Whitepaper

Are End-To-End CDMO Partnerships The Solution To Drug Development And Manufacturing Upheaval?

Optimizing drug development, manufacturing and supply is critical if pharmaceutical companies are to translate innovation into therapeutic and commercial gains that balance health benefits with affordable access and durable revenue streams. Yet the bar for achieving this kind of synergy, in an unpredictable operating environment, keeps getting higher.

Drug development costs continue to rise as deeper understanding of disease pathogenesis and pathways ramps up treatment specificity and complexity, all against a backdrop of more stringent drug regulation and payer scrutiny of product value. Even the lowest estimate for the average cost of bringing a new drug to market is $1.3 billion.

As a result, industry is forever looking for new ways to boost productivity, quality and efficiency in drug development, production and supply, all the way from bench to bedside. Clinical research as well as manufacturing equipment and facilities, are key pressure points. These challenges are amplified by the biotechnology revolution and associated demand for new technologies, capacity and expertise.

Productivity, quality and efficiency are especially important for small and medium-sized companies with limited resources. They must choose between investing in internal capabilities, partnering with larger players, or outsourcing to a contract development and manufacturing organization (CDMO). These companies also need to be future-focused, taking on board lessons learned from the normalization of digital tools and virtual interactions during the COVID-19 pandemic.

For example, COVID-related restrictions have shown that virtual inspections to monitor drug safety and adherence to good manufacturing practices (GMP) are a feasible alternative to in-person oversight. And supply chain disruptions during the pandemic are shaping new attitudes to sourcing of active pharmaceutical ingredients (APIs) and finished products.

Growing complexity and risks in drug development and supply also have implications for outsourcing models. Companies must consider how best they can structure and manage CDMO partnerships to weather a future in which uncertainty and disruption may become increasingly routine.

Why Cambrex?

Cambrex provides drug substance, drug product and analytical services across the entire lifecycle.

We deliver quality in every aspect of our work, across all of our facilities, systems and teams.

About Cambrex

Cambrex is **the** small molecule company that provides drug substance, drug product and analytical services across the entire drug lifecycle. Enjoy working with our experts to accelerate your small molecule therapeutics into the market.

With 40 years' experience and a growing team of over 2,100 experts servicing our global clients from our sites in North America and Europe, we are tried and trusted in branded and generic markets for API and dosage form development and manufacturing.

Driving Cost Efficiencies

Recent surveys conducted by Informa Pharma Intelligence and Cambrex provide insights into how pharmaceutical companies are addressing these challenges and their impact on strategic planning and day-to-day operations. Given the pressure to get drugs to market more quickly and effectively without overwhelming R&D budgets, cost efficiencies inevitably come into play.

They should not, however, obscure the importance of quality and specialization geared to increasing pharmaceutical market complexity. Nor can companies ignore the need for more considered globalization strategies that reflect the changing priorities in supply chain management highlighted by COVID-19.

As the Informa/Cambrex surveys indicate, companies are taking a variety of approaches to optimize cost efficiencies, with effective project management, partnerships and sustainable processes (in that order) the three strategies most favored across the Americas, EMEA and APAC regions. While outsourcing was cited as a cost-efficiency mechanism by only 20% of respondents, it is nonetheless widely employed across the industry.

For example, two-thirds of organizations reported outsourcing at least some elements of drug development, in particular clinical research (20%), clinical manufacturing (15%), commercial manufacturing (13%) and packaging (13%). Not surprisingly, small biopharma companies were far more dependent on outsourcing than their larger counterparts.

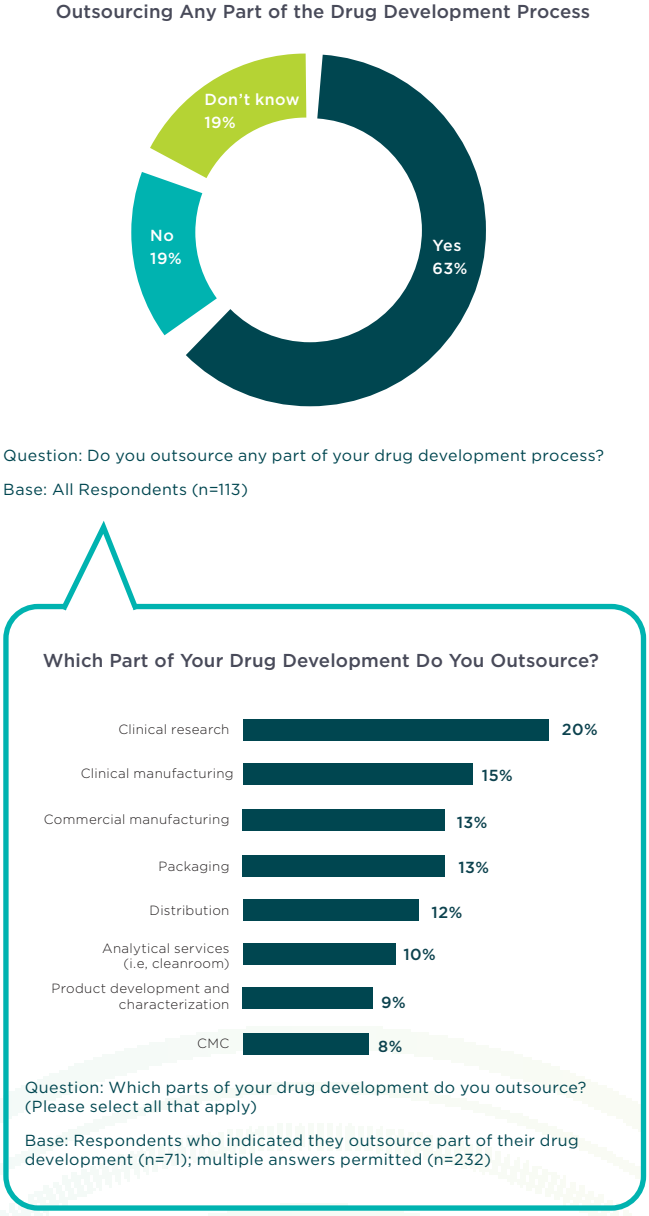
Among small biopharma companies, 57% and a further 14%, respectively, said they were outsourcing more than half or 31-40% of all drug development. Cost efficiency clearly factored into these decisions, with 51% of survey respondents who outsourced at least part of their drug development saying they had made cost savings since outsourcing; only 13% had not.

Survey participants identified the unpredictability of candidate success as the biggest challenge to achieving cost efficiencies in drug development (38%), followed by time delays (25%) and scale-up (21%). These figures again underline how outsourcing decisions must be taken in a setting of high risk, along with increasing complexity and uncertainty.

The indications are that outsourcing will continue as an essential and growing resource that allows companies to focus on core competencies while leveraging the significant capabilities available from specialized external providers. This is especially pertinent to small or medium-sized companies with limited means or leeway to achieve economies of scale.

A majority of survey respondents (46% versus 32%), for example, were investing in their own manufacturing equipment, with 50% of those companies realizing cost savings from their investment. However, only 29% of small biopharma companies were investing in their own manufacturing capabilities, compared with 47% of mid-sized and 83% of large pharma organizations, respectively.

Figure 1: Outsourcing Drug Development Processes



Virtual Inspections Are Here To Stay

One area in which industry stands to make time and cost savings is by virtualizing regulatory inspections to ensure drug safety and GMP adherence. Here, COVID-related disruption has accelerated the adoption of digital technologies that enable inspections to be conducted at a distance.

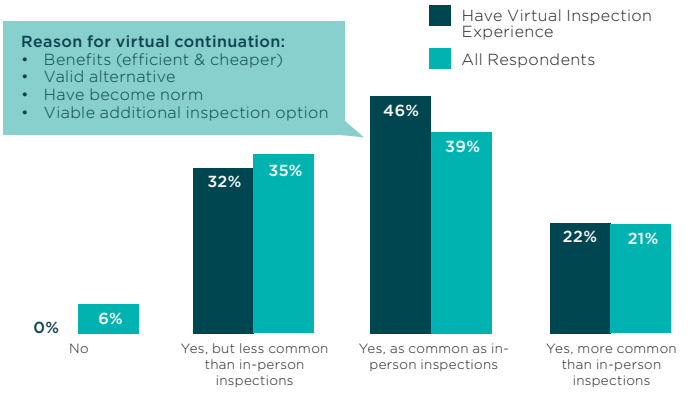
The scale of that change is evident from an Informa/Cambrex survey in which 57% of respondents had never undertaken a virtual inspection before the pandemic hit. Now, both regulators such as the US FDA and industry organizations like the European Federation of

Pharmaceutical Industries and Associations (EFPIA) are voicing support for virtual inspections as an ongoing and welcome trend.

Going virtual is not just about cost efficiency, though, even if 54% of survey participants recognized cheaper travel and accommodation as a key benefit of virtual versus in-person inspections. Virtual inspections can also improve interactions with regulators.

In this respect, 48% of all respondents felt the flexibility of virtual inspections allowed for more frequent engagement with regulatory agencies. And 34% (with 37% of these respondents having virtual inspection experience) cited more time to review and question when communicating virtually. There are also gains for the environment, and for the industry's sustainability commitments, in reduced travel: with 39% in total and 44% of virtual-experienced respondents identifying this as a top-two benefit.

Figure 2: Will virtual inspections still be utilized after the COVID-19 pandemic?



Question: Do you expect virtual inspections to still be utilized after the COVID-19 Pandemic?

Base: All Respondents (n=109)

Furthermore, survey participants were strongly convinced that virtual inspections are here to stay. Not only did 91% feel that COVID-19 had significantly accelerated the digital transformation of regulatory inspections, but 95% of respondents expected virtual inspections to continue post-pandemic. And 60% overall (68% of virtual-experienced respondents) believed they would be at least as common as in-person inspections.

There are some caveats, though. Among the drawbacks of virtual inspections, most cited by survey participants were potential for technical/connectivity issues (52% of all respondents), lack of face-to-face interaction (51% in all, 60% of virtual-experienced respondents) and limits to what can be observed virtually (50% in total, 40% of virtual-experienced respondents).

The varying responses of survey participants with or without virtual inspection experience suggest some of these concerns can be ironed out in practice. They also emphasize how outsourced providers with specialist capabilities in this field need to ensure that their clients are confident that inspections can be handled virtually (and externally) without any loss of focus, quality or efficiency.

As the Informa/Cambrex survey demonstrated, regulatory excellence is a prime consideration in selecting outsourcing partners, with 96% and 65%, respectively, of respondents regarding it as important or very important. For virtual inspections, that also means having access to key technologies such as document sharing and video capabilities.

Among survey respondents, 41% saw document sharing and 34% video capabilities as the most important technological considerations, while 22% cited technical staff who could effectively deploy and maintain these tools. It was also clear these capabilities will have a marked impact on companies' choice of outsourcing partners as technologies enter the mainstream. Specifically, 60% of respondents said the opportunity to conduct virtual site audits would influence their outsourcing partnership decisions either significantly (20%) or slightly (40%).

Supply Chain Resilience

The COVID-19 effect was also felt deeply in the pharmaceutical supply chain, as national lockdowns and border closures threw into question the whole infrastructure of long, highly globalized supply routes that had enabled companies to diversify and cut costs in an era of relatively seamless cross-border trade.

This occurred at a time of unprecedented demand for some products, prompting crackdowns on API and finished product exports in key supply markets such as India and China. The US FDA had already highlighted industry's heavy reliance on APIs sourced overseas as a potential national security risk. Among survey respondents, only 16% said their supply chains had been unaffected by COVID-19 and 19% felt the impact had been substantial.

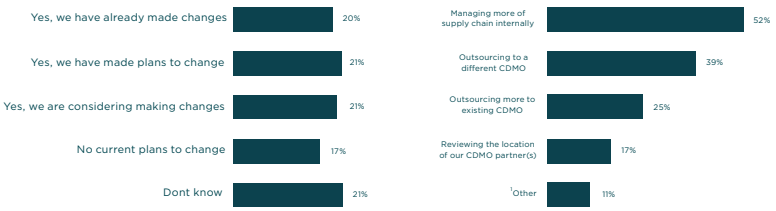
Among the 66% of respondents whose supply chains had been disrupted, 65% cited difficulties maintaining supply, 29% distribution constraints and 19% reductions in on-site workforce, while 19% and 18% respectively faced increased or reduced demand. These experiences have prompted broader reflections on supply chain resilience, even if 71% of respondents still believed their current supply chain was 'quite' (56%) or 'very' (15%) effective.

Among the main concerns about supply chain effectiveness were cost (28%), responsiveness (25%) and shortages of product and/or packaging (21%). Moreover, 20% of respondents reported already having made changes to their supply chain, 21% had made plans for changes, and 21% were considering changes. In some cases, that meant more dual sourcing of key products, with just over one third of organizations considering this as a risk-mitigation strategy against pandemic related disruption.

Nonetheless, tightening up supply chains does not necessarily mean more outsourcing. In fact, 52% of respondents anticipated managing more of their supply chains internally. At the same time, a significant minority of companies were thinking about outsourcing to a different CDMO (39%), outsourcing more to an existing CDMO (25%), or reviewing the location(s) of their CDMO

partner(s) (17%). In other words, the opportunities are there for CDMOs that can offer future-proofed supply chain strategies capable of absorbing any disruptions to come.

Figure 3: Anticipated Pandemic Changes to the Supply Chain



Question: Do you anticipate your supply chain management approach will change as a result of the COVID-19 pandemic?

Base: All respondents (n=117); multiple answers permitted.

Question: What changes do you anticipate? (Select all that apply.)

Base: Respondents considering changes to the supply chain management approach as a result of COVID-19 (n=71); multiple answers permitted.

Other[1] includes Go Fund Me campaigns to support litigation expenses; Have more suppliers (x2); Increase supply; More products in on shipment; Stockpiling; Supply chain solutions

Along with cost efficiencies (49%), survey respondents cited in particular access to infrastructure, machinery and equipment (49%), boosting manufacturing capacity (40%) and early development support (40%) as reasons to outsource in this context. They also valued backwards integration as a means to ensure supply chain consistency and quality, with 49% of respondents viewing this as 'quite important' and 24% as 'very important' when selecting CDMOs.

Respondents also wanted to work with CDMOs at the cutting edge of new technology. Almost all of them expected CDMOs to deploy automation, along with digital and analytics tools, to improve agility and transparency in the supply chain. More than two thirds expected CDMOs to use these resources 'extensively' (45%) or 'very extensively' (22%).

Reshoring Drug Supply

One further consequence of COVID-19 is more attention to localization of CDMO partners and their facilities/resources, reflecting concerns about the fragility of modern, highly globalized supply chains and a shift to reshoring of key components in those chains. Asked about CDMO partner locality, 35%, 21% and 16%, respectively, of respondents preferred a domestic, regional or international partner.

Furthermore, 29% said their preference on locality had altered due to the COVID-19 pandemic, while 44% of respondents had plans to change the locality of their CDMO partner within the next 18 months. In fact, 11% of respondents had already reshored API sourcing distribution logistics and other components of the supply chain. And 79% expected some kind of permanent shift (14% definitely, 44% probably, 21% possibly) post-COVID from global supply chains to more localized, lower-risk chains.

This is a relatively new consideration for both pharmaceutical companies and CDMOs. However, COVID-19 has exposed serious vulnerabilities in the globalized supply of medicines that were already recognized before national lockdowns made them impossible to ignore.

If reshoring of the supply chain is becoming an ethical, pragmatic and competitive imperative for pharmaceutical companies, it does not mean they must sacrifice the productivity and efficiency gains once achieved through aggressive globalization. Instead, companies can build new, digitally enabled supply chains that avoid the inefficiencies of the 'old' local networks they discarded in favor of globalization, while at the same time mitigating the vulnerabilities of globalized networks.

Bolstering supply chain resilience by working with CDMOs that maintain a strong domestic or regional presence in key regions can also help to overcome some of the typical challenges of outsourcing partnerships. For example, 38% of survey respondents saw communication problems as one of the main barriers to successful outsourced manufacturing, with a comparable percentage citing project management. Partnering with CDMOs that operate in similar time zones and with similar business cultures should make these issues far easier to manage.

End-To-End Partnerships

As outsourcing of drug development and manufacturing continues to flourish, the range of services offered by CDMOs has expanded in parallel. Companies must now determine whether their needs are best served through a flexible network of multiple CDMOs, each offering specific expertise; or by committing to end-to-end partnerships with individual providers whose capabilities touch all points in the development and manufacturing cycle.

First, companies should consider what their motivations are for choosing multiple partnerships. When participants surveyed by Informa/Cambrex were asked why they changed partners at different stages of drug development, the main reasons were access to specialist expertise (30%) or to specific equipment/facilities (29%), followed by pre-existing relationships (25%). Lack of specialist expertise in both drug substance and drug product development was also identified by 22% of respondents as the second biggest challenge in partnering with a single CDMO.

This suggests that an end-to-end CDMO – with not just facilities, equipment and technology covering the full spectrum of drug development, but also the consulting expertise to guide strategic decision-making along that pathway – can offer a compelling alternative to multiple partnerships. Nonetheless, in the Informa/Cambrex survey, concerns about breadth of expertise were overshadowed by the perceived risks of dependence on a single provider, with one third of respondents citing this issue.

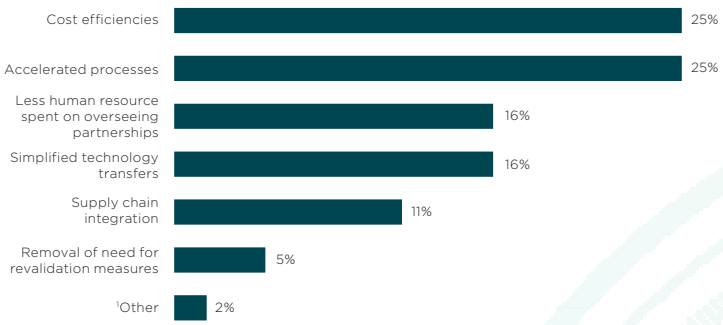
This is not surprising, given the extraordinary circumstances of COVID-19, in which geographical lockdowns and supply chain disruption exposed the potential vulnerabilities of single partnerships. Without the ability to switch CDMOs in affected countries or regions, an end-to-end partnership could have resulted in complete cessation of product supply or development.

There is a flipside to this issue. As noted above, the pandemic also prompted or accelerated a trend towards reshoring of drug manufacturing and development facilities to improve supply chain resilience and oversight. CDMOs offering end-to-end, closer to home services in regions with an increased pharma presence due to reshoring – such as the US or Europe – can plausibly offer more security than broadly distributed partnerships in countries more likely to be hit severely by supply chain disruption.

Another argument for end-to-end partnerships is the prime importance (cited by 67% of survey respondents) of CDMOs communicating effectively with their clients. In a single partnership, a good deal more trust, reliance and risk are invested in one CDMO to manage drug development and/or manufacturing from start to finish. A truly competitive CDMO is therefore likely to make sure that its client is always in the loop.

All the same, the main benefits seen by survey participants in end-to-end partnerships all had to do with efficiency. Namely, 25% apiece of respondents referred to accelerated processes and cost efficiencies, 16% to reduced resources needed to oversee single partnerships, 16% to simplified technology transfers, and 11% to supply chain integration.

Figure 4: CDMO End-to-End Partnership Benefits



Question: What are the main benefits of partnering with one CDMO for end-to-end drug development? (Select up to three.)

Base: All respondents; three answers permitted (n=308).

[1]Other includes: Do not know, Product history, Established relationship, Rely on expertise & We don't have the capacity.

The question then is whether these benefits are outweighed by costs. On the surface, an end-to-end partnership may seem to require more financial outlay than opting for the most competitively priced options at each stage of drug development/manufacturing. Yet efficiency, quality or even cost-effectiveness benefits may emerge further down the line, in the shape of faster market access.

Switch Delays

Switching from one CDMO partner to another at different stages of drug development/manufacturing can result in significant delays, particularly if it involves complex technology transfers. Of course, these transfers also occur when a drug moves from one team to another within a single CDMO. But shared systems and more fluid communications within a single provider should make the whole process more seamless, intuitive and quicker to resolve.

Human resource savings, which came joint second with simplified technology among the perceived benefits of end-to-end partnerships, also have broader implications for efficiency and value. They enable companies to redirect human resource spending to business growth activity and pipeline assets, with potential to deliver financial rewards over the longer run.

For all that, pharmaceutical companies remain somewhat conservative about embracing end-to-end CDMO partnerships. In the survey, 65% still favored the established strategy of working with different partners at different stages of drug development, although 45% were open to switching to an end-to-end arrangement with a single CDMO. Moreover, 58% of those respondents had plans to switch within the next 18 months.

One other key issue in assessing the respective benefits of single versus multiple CDMO partnerships is timing. These partnerships are most effective when formed early in the drug development or manufacturing process. If partnerships are established at a later stage, the CDMO needs to familiarize itself with the product history and potentially engage in complex technology transfers without prior experience in that context.

Survey responses reflected these considerations, with 62% preferring to approach partners in the early development stage. Moreover, these early stages were seen as benefiting most from CDMO support: 33% apiece of respondents cited product development/characterization and clinical manufacturing, while 22% felt commercial manufacturing was where CDMO input was most valuable.

End-to-end providers should therefore be talking to potential clients as early as possible in the development and manufacturing process. They should stress that establishing a relationship at the beginning of that lifecycle enables CDMOs to transition more seamlessly from one stage or function to another, building up applicable expertise, knowledge and value on the way.

Call To Action

In a turbulent environment for drug development and manufacturing, innovation, quality and specialization are key to maintaining the momentum of outsourcing as a lever for efficiency and a gateway to new capacity and expertise. These attributes are all the more valuable when applied across the broad range of activities and geographies involved in bringing medicines from the laboratory to the pharmacy shelf. At the same time though, CDMOs must recognize growing demand for the

stability and accessibility of shorter, more locally oriented pharmaceutical supply chains.

As pharmaceutical companies re-evaluate their relationship to globalization, risk and external partners, they need to understand the benefits inherent in end-to-end CDMO partnerships that offer specialist expertise along the spectrum of drug development and manufacturing, combined with localized facilities and capabilities that can ease concerns about supply chain resilience. For their part, CDMOs offering end-to-end services must convince potential clients that these relationships are not just about cost, but long-term value and risk mitigation.

That reflects increasing pressure to realize efficiencies in drug development and manufacturing, to embrace digital as a sustainable way forward, and to offset supply chain vulnerabilities. Ultimately, the whole pharmaceutical value chain, from businesses to health systems to payers to patients, will benefit from more considered outsourcing strategies fit for a market in rapid and continuous evolution.