CPHI Online

The Nexus Between Patient and Big Pharma

Patient-Centricity Considerations for CDMO and CRO Collaborations in Novel Drug Development

In Partnership with ThermoFisher SCIENTIFIC

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As outsourcing partners for pharma and biotechs alike, CDMOs and CROs are in a unique position to service both the clients who depend on their skills and expertise, and the patients at the end of the drug development and manufacturing pipeline.

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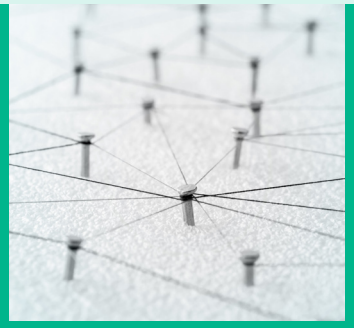
Partnerships Between CDMOs and CROs: Harnessing Synergies for the Patient

The line between a CDMO and CRO is becoming increasingly blurred as outsourcing service providers incorporate more and more capabilities into their service offerings. Additionally, CDMO and CRO collaborations are proving to be more than just a trend – the benefits of these partnerships can, if done with the right focus, only serve to benefit patients in the end.



06

Mergers and Acquisitions

Collaborations between CDMOs and CROs are not stopping at partnership agreements – the outsourcing sector has seen a number of M&A agreements in the last decade, with these investments only set to increase in the coming years, most experts predict.

Key Findings

1 Optimising efficiency in the supply chain benefits all

As a highly intricate network, the pharmaceutical supply chain is vulnerable to operational disruption, as we have seen during the COVID-19 pandemic and the War in Ukraine, which have both impacted patients' access to essential medicines. It comes as no surprise therefore that ensuring supply chain resilience is now an increasing focus for pharma companies who are looking at new ways to connect the drug development, manufacturing, and commercial pipelines. Increasing operational efficiencies across the supply chain is a key factor in mitigating reduced access to treatments for patients, clinical trial participants, and healthcare providers [i].

2 Mergers and acquisitions leading collaborations

Collaborations between contract development and manufacturing organisations (CDMOs) and contract research organisations (CROs) have shifted toward a model of dynamic mergers and acquisitions, with a drive to consolidate manufacturing capabilities for novel drug modalities, innovative vaccines in response to infectious diseases, and additional capabilities for viral vectors, cell manipulation, and nucleic acids and lipid-based formulations [ii]. With 244 publicly announced M&A agreements involving CDMOs between 2017 and 2021, integrated CDMO models have dominated the CDMO landscape in recent years [ii].

Key Findings

3 Dosage for rare diseases: meeting patients where they are

Advanced therapy medicinal products (ATMPs) offer groundbreaking modalities for the treatment of rare diseases, but their manufacturing and commercial scaling can be a challenge for pharma companies and manufacturers lacking the necessary expertise. Rare diseases have led the way for many CDMO/CRO M&As, with 43% of pharmaceutical mergers and acquisitions in 2022 comprising rare-disease-led venture funding – oncology itself comprised 16% of rare-disease deals [iii].

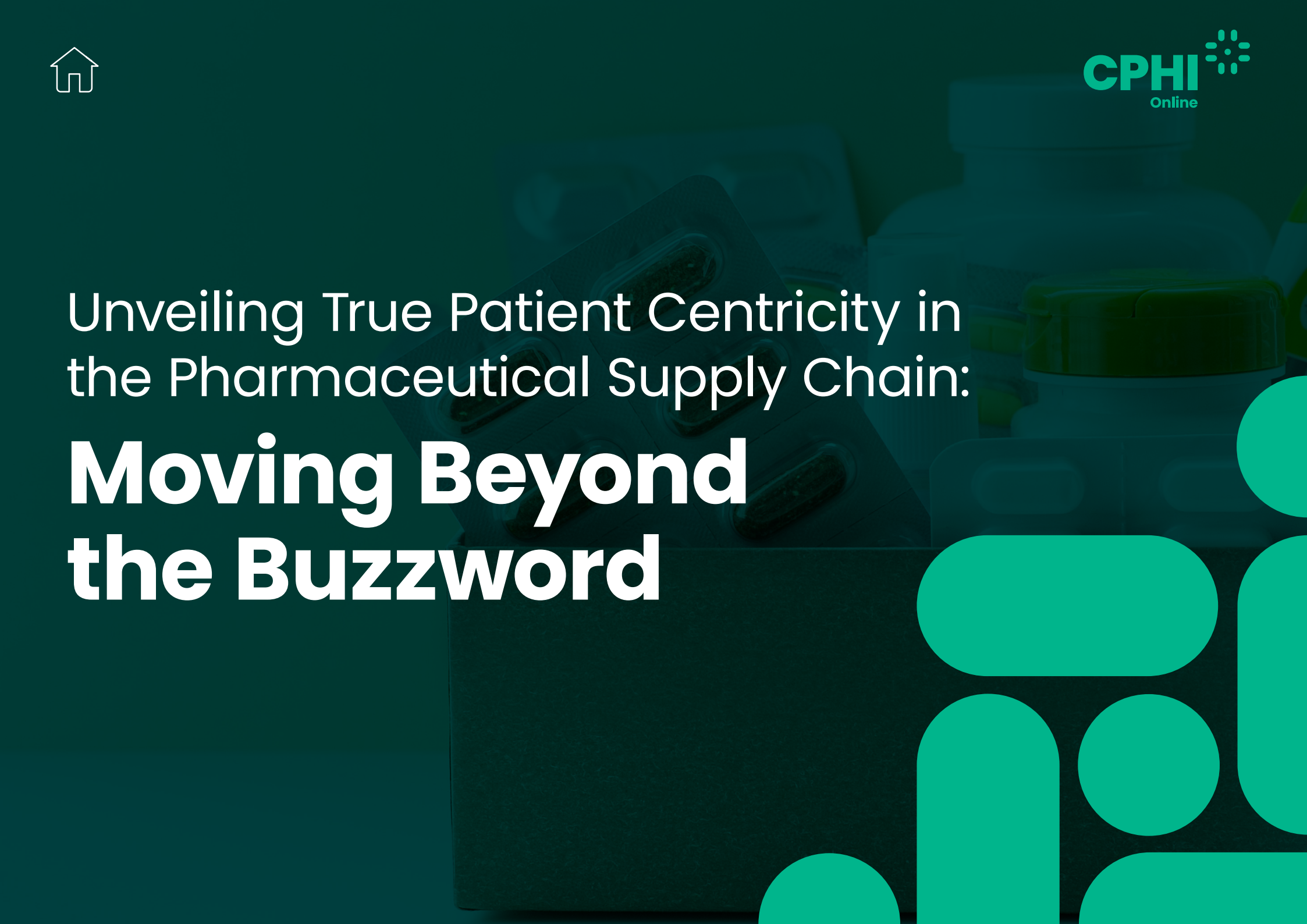
4 Continuous manufacturing continues to shine

While continuous manufacturing is nothing new, the benefits of an approach that enables an uninterrupted production line and reduces human error now outweigh previous concerns around start-up costs, technology implementation and integration and staff training. Some integrated CDMOs and their sponsor companies are implementing continuous initiatives into their operations [v], and patients may emerge as the ultimate beneficiary, with effective risk communication and management facilitating dialogues between patients and regulators/ the industry on pharmaceutical products and technologies [vi]. However, the full-scale adoption of continuous manufacturing is yet to be seen and its full potential yet to be harnessed.

Key Findings

5 Working with clients and patient groups beyond manufacturing now an expectation

As the world slowly recovers from the supply chain disruptions catalysed by the COVID-19 pandemic, pharmaceutical service providers are now expected not only to be experts in the services they offer but also working with all key stakeholders including patients, patient advocacy groups, and healthcare providers in activities throughout the manufacturing process. These activities can include clinical and commercial launch, as well as beyond the manufacturing and development pipeline [ii].
The supply chain for CDMOs is increasingly becoming a value chain, and increased collaborations (or mergers) between CDMOs and CROs reflect this shifting market expectation [ii].



Unveiling True Patient Centricity in the Pharmaceutical Supply Chain: Moving Beyond the Buzzword

Unveiling True Patient Centricity in the Pharmaceutical Supply Chain:

Moving Beyond the Buzzword

While discussions surrounding the patient experience during drug development, research, and commercialisation have been ongoing for several years, to what extent is 'patient centricity' over used as a buzzword, rather than a strategy?

Various definitions and corporate analogies exist. "Patient-centricity should be defined as 'putting the patient first in an open and sustained engagement of the patient to respectfully and compassionately achieve the best experience and outcome for that person and their family'" states a BMJ article [vii]. In consumer marketing, patient centricity has been likened to the customer journey as a series of interactions between a customer and company as the customer pursues a specific goal [viii]. Some experts claim that 'patient-value' would be a more accurate way of approaching the topic from a business point of view: "We are businesses so it's not exactly all altruistic, it's finding that important intersection where you have a better patient outcome and there is business benefit. It's that intersection that we are looking for" [viii]. **Tiffany McIntire, Principal Human Factors Engineer at Roche,** comments that "Good patient centricity depends on the situation. For some molecules, it means looking at what's on the market and improving the patient delivery experience. In other situations, it might mean getting the therapeutic out as fast as possible."

"I think patient-centricity is a sensibility note now," claims **Bikash Chatterjee, President and Chief Scientific Officer at Pharmatech Associates.** "Thanks in part to telemedicine, patients now want to be a part of their overall healthcare. There are patient advocacy groups and patient chatrooms where individuals with a particular disease collaborate and talk about their treatment, side effects, and their experience

with the trials, which is incredibly rich data.

Drug sponsors looking to get ahead are going to find that incorporating that type of feedback into the drug development process is going to put them way ahead of the game, fostering patient engagement, reducing dropout rates, and building a foundation for therapy adoption and compliance. It is a new sensibility for drug developers – the industry has always said we keep the patient in mind, but the reality is that drug development integrates little to no formal evaluations of the patient consequences beyond clinical studies."

Panteli Theocharous, Global Vice President, Cell and Gene Therapy Lead at the PPD clinical research business of Thermo Fisher Scientific, adds: "We need to ensure that we understand the patient journey and the patient experience, and how we can influence it. We think about patient-centric processes and there's a lot of different dimensions to this – from my perspective, I think it's about how we evaluate the opportunity for patients but also how we minimise the burden on the patient and caregiver as well as the clinical trial site."

How can pharma companies move past these varying definitions and translate them to the real world, finding that intersection between better patient outcomes and business benefits?

A Closer Look at Patient Centricity in Pharma

A Closer Look at Patient Centricity in Pharma

For patient advocates like **Heidi Floyd,** the key to patient centricity in healthcare spaces involves bringing all stakeholders together, including patients and patient advocates. “Bring everyone to the table,” she says. “Invite them in and say ‘I’m going to pay you a decent salary and I’m going to invite you to every meeting’. Make that person understand that they are dealing with this [pharmaceutical] company not because they all want a lot of money, but because they are trying to save the lives of someone just like [the patient advocate].”

Here we look at some of the ways patient centricity is already being implemented throughout the pharmaceuticals pipeline.

Decentralised clinical trials for patient centricity

For clinical trials, implementing a patient-centric approach should mean that all planning, execution, and goals consider the patient as the top priority [ix]. Patients are increasingly looking to have access to healthcare and treatments in the home setting, clinician home visits for example. However, implementing home healthcare during clinical trials has been a steep learning curve for sponsors due to concerns regarding patient safety and accuracy of data gathered. Decentralised clinical trials (DCTs) have emerged as an alternative method of conducting trials to boost patient recruitment and increase adherence and retention [x]. Ultimately, optimising the patient experience by designing trials that fit the needs of those being treated will lead to higher engagement, more accurate data collection and improved insight throughout the drug development lifecycle.

"When you start thinking about patient centricity, this is where the aspect of clinical trial design diverges because of the recent, novel focus on the patient component of the clinical experience," Chatterjee comments. "That can inform and assist drug sponsors in getting products to the FDA but also provide insight as to where the CRO can influence this," he states.

Advanced therapeutics portfolios

Advanced therapy medicinal products experienced rapid interest, growth, and formal evaluations by national and international agencies in recent years. The European Commission and EMA, for example, published a joint action plan on ATMPs in October 2017 that aimed to streamline procedures and requirements for ATMP developers [xi]. Increased guidance and training materials continue to be updated, however, ATMPs still pose a significant challenge to the pharmaceutical supply chain. As they are not standard pharmaceuticals and often patient-specific therapeutic agents, their manufacturing and management deviates from that of standard pharmaceuticals [xi].

Many challenges ATMPs face, that small molecule or even biologic therapeutics may not be subject to, are often found in the manufacturing, analysis, distribution, and sourcing of raw materials. Cell and gene therapies or tissue engineered products for example, sometimes only serve one patient per batch in comparison to large batch sizes for small molecule and generic drugs. The assays required to analyse the batches and the systems needed to distribute therapeutics with specific shelf-life conditions or technician skills are still in their infancy for ATMPs [xii]. **Peter Shapiro, an independent pharmaceutical consultant,** comments that "True personalised medicines such as ATMP biologics (including cell and gene therapies) still have very low adoption rates. The number of patients has been kept low by high prices and limited efficacy."

Despite these challenges, there are still important incentives for drug sponsors to continue to invest in the development of ATMPs. McIntire addresses possible opportunities in advanced therapeutics and rare diseases for implementing a patient-centric mindset. "If you're in a highly underserved market, sometimes that molecule is just going to be that much more important. From a formulation perspective, this means looking earlier at the different ways you can get the drugs into the body, what methods are currently being used, and ultimately trying to find better pathways."

"Adoption of these personalised medicines will require greater spread of sophistication in diagnostic technologies," Shapiro states. "Hopefully, this spread of diagnostic technologies has been a positive result of the COVID-19 pandemic."

An industry-wide mindset shift

Whether a drug sponsor can call themself truly patient-centric is a difficult attribute to quantify. Patients are increasingly looking to become more involved in their healthcare decisions and many experts, while maintaining realist perspectives, do recognise the need for drug sponsors to balance business goals with the needs of the patient.

Thermo Fisher Scientific's Executive Director, Integrated Supply and Delivery Services, Brenda Bruker states that:

> **"Companies and their leadership have to be very intentional about the values that they are embedding into the organisation... a shared vision and values from the top and across all teams is critical. That's part of what we do – we drive that level of communication and training across the organisation to ensure that everybody understands their role in the process, even down to each individual and what role they can play in maximising the customer experience."**

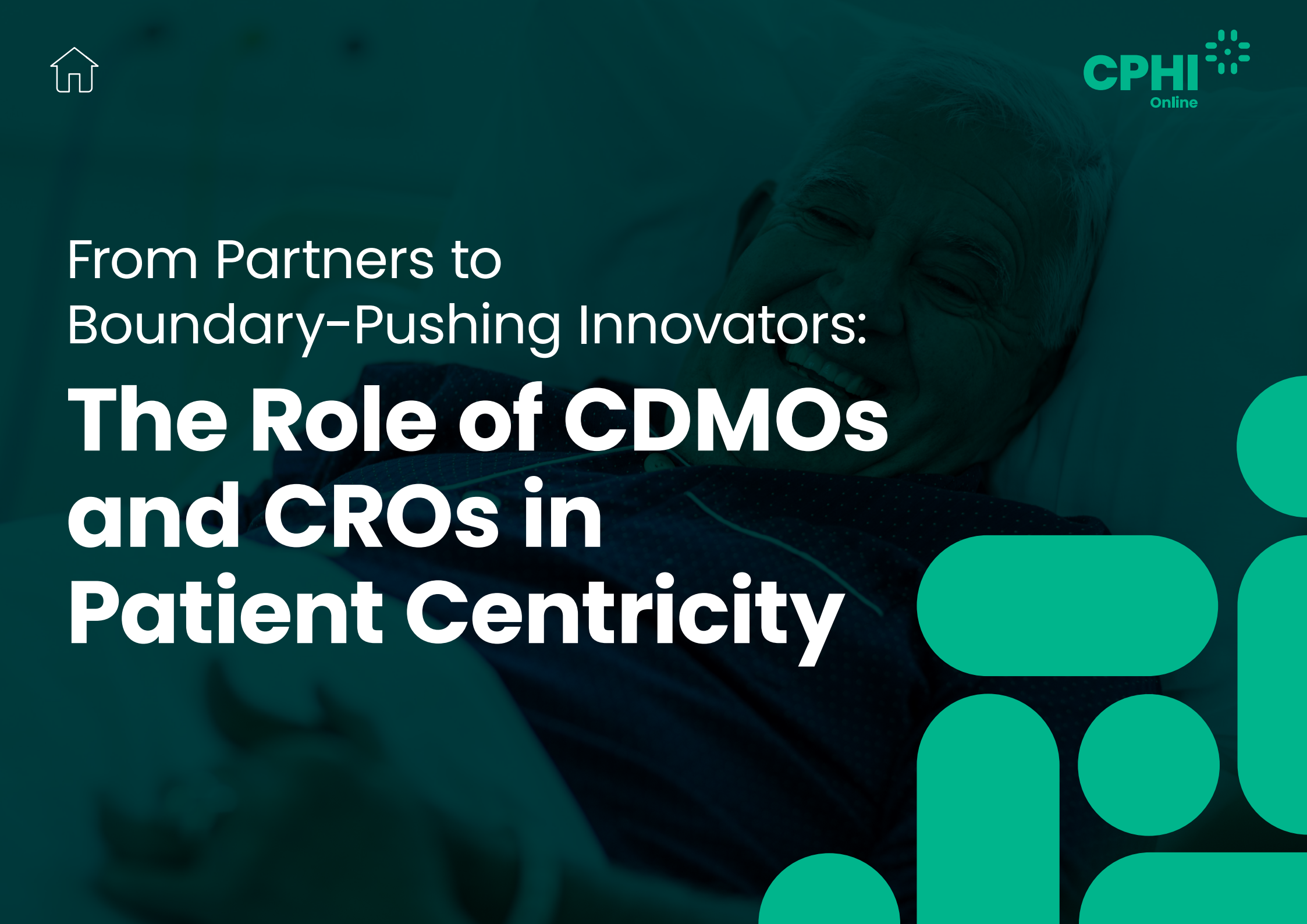
End-to-end oversight throughout the pharmaceutical supply chain both mitigates risk and realises pipeline efficiencies that help get medicines to market and, ultimately, to patients faster – a win-win situation Bruker advocates. Floyd echoes this industry-wide attitude shift, citing some examples already in practice: "Bringing patients in from the beginning is a really good way to include people. Instead of having them come in at step three, have them come in at step zero. There is one company in Canada that has hired a patient to be on-site, which is really innovative. She does not have a marketing degree, and has never been a nurse or a doctor. They just hired this woman, who was a patient herself, to interact with other patients and bring them in, which is revolutionary."

As the expectation for patient-centric mindsets permeates throughout the industry, how are CDMOs and CROs evolving to meet the demands of both their drug sponsor clients and the end-users?

Ultimately, where is the balance to be found between industry and patient?

From Partners to Boundary-Pushing Innovators:

The Role of CDMOs and CROs in Patient Centricity



From Partners to Boundary-Pushing Innovators:

The Role of CDMOs and CROs in Patient Centricity

While outsourcing pharmaceutical operations and activities is nothing new to the industry, the CDMO and CRO sectors have seen an explosion of growth in the last decade – experts expect the market for these service providers to grow at a CAGR of 7.29% until 2028 with little sign of slowing down [iv]. Biotechs and biopharmaceutical companies have seen a steady decrease in their returns from drug R&D, leading to the outsourcing of pharmaceutical research, development, manufacturing, and distribution activities to contract partners [xiii]. Key factors driving the outsourcing of pharmaceutical industry operations include the rising costs for product development, improving a clinical trial's reach to patients and participants, and expanding a company's scope of solutions and technologies [xiii].

"Historically, in terms of the primary services they offer in the overall drug development supply chain, you have two paths to clinical and commercial manufacturing for drug developers," Chatterjee explains. "You have the traditional innovators that have vertically integrated manufacturing capabilities. However, the high cost of debt financing is giving all but the largest drug sponsors limited options to build integrated manufacturing capability. This leaves equity financing, asking drug sponsors to forgo future revenues in order to realise manufacturing capability now. The other path is to seek out a contract manufacturing partner to support clinical and commercial manufacturing."

Chatterjee differentiates CROs from CDMOs as typically involved early in the drug development process, including drug discovery and development and early human testing

in healthy volunteers, studying the PK/PD behaviour of a drug. "The decision to engage a qualified CRO and transition to a commercial-capable CDMO is a strategic decision that includes a broad set of technical, business, and quality considerations. Patient centricity makes a strong case as an additional consideration when evaluating and selecting a contract service partner for a drug sponsor."

Drug sponsors will look for different qualities when considering which CDMOs and CROs to work with, however **Life Sciences Industry Strategist, Cornell Stamoran** sees some flexibility within the roles each organisation might play:

> **"Historically, the boundaries between what CROs do in development and what CDMOs do have been a little fluid – if you look at some of the larger CDMOs, they have at times practised what we would call CMC development activities. Some industry participants believe there are more synergies between these companies and have invested in both as offerings."**

Where patients are concerned, CROs may be thought of as pushing the boundaries of where the voice of the patient can be integrated into the drug development, manufacturing, and commercialisation pipeline. In a survey published by the Life Science Strategy Group, LLC (LSSG), 87% of drug sponsor survey respondents were found to be discussing patient-centric approaches to implement in the development of clinical trials, with half expecting these processes to be deployed in the next 1–3 years [xiv]. As the link between drug sponsors and patients through the orchestration and organisation of clinical trials, CROs have a unique position in relaying patient feedback, facilitating patient outreach, and engaging patient advocacy groups to drug sponsors in adapting trial designs [xiv].

But where does this leave CDMOs? While they may be thought of as quite separate from the end-user of their product (i.e. patients), CDMOs can still implement a strategy of customer centricity into their workflows through a shift in mindset concerning patients, which trickles down to operational initiatives and innovations.

The improvement of timelines, efficiencies, and support services is not only for the benefit of the drug sponsor at this point; the patient becomes an inherently important consideration in business and operational decisions.

Partnerships Between CDMOs and CROs:

Harnessing Synergies for the Patient

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While both CDMOs and Contract Research Organisations (CROs) contribute to the pharmaceutical industry, they have traditionally served distinct purposes. CROs primarily focus on preclinical and clinical research, conducting trials to assess the safety and efficacy of new compounds. CDMOs however offer a more comprehensive range of services, encompassing formulation development, manufacturing, and regulatory compliance - bridging the gap between research and commercialisation.

From the initial discovery of a molecule, to clinical trials and eventual manufacturing and distribution of a drug product, bringing a therapeutic product to market can take 10+ years and require USD $1 billion [xv] of investment. Strict regulatory requirements in a controlled environment further complicate the process. Outsourcing partners can help to simplify this process and offer access to specialised expertise and resources.

Increasingly, pharma companies requiring outsourcing services have opted away from multiple contractors, to work with a single vendor to optimise speed-to-market, investment and to eliminate burdens in tech transfer and product transportation [xv].

The rise of the 'One-Stop-Shop'

"We speak separately about the CDMO and CRO markets, both as key components of the complex pharma discovery, development, and commercialisation services industry, but

there has been a quiet shift in the services space driven by those at the heart of the supply chain: the vendors," states **Dan Stanton, Editor at Informa Connect Life Sciences and BioProcess International.** "In an industry that has seen equipment shortages and lead times that make the accuracy of forecasting on par with fortune-telling, vendors taking control of manufacturing makes some sense to the drug sponsor and, ultimately, the patient," he explains. Though smaller pharmaceutical companies and virtual and/or start-up biotech companies have historically driven major changes within the contract industry due to their inherent reliance on outsourcing activities [xv], many well-established service providers are choosing to partner with integrated CRO/CDMO service providers. "A direct line to the equipment needed and, presumably, a favourable cost price make these CDMO units stand out to end-users looking for security after years of supply chain turbulence."

The need for high-quality services and expert support in preclinical and clinical research, regulatory affairs, manufacturing, packaging, and transportation – essentially end-to-end services – by pharmaceutical and biotech companies are driving many CDMOs and CROs to integrate their services, whether by partnership agreements or outright M&A decisions.

"The phrase 'one-stop-shop' has been banded around for years, describing some of the more extensive CDMOs. But when a services firm can offer a pharma or biotech company everything from preclinical testing, to trial management, to clinical and commercial manufacture, along with all the nuts and bolts and single-use bioreactors and growth media needed along the way, then surely we are approaching a world of all-encompassing services firms with far simpler supply chains," summarises Stanton.

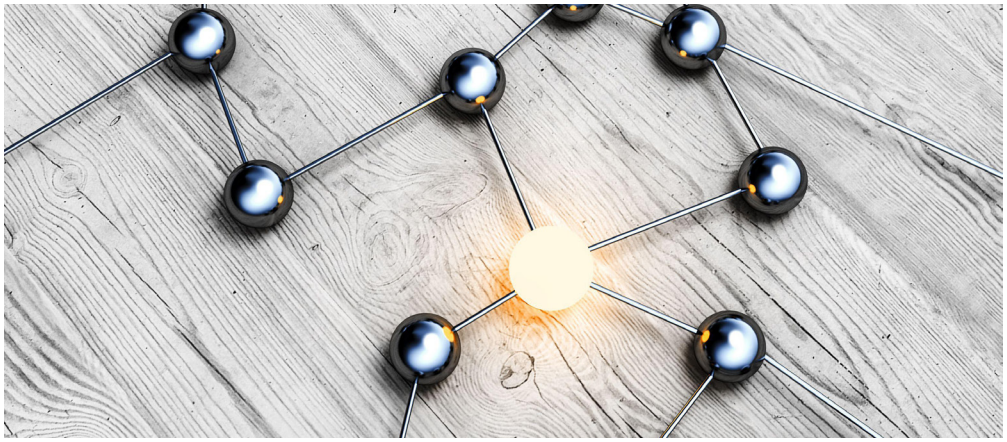
Clinical trial support

By far the biggest attraction for pharmaceutical and biotech companies when it comes to choosing a CRO is how the orchestration of a clinical trial occurs. Drug sponsors are increasingly turning toward CROs to combat clinical trial disruptions caused by global events that result in slower

patient recruitment and decreased participant retention [xiii]. **Aurelio Arias, Director, Thought Leadership at IQVIA,** paints a portrait of the intricacies in the current clinical trial landscape: "The clinical trial landscape is getting ever more crowded, and therefore demand for trial participants is increasing. At the same time, there is a trend toward geographic concentration. Add to this the shift in R&D activity toward specialty care and rare diseases – as well as a trend toward more complex inclusion and exclusion criteria – and identifying, recruiting, and retaining eligible patients becomes increasingly challenging. Under-enrolment is now a significant factor in the overall decrease in trial performance."

A strong partnership between a CDMO and CRO with clear and concise communication throughout can provide pharmaceutical companies with expanded reach into a specific geographic region, expertise in a specialised therapeutic area, and patient-centric clinical trial frameworks [xvi].

"There are a variety of models of investment. Some are early stage preclinical and early clinical (phase I) providers looking



at the integration in phase I for continuous trial reformulation to optimise the formulation that you would then take into later stages. So it's a very close integration model at the early phase," Stamoran says. "What that means is that you have a formulation development laboratory connected very closely to a phase I unit essentially, and it's usually focusing on a small molecule drug (often oral drugs). You do a small phase I study and then you look at the PK/PD outcomes. Then you can rapidly reformulate and take it to the second phase I unit where you can optimise results."

"There are more and more of these integrated CDMOs which work alongside a drug sponsor that has chosen not to finalise the dosage form until phase II, maybe post-phase II. When you do your preclinical safety studies, you establish a toxicological ceiling. Sometimes that toxicological ceiling becomes a constraint in terms of the dosage form modality you choose," Chatterjee illustrates this in the formulation design of products where the toxicological ceiling may not match up with the dose needed to achieve a desired therapeutic effect. "Some drug sponsors are formulating early-stage dosage forms for phase I that are designed to minimise the impact of the dosage form on PK/PD in healthy humans before they finalise the dosage forms. So, you can go from a capsule to a tablet, or a solution to a tablet, in phase II. Stringent regulatory authorities like the FDA require you to notify them that the drug sponsor is using this approach as the FDA will adjust its participation in the review process. This greater involvement with regulatory bodies does reduce the likelihood of missed commitments and misunderstandings which ultimately lower the overall program risk. That's where an integrated CDMO/CRO could be really interesting. You're

now marrying the clinical trial design with the formulation sciences (CMC science) to make sure you're taking maximum advantage of the characteristics of your drug. That's where we're seeing more and more folks looking for a CMC strategy for development there.

What some companies are doing is bringing patient advocates in at literally the TPP development level so that you're understanding the sensibilities and the endgame of the target population – whether that's through focus groups, through surveys, through expert participants and patient advocacy groups," he states.

These shifting R&D models boost the capabilities and expertise of all parties involved. The rapid exchange of information and quick turnaround of formulation changes resulting from partnerships between CDMOs and CROs can both improve a patient's experience throughout a clinical trial, and attract drug sponsor partnerships looking for efficiency in their clinical trial operations. As Chatterjee explains when it comes to submitting regulatory applications: "We're mostly looking at the clinical outcome likelihoods of the clinical study designs we adopt, of the dosage forms created, of the analytical tools used to measure etc. Sometimes these clinical endpoints are less definitive. Pharma could benefit from talking to patient advocates about what is important to them. Oftentimes, there can be a secondary or a tertiary component of the disease treatment that's really important to the patient population but is not a primary endpoint of the clinical protocol. Incorporating these measurements as a formal part of the clinical study could help a drug sponsor in their argument for approval if clinical outcomes are positive, but only marginally so, because a collateral clinical outcome is important to the patient population."

Enabling efficiencies and speed-to-market

Ultimately, a CDMO/CRO collaboration aims to increase the efficiency of the drug discovery and development process through to preclinical and clinical trials and finally commercial manufacturing and distribution. In a so-called

'one-stop' service provider, the transfer of samples, products, or technologies between groups is expected to be smoother, with fewer disruptions to timelines and product availability [xv]. This increased efficiency is at the heart of CDMO/CRO partnerships, says Bruker: "The collaboration is truly what drives patient centricity, and understanding what materials need to go to what sites, working together for proactive forecasting of supplies to keep clinical trials on track – that's the key to success. Being able to be reactive to changes that might come up in the trial with open and collaborative communication will ultimately ensure supplies get to patients on time. We want to make sure that the process is as seamless and easy on the patients, and it's our job to make sure that we're connecting the dots and minimising the white space across the entire value chain."

Floyd summarises: "If [a CDMO/CRO collaboration] is focused and done right, I don't see how it could do anything except help patients. That's the goal of everything that these companies are creating, even if you're outsourcing things. The goal is to get something to patients quickly that will improve their lives, if done properly, which includes bringing patients in. A separate group of individuals can be brought in and because you have access to different people and different dialogues, a patient or patient advocacy group can bring up a point down the supply chain stream that has never been addressed. It's all about information sharing – if we're transparent and help patients AND the companies in the end, how can the right [CDMO/CRO partnership] do anything but help?"

> **"We want to make sure that the process is as seamless and easy on the patients, and it's our job to make sure that we're connecting the dots and minimising the white space across the entire value chain."**
>
> **Brenda Bruker,** Executive Director, Thermo Fisher Scientific

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Mergers and Acquisitions

Mergers and Acquisitions

In just the last 5 years, the world of CDMO/CRO collaborations has been witnessing a surge in the value and significance of M&A transactions between some of the biggest names in the game [xvii]. With drug sponsors now looking for many of the qualities mentioned, including increased operational efficiencies and supply chain risk management and mitigation, this trend of investing in M&A transactions is only set to increase in the coming years, most experts predict.

"As a standalone industry, up to 80% of the market is led by just a handful of players: Cytiva (which recently incorporated Pall), Thermo Fisher Scientific, Millipore, Sigma, Sartorius, and – to a lesser extent, revenue speaking – Repligen," Stanton says, describing the current bioprocess vendor M&A landscape. "These companies have spent years consolidating the market through mega-mergers and bolt-on acquisitions: Thermo Fisher Scientific's USD $13.6 billion acquisition of Life Technologies in 2014; Millipore's USD $17 billion Sigma-Aldrich buy the following year; Sartorius' recent USD $2.6 billion acquisition of transfection reagent and plasmid DNA specialist Polyplus, to name just three. But beyond the reagents, bioreactors, and plastic tubing, the sector has made deeper in-roads into the pharma supply chain. Bolstered by the manufacturing heritage of its parent company Merck KGaA, the Sigma-Aldrich deal brought Millipore a CDMO business. Meanwhile, the opening of Thermo Fisher Scientific's war chest brought the life sciences vendor first Patheon, then Brammer Bio, and has made it one of the largest CDMOs in the sector. Cytiva's parent firm Danaher Corporation, meanwhile, acquired Aldevron in 2021 and has been rumoured to be eyeing up other CDMO acquisitions, including Catalent (though alleged talks have allegedly ended for now)."

In addition, in December 2021, Thermo Fisher Scientific completed the acquisition of PPD for $17.4 billion. With

the addition of PPD, Thermo Fisher Scientific offers a comprehensive suite of world-class services across the clinical development spectrum - from scientific discovery, to assessing safety, efficacy, and health care outcomes, to managing clinical trial logistics, to the development and manufacturing of the drug product. As of August 2023, Thermo Fisher Scientific also completed its acquisition of CorEvitas, a leading provider of regulatory-grade, real-world evidence (RWE) for approved medical treatments and therapies for $912.5 million in cash.

Motivations behind M&A activities versus less attached partnership agreements can be as simple as saving even more time to market, as Chatterjee states: "In 2017, Recipharm went into a collaboration with bioclinical consultants. The motivation was they wanted to be able to bring together early-stage formulation clinical sensibilities into the CDMO and accelerate those considerations. The whole opportunity here, whether a CDMO and a CRO are pursuing a collaborative or entering an acquisition deal, is in the time-to-market; how can we save time-to-market?"

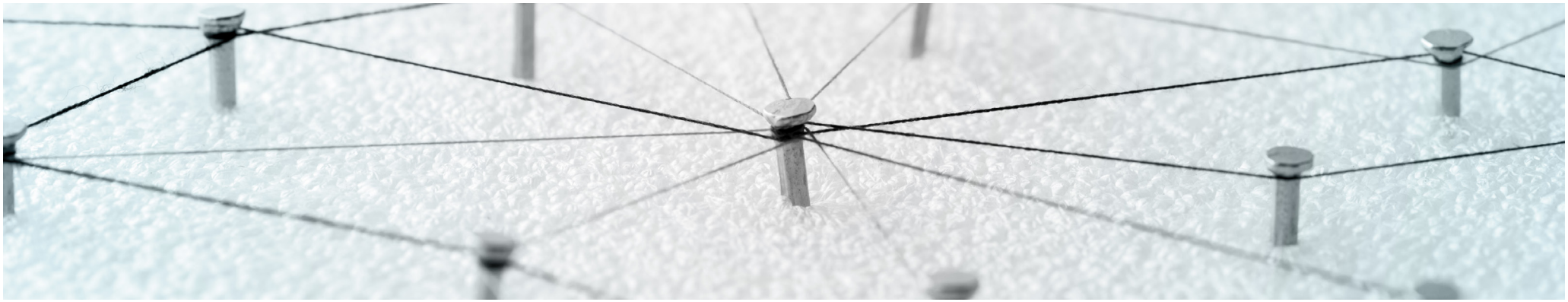
Collaborations, Chatterjee explains, may be a step toward a full M&A agreement. "I think this is where you're going to find organisations working together from different cultures, mindsets, and markets who are geographically separate. In situations like these, companies may try and collaborate as a trial for the two entities to test the synergy there – to see if they've got the energy to spend the time to harmonise two institutions and two different cultures, and bring together the best of both worlds," he states. The world of pharmaceutical M&As becomes even more frantic when advanced therapeutics are brought into question, as Shapiro explains: "A significant percentage of American CDMOs are owned by private equity, which usually have a short, 3-year investment cycle. These private equity companies, once near the end of their investment cycle, will either sell off the CDMOs or take them public. Right now, it's not clear that they're capable of taking anything but ATMP CDMOs into the current marketplace because there's such an extreme scarcity of companies that can produce ATMPs for clinical trials, compared with the large number of pipeline companies that have products in development. There's a real prize for companies that are able

to increase the efficiency of their ATMP production, leading to more M&As."

"You'll see M&As where folks are trying to offer a service to any challenge a drug sponsor is going to have. The challenge for drug sponsors and CDMOs alike is the high turnover rate in CDMOs. They tend to have some very senior people and the rest of the organisation tends to churn. For a drug sponsor, if you don't have an informed third party (could be a consultancy or an individual, a clinical expert or an MD) sticking with the process and making sure that the CDMO's team is informed and capable, it is easy to stumble, incurring delays, additional costs, and adding program risk. A larger company that has chosen to integrate [CDMO and CRO services] might be in a better situation to provide consistent and stable expertise," Chatterjee continues.

Collaboration or proliferation?

And the industry is moving as predicted: there is strong investor interest in life sciences in general, and pharmaceutical manufacturing has seen 48 deals made just



in the first half of 2021 [xvii]. As the world moves further away from the onset of the COVID-19 pandemic, M&A activity has declined slightly from the second half of 2022 and the first half of 2023, but many experts and investors predict that Big Pharma deals are set to increase in the later half of the year [xviii]. With the implementation of the US Inflation Reduction Act to clarify pricings and ease uncertainties around industry activities, M&A activity is expected to see increased attention [xviii]. From 2018–2022, the CMO industry witnessed a huge 479 deals of either whole companies or individual facilities [xviii].

Large-scale integrated CDMO businesses are likewise predicted to become one of the main types of business models by 2030 [xix]. Giants such as Recipharm, Lonza, and Thermo Fisher Scientific are scaling their operations quickly in all directions to offer a broad range of services. Vertical expansion focusing on product development and adjacent services – including regulatory and quality control – will enable their clients to follow each step along the value chain for their molecule [xix].

Yet, the infamously fragmented sector of pharmaceutical service providers might also be seeing both a trend of consolidation AND proliferation [xx]. For as many unions are made, there are over 3,200 R&D service providers in the US alone [xx].

With new start-ups entering the pharmaceutical services sector every day, some are left wondering which business strategy will prevail: collaborative relationships and mergers for full, end-to-end services from discovery through to commercialisation, or the propagation of smaller CROs/CDMOs with focused service offerings throughout different parts of the supply chain?

Experts differ on their outlook for the types of business model that will emerge, but there is consensus that the demand for CDMOs and CROs will not wane any time soon. "The goal is to increase the timeliness of processes and coordination between the manufacturer and clinical trials," Shapiro describes what he believes will be the proportion of new vendors and integrated players:

"On one hand, this makes it a lot easier for start-ups that have relatively little knowledge of these spaces to enter and make themselves known. On the other hand, they might become dependent upon the strategic partners, and these strategic partners can charge significantly more, which is why they're doing it. We should really expect more mergers in this space. The currency of interest rates will encourage organisations like private equity firms to offload the CMDOs that they've purchased during a long period of 0% interest rates. Additionally, the CRO market was really impacted – those CROs that were not involved in COVID testing, who had specialties other than infectious disease were hurt by their inability to conduct trials during COVID."

What customers want

For any business, the decision made will rely upon what the customer wants. For contract organisations, this means not only drug sponsors but also patients, clinical trial participants, and healthcare providers. Most advantages related to M&A type collaborations between CDMOs and CROs have to do with the leveraging of the same tools and systems to provide a seamless pipeline. Bruker explains: "I think the 'all-under-one-roof' approach is probably more advantageous [than other collaborative agreements]. It enables teams to leverage the same tools, systems, and processes across all service offerings to maximise efficiency and ensure data transparency and visibility. When we think about the sales process, which is where these consultative services come into play, we are able to collaborate very openly across all our partners and our customers to create the right solution. I think if you are working in a non-M&A environment, there could be some competitive reasons why that wouldn't be possible. So, it is definitely an advantage if you are all in one company – you can certainly do those types of things."

Bruker also offers a more holistic overview of the drug discovery, development, and manufacturing pipeline: "A true benefit in this company (Thermo Fisher Scientific) is that we are able to cross-pollinate talent across the different businesses and that gives people a more holistic, 360 view of the clinical trial processes, and what that means to patients and our customers. I think that ultimately provides a much better experience when you are able to have everybody in the same type of company environment."

McIntire adds that choosing which service provider to work with is itself a strategic collaboration for the drug sponsor: "Sometimes with the bidding process, what ends up happening is that you waste so much time sending it out to all these different people. If I'm being honest, it depends on the flexibility of that supplier. It's good to have several suppliers in mind but knowing one does a particular thing really well and giving them all of that work (while not allowing complacency and keeping checks and balances in place) is part of supplier management and having a good supplier relationship."

"Making the right design decisions depends on who owns the relationship with the customer," Stamoran states. "On the CDMO side, it may not be easy to get to the right people, so if you're a CDMO business sitting within a larger CRO company, they may be talking to those on the customer and sponsor side. I think it's just recognising that for larger and medium-sized companies, there are different buyers who are motivated by different things, they also play at different times in the product lifecycle."

> **"You want to be able to touch the customer or sponsor directly to the development experts and the clinical trial experts. That's where I see the complexity come into play."**
>
> **Cornell Stamoran,** Life Sciences Industry Strategist

Continuous improvement through continuous manufacturing?

One aspect of the sector that has yet to be touched upon but may be as impactful as the dealings between companies is how the manufacturing process itself is conducted. While the concept of continuous manufacturing, in which pharmaceutical products are manufactured end-to-end in a single, uninterrupted production line [xxi], is nothing new to the pharmaceutical industry, its implementation has only seen an increase in momentum in the last decade [xxi]. Traditional batch manufacturing presents several limitations such as a lack of flexibility in batch size to respond to fluctuations in patient supply and demand [vi].

Such inflexible capabilities could even potentially lead to a drug shortage if production cannot keep pace with increasing demand [vi]. The ability to produce and scale manufacturing output of drug products to current demands is made possible with highly specialised and integrated manufacturing capabilities, streamlining the process to fewer steps.

The benefit to patients is without doubt. The ICH Q9 'Quality Risk Management' guidelines present concepts regarding risk communication as a measure of overall quality risk management [xxi]. The effective communication of information relating to processes is fundamental consideration when weighing the potential benefits (or disadvantages) to patient groups. Continuous manufacturing, within the context of the guidelines set out by Q9, encompasses the collaborative communication of risk throughout the product's lifecycle [vi]. With technological platforms to support continuous manufacturing like Process Analytical Technology and Real-Time Release Testing, the relaying of risk throughout a drug product's lifecycle can facilitate a holistic overview of conserving resources to keep up with demand, streamlining the development and manufacturing process, and establishing an efficient dialogue with regulators, all in benefit towards the effort of

ensuring the product gets to the patients who need them [vi]. The advantages of risk communication certainly extend to drug sponsors as well – pharmaceutical companies looking for a nurturing relationship with outsourced service providers can expect to be informed throughout the development, manufacturing, and clinical trial pipeline of their product with continuous manufacturing.

However, large-scale investment into assets required to implement continuous manufacturing is yet to be seen industry-wide [xxiii]. Many companies remain risk-averse when investing into technologies and protocols to manufacture a product that may ultimately fail at clinical stage, or remain unapproved. Additionally, companies will need to grapple with transferring existing products manufactured in batches to the procedures of continuous manufacturing, some of which may not be suitable in design [vi].

Despite slow adoption, the collaborative integration of CDMOs/CROs can help overcome the various challenges in implementing continuous manufacturing and processing, ultimately benefitting the patients and end-users of drug products. Concurrently, industry goals aimed towards the implementation of continuous manufacturing may see a greater call for collaborative agreements between CDMOs and CROs, and potentially other outsourcing vendors and biopharmaceutical innovators [xxiii].

So, while continuous manufacturing may be a rising interest for many, its implementation into the core processes of manufacturers remains to be seen. The advantages of ensuring sufficient supply of drug products can only be of benefit to patients, but it will be up to pharmaceutical companies and their service providers whether the shift to continuous manufacturing is of benefit to all.

Business-driven or patient-driven decision making?

Business-driven or patient-driven decision making?

The question remains as to whether patient centricity will be a natural consequence of certain collaborations, or if companies should proactively consider the patient perspective in each of their business decisions, including partnerships and M&As.

A survey conducted by The Harris Poll, commissioned by Charles River Laboratories, asked US patients about the quality of healthcare they received, and revealed that patients believe it would only increase if industry players worked together more [xxiv]. Though only 10% of respondents demonstrated some knowledge of the drug development process, over 90% of those surveyed agreed that a united effort from all key players in a drug product's lifecycle would improve overall healthcare quality [xxiv]. Along with the advantages of having all operations under the same theoretical roof, this expectation of collaboration may itself fuel the partnerships and collaborations between CDMOs and CROs and inform drug sponsors in their search for an integrated service provider.

"Companies and their leadership have to be very intentional about the values that they are embedding into their organisation. When you have everything reporting into the same organisation, that certainly makes it easier to drive that patient-centric culture," Bruker states. "A shared vision and values from the top and across all teams is critical. So that is part of what we do – we drive that level of communication and training across the ENTIRE organisation to ensure that everybody understands their role in the process, even down to each individual and what role they can play in maximising the customer experience."

Intentional collaborations between CDMOs and CROs established with patient centricity as a part of their decision

can not only make for a sound business practice (in increasing operational efficiencies and potentially reduce disruptions and/or costs), it can also improve the quality of healthcare experienced by patients, as Bruker explains: "Oversight of the project from end-to-end makes it easier to mitigate risks and realise these efficiencies to streamline the drug development journey, which helps accelerate getting medicines to patients faster, and ultimately getting drugs to market faster for our customers."

Some experts, however, are slightly more cautious when thinking about business transactions and the patients they claim to serve: "Certainly some very large companies – and this is not just true in Pharma – say they want to be strategic with their vendors but often strategic means wanting a lower price and not truly collaborating," Stamoran claims. "Many of the relationships (not all) are still characterised by what I would describe as tactical rather than strategic, which is a whole separate conversation." Stamoran counterpoints certain claims that some CDMO/CRO collaborations may even be worth sacrificing when a "best-in-class" service

offering is required, which may not be provided by an integrated company.

Even so, most experts agree that driving efficiencies within the pharmaceutical supply chain can only benefit the patients that are ultimately served, and the partnerships between CDMOs and CROs seen in recent years has demonstrably achieved these efficiencies: "The aspect that works in a patient's interest for an M&A would be to try and streamline and bring some of the clinical sensibilities into the early-stage drug development question. This means looking at formulation, at dosage form modality, at packaging, and at the endpoints at the TPP level. Anytime you think two steps down the road, you are going to likely be ahead of the game," Chatterjee advises.

Additionally, Floyd comments that any partnership must "bridge the gap between patient and company and form a true relationship. If a patient is on a clinical trial, monitor all the physical things you normally would, but also have someone on staff who is a mental health advocate or a patient advocate who can check in with the patient. Do you necessarily need an advocate? Maybe not. But if you do, that will be the aspect of the trial that patients appreciate and will feel understood, especially if somebody on the project or committee themselves has the ailment or disease being treated. They can advocate for the patient AND the trial, and help with issues such as non-adherence and quitting the trial. You see it in the data. People stop taking the medication and the company will ask a series of basic questions but they won't dig into it because there's no relationship there. If you have a patient advocate on the team who is passionate, they will be relentless throughout the trial."

"When you have these entities working so intimately hand-in-hand, we're able to understand and influence stakeholder input, whether it is an SME, a particular technical expert, or an expert in the logistics or the clinical trial side," Theocharous comments from an industry perspective. "I am in the delivery side of the business, delivering on the promise for patients. I think it's about developing a strategy that encompasses all those elements in a cumulative manner. What I mean by that is understanding the practicalities of orchestrating complex

logistics, transport, distributions etc. and I think that comes through the synchrony of a CDMO and CRO working together. It allows for the leveraging of relationships with clinical trial sites. The ecosystem is very complex, but if there are ways that we can build in efficiency by working more intimately together, then I think that allows us to influence time, process, and instil more efficiency because we're minimising handoffs to third parties. We can encompass many critical activities under one umbrella, influencing 1) a very practical process and 2) the patient journey. I think that is a highly impactful and differentiated approach that not many organisations can offer."

The ultimate collaboration: incorporating the patient voice

The most crucial collaboration is that of the pharmaceutical industry with the patients they serve. Arias states:

"Early and persistent engagement with patients and patient organisations can be an effective way to improve trial recruitment by establishing rapport with potentially eligible patients early on, and by incorporating patient needs and preferences into the trial design. These can include endpoints, as well as trial setup and execution. Understanding the profile of 'real-world' patients can help define realistic inclusion and exclusion criteria. Ongoing patient engagement can also serve to establish and maintain patients' trust in the trial process."

As a result, the answer to whether CDMO/CRO collaborations will result in better experiences for patients throughout a drug product's lifecycle or if CDMOs and CROs need to implement patient-centric values into their collaborations may be a positive feedback loop of symbiosis – including the patient voice into business operation decisions, including collaborations and M&A transactions, will ultimately result in partnerships that are patient-centric at their core.

Towards a patient-centric future

Towards a patient-centric future

"The vogue for the 'one-stop-shop' – a contractor that offers end-to-end service offerings – is a trend often cited in articles about the CDMO space" claims a CPHI article on what drives CDMO activities, published in 2020 [xxv]. As the past few years have demonstrated, supply chain collaborations and mergers between CDMOs and CROs have matured beyond an industry trend.

As patients become more invested in taking control of their healthcare outcomes, drug sponsors and their service providers must look inwards at ways to increase efficiencies, minimise risk, and ensure that drug products reach patients who need them, and that they are administered in a way that encourages both adherence and experience. The implementation and execution of patient-centric values and actions must be at the heart of business decisions.

Mergers and acquisitions are leading the way for the types of CDMO/CRO collaborations seen in the service provider sector [xxvi]. The biopharmaceutical CDMO and CRO market is expected to see more M&A activity in a bid for service providers to streamline the processes and provide integrated offerings to their clients and stakeholders.

These efficiencies aim to bring drug products to market faster and eliminate miscommunications between various third-party organisations that may disrupt the supply chain. Integrated CDMOs with specialisations in advanced therapeutics may find themselves in high demand for collaborative partnerships with other CDMOs/CROs and drug sponsors.

Ultimately, an intentional collaboration between integrated CDMOs, drug sponsors, and the patients they serve will naturally produce drug products, trials and treatments that are inherently patient-centric.

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