaches, proactive risk management, and the flexibility to adapt strategies as products progress through development toward commercialization.

Companies that master such a balance will position themselves to navigate effectively the complex journey from laboratory to commercial manufacturing and distribution, ultimately bringing

life-saving therapies to patients as quickly and reliably as possible. The key lies in learning from past challenges, embracing technological innovation thoughtfully, and maintaining the flexibility to adapt as both science and markets evolve.

Biopharmaceutical outsourcing continues to evolve, driven by economic pressures, regulatory expectations, and the need for operational efficiency. As expert insights reveal, the most successful organizations will be those that strategically balance in-house capabilities with external partnerships, maintain appropriate quality oversight without bureaucratic excess, and never lose sight of the human element in manufacturing operations. The key is finding an equilibrium among expertise, efficiency, and accountability while keeping patient safety at the center of all decision-making.

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