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A Consultative Approach to Pharmaceutical Outsourcing

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Drug Development and Manufacturing

INSIGHT FROM:

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Picture the following scenario. You've spent several years, and hundreds of millions of dollars, developing your new critical therapy that is destined to improve the lives of patients around the globe. You're approaching commercial launch. You know that, for every single day your drug launch is delayed, you could lose millions of dollars in revenue, with estimates varying from $600,000 to $8 million per day[1]. Not to mention the suffering of patients who are unable to access your critical therapy to treat their condition. Ideally, this would not happen. But—critically—you did not conduct the proper long-term due diligence on your chosen CDMO partner(s), and your development and

manufacturing strategy was suboptimal. As such, not only are delays a possibility, they are inevitable.

In this Q&A, PCI Pharma Services' Shawn Cain and Louise Carpenter discuss best practices when it comes to outsourcing development and manufacturing programs, covering both sterile, non-sterile and highly potent drug products, and why it's so important to choose the right CDMO partner to accompany you throughout the drug product lifecycle. Louise specializes in solid oral and liquid dosage forms in the high potent space, and Shawn's area of expertise is sterile fill-finish and lyophilization. Together, they bring a vast amount of experience in their fields, and share their experiences across multiple dosage forms.

Q: What are the essential attributes of an industry-leading CDMO?

Louise Carpenter: In terms of technology and manufacturing equipment, it's incredibly beneficial to work with a CDMO able to conduct small-scale development and manufacture (D&M), while also offering in-house scalability for late-stage clinical and, ultimately, commercial supply. This flexibility, and access to an extensive range of equipment and processes, ensures that various challenges can be addressed, and the most suitable solution for each unique project can be found. A major benefit of in-house scalability is that no additional tech transfers are required; switching CDMOs throughout the product's lifecycle can be costly and introduces additional risk.

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But equipment and facilities are only as good as their staff. Successful D&M requires strong cross-functional collaboration between highly experienced teams across a variety of disciplines, such as analytical, manufacturing, quality assurance and control and, of course, formulation development. A deep knowledge of their equipment and processes, and a strong awareness of alternative D&M methods enables them to determine how various formulation attributes can impact the final drug product, both positively and negatively, and advise their sponsors accordingly throughout the process.

Shawn Cain: You should be searching for a CDMO that has both the analytical equipment and experience to efficiently develop or transfer your analytical methods. If you select a core team that has the experience and flexibility to work with new products or technologies, you can always acquire equipment to support complex or novel technologies. Without

effective analytical capabilities in place, it would be difficult to develop and manufacture the product.

A CMDO that supports multiple products in various countries is another critical factor if you plan on trialling or commercializing your drug products globally. If so, the regulatory support you'll need is multifaceted. Another question to ask is: is your selected CDMO experienced with drug product, medical device, and combination products? If so, this demonstrates that the CDMO's quality systems are robust and flexible enough to meet the requirements of a specific region.

Other fundamental questions to ask of your CDMO candidates are:

- What is their regulatory inspection history? Have they been successfully audited by major regulatory bodies, such as the FDA, EMA, MHRA, or ANVISA?
- Is your product in its final presentation, or is additional work needed? And if so, does your CDMO have development capabilities and phase appropriate guidelines in place?
- If your product requires lyophilization to ensure stability, does your CDMO have the experience and equipment to develop an efficient, but robust lyophilization cycle?

For example, analytical research equipment for lyophilization development, such as Modulated Differential Scanning Calorimetry (mDSC) and Freeze-Dry Microscopy (FDM), help define and understand the physical characteristics of the formulated product, such as a product's freezing point, glass transition, eutectic temperature, and collapse temperature. This enables the CDMO to tailor a lyophilization cycle that will produce a stable and elegant pharmaceutical product. Additionally, the use a 'sample thief' to collect numerous samples during development lyophilization runs to assess moisture content or residual solvents in real-time can be instrumental in establishing an efficient secondary drying cycle and to fully characterize the lyophilization process parameters.

Louise Carpenter: From a solid oral dose perspective, understanding the CDMO's containment strategy is vital when outsourcing highly potent programs. You need to understand the containment measures in place and the level of potency the facility is able to handle safely. Oncology dominates the formulation development market, with a 25% share in 2022 and an estimated Compound Annual Growth Rate (CAGR) of 8.3% to 2030[2]. Around half of oncology drug candidates contain highly potent APIs, so along with scalability and development capabilities, safe handling of these dangerous substances is a key consideration.

ARTICLE

Cleaning Validation and Verification in a High Potent Granulation Suite

Q: What are the main challenges facing CDMOs during D&M programs?

Louise Carpenter: Clients occasionally withhold critical reports and information about the product or overall project strategy, preventing their CDMO partner from analysing the data themselves and being able to develop a longer-term strategy for their product. This lack of transparency can lead to issues that surface when problems arise, making it difficult for the CDMO team to address them effectively. It also means the CDMO's processes are generated based on second-hand information, increasing the risk of critical information being missed by the CDMO.

Another challenge is the establishment of unrealistic or aggressive timelines, which can force the acceleration of development activities. This rushed approach may create problems during later stages of development and scale-up, potentially compromising the overall success of the project, as more formulation development may inevitably be required at a later, more time-critical stage.

"Another challenge is the establishment of unrealistic or aggressive timelines, which can force the acceleration of development activities."

Shawn Cain: The ability to perform analytical or bioactivity testing quickly after each experiment or lyophilization cycle allows the program to move as efficiently as possible through the experimental design plan. Outsourced testing could become a bottleneck for a development program if turnaround times to receive test results take longer than originally anticipated. Planning ahead is critical.

Another important factor is the early understanding of the container closure system and the nature of the filters used to sterilize the product. In today's supply chain, choosing a filter, stopper or vial that is not available slows down many development programs; it's not uncommon to experience lead times over 50 weeks with some components. When choosing key product components, there should be a risk-based approach taken with considerations of secondary suppliers, purchasing strategies, and key alliances. This could ensure on-time development of your program, avoiding delays to clinical and commercial timelines caused by supply chain difficulties.

Louise Carpenter: Limiting the amount of development activity prior to the clinical trial manufacturing (CTM) stage can also pose difficulties. Of course, limited development can be the result of a limited budget, but open and honest discussions during proposal stages enables the CDMO partner to advise what is possible within the sponsor's proposed budget.

Similarly, a limited supply of API can result in compressing multiple trials into a single batch. This reduces the usefulness of the data produced, making it challenging to draw meaningful conclusions from the results. Again, often this may be beyond the client's control, but it does have an impact on the quality of formulation development activities and the data gleaned during the process.

Q: What can sponsors do to maximise the efficiency of D&M programs?

Shawn Cain: Talk with your CDMO early to ensure the stability-indicating methods are optimized. CDMOs with the capability to develop methods in-house can work with you to execute multiple development activities in parallel. The more information you can share with the CDMO about your molecule's solubility, stability, pH sensitivity, intended route of administration, and possible degradation pathways (light, oxygen, temperature), the quicker the development team can get your product to the clinic—and, of course, to commercial launch.

Louise Carpenter: It's essential to perform excipient compatibility and forced degradation studies upfront. These studies help identify potential incompatibilities or stability issues early in the development process, allowing for timely adjustments and mitigations.

Considering the scale-up process during development stages is also important. Doing so enables the formulation team to design processes that are more easily scaled, reducing potential challenges and delays during the transition from development through clinical to commercial manufacturing. Considering scale-up early, along with clearly defined scopes of work, improves the workflow between the formulation and manufacturing operations teams within the CDMO, and contributes to a strong collaborative relationship between the CDMO and their sponsor—a relationship based on effective communication and a deep understanding of the long-term program goals.

ARTICLE

Accelerating Drug Development Using Robotic Sterile Fill-Finish Platforms

Shawn Cain: It's advisable to take a proactive approach to ensure phase-appropriate development to speed up progress and minimize API or BDS loss. A few examples of this would be to develop an intravenous formulation for your Phase I clinical studies, even if you know you'll be going to subcutaneous or intramuscular administration in the future. The same can be true of opting for a simple vial presentation for your early-stage work while you're finalizing your dosage or going with a frozen liquid at an early stage, instead of spending the time and money on lyophilization development and manufacturing. If the clinical program is successful, you may

choose to spend additional time and money on further development as the product progresses through the clinical stages.

One newer technology that allows one the opportunity to explore speeding up the time to GMP clinical supply is a small-scale fully robotic fill-finish system. These advanced technologies not only expedite the filling process with automation, but also enables the flexibility to pivot between filling multiple dosage formats, bringing even broader sterile fill-finish solutions to PCI clients across the entire drug product lifecycle and bringing therapies to market with increased speed and safety.

Q: Can you briefly describe a real-world case study where D&M programs have been affected by poor strategy?

Louise Carpenter: One customer had experienced issues related to powder static and poor flowability of the blend during the development phase. However, this critical information was not shared with PCI at the time. It only came to light when the client requested that we use debossed tooling on the tablets. During the scale-up of the project using the new tooling, tablet splitting issues were observed halfway through the production run. The investigation into the cause revealed that the client had experienced these issues during the development phase.

Powder characterization is essential, as it provides insights into critical powder properties, such as particle size distribution, morphology, density, and flowability. In this particular case, powder characterization of the blend during the development stage could have identified the issue with static and flowability, allowing the problem to be addressed during development rather than at the scale-up phase.

"Powder characterization is essential, as it provides insights into critical powder properties, such as particle size distribution, morphology, density, and flowability."

A thorough understanding of powder properties and their impact on processing performance is crucial for the successful development of solid dosage forms. Techniques including particle size analysis, bulk and tapped density measurements, angle of repose, and shear cell testing can be employed to assess the flow properties of a powder blend. With this information, formulation scientists can modify the blend composition or implement suitable processing techniques, such as granulation, to enhance the flowability and processing performance of the blend.

Shawn Cain: PCI sees hundreds of programs every year. We see regulatory strategies employed that are accepted, and others that are rejected. Just this past year, we worked with several smaller companies to develop

plans for phase appropriate CPP (critical process parameter) development, scale-up, and filter and stopper pressure validation leading to successful process validations and filings. However, some clients are set on using their own strategy rather than tapping into our expertise, which has led to challenges that could have been avoided.

We had one client who wanted to move forward without performing mixing studies, resulting in two failed batches due to out of specification (OOS) results. Another client wanted to perform concurrent Process Validations (PV) with their regulatory submission. We advised them that the Agency was not always open to this approach. They filed anyway, and it was not accepted.

It's important to remember that the right CDMO is there to help you achieve your clinical and commercial goals. They know their processes and equipment trains, and have a vast amount of experience in their areas of expertise. By identifying the right CDMO and establishing a strong collaborative relationship during the development stage, sponsors can be rest assured that their drug product will achieve speed to patient, study, approval, and commercial launch.

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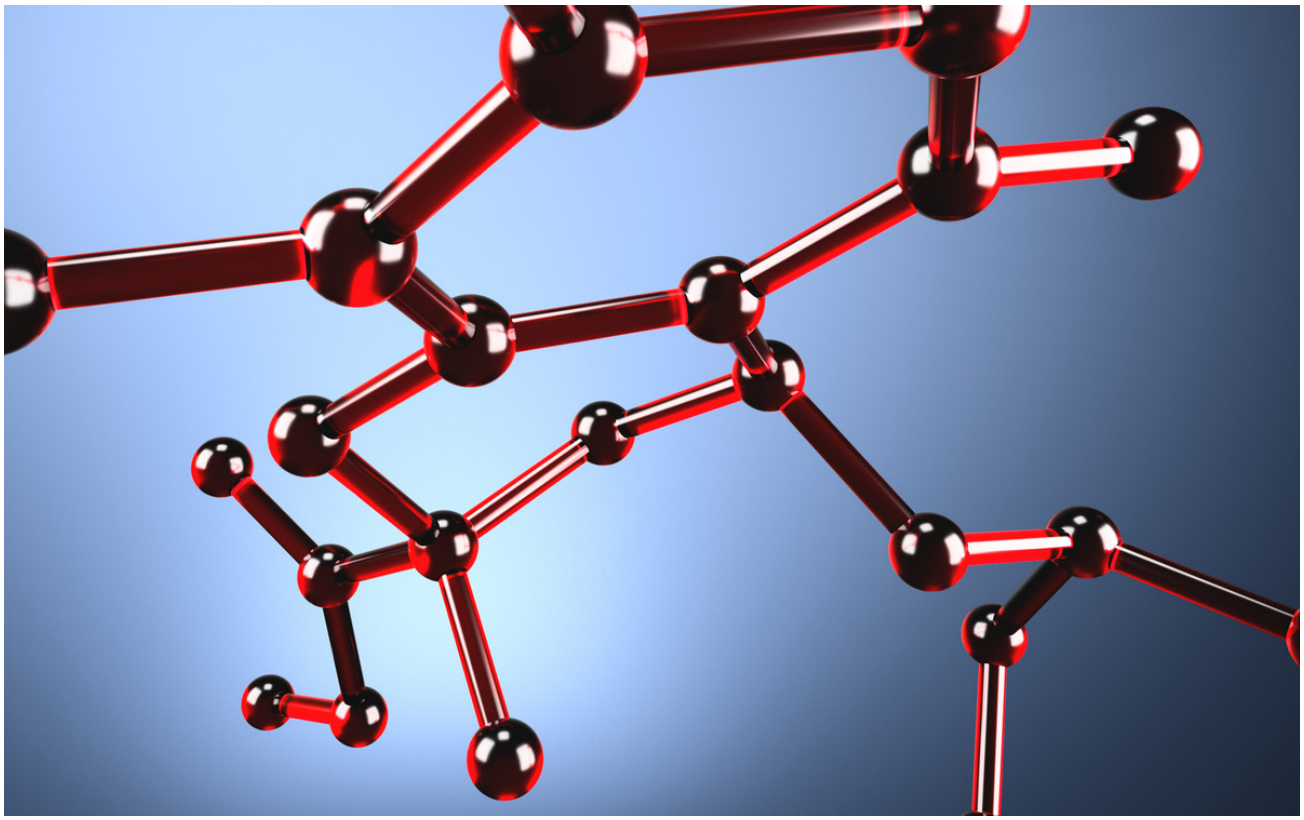

Clinical Trial Supply

By partnering with specialized CDMOs, companies can leverage their expertise, state-of-the-art facilities, and streamlined processes to ensure efficient packaging and labeling of investigational drugs.

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The pharmaceutical industry landscape is dynamic and ever evolving. With the market predicted to grow at a CAGR of around 8% to 2028[1], and the number of clinical trials conducted globally increasing each year, outsourcing clinical packaging and supply has emerged as a strategic choice for pharmaceutical companies seeking to optimize their operations and streamline the drug development process, ultimately ensuring speed to market for their life-changing therapies.

Industry-leading CDMOs have witnessed first-hand the transformative and positive impact of outsourcing on clinical packaging, supply, and logistics. By partnering with specialized CDMOs, companies can leverage their expertise, state-of-the-art facilities, and streamlined processes to ensure efficient packaging and labeling of investigational drugs. This, in turn, enables companies to focus their internal resources on core competencies such as research and development. Furthermore, outsourcing clinical packaging provides flexibility, scalability, and cost-effectiveness, allowing companies to adapt to changing market dynamics and manage their budgets more efficiently.

Preparing for Change

In an industry where dynamic growth is the norm, change is inevitable. To prepare for change, a leading CDMO should focus on embracing new technologies, ensuring regulatory compliance, offering customized solutions, building reliable and visible supply chains, and enhancing quality control processes.

It is vital for CDMOs to embrace and integrate the latest technologies and innovations available in the industry. This includes, but is not limited to, smart packaging technologies, eco-friendly materials, personalized packaging solutions, and systems that allow real-time visibility of data, and CDMOs should invest heavily in research and development to stay ahead of the curve and ensure they can offer their clients the most innovative and efficient packaging solutions.

There is a growing demand in the clinical packaging industry for customized and personalized packaging solutions. Such a demand requires building strong partnerships with sponsors to understand their unique requirements, which enables CDMOs to offer tailored solutions that meet the specific needs of each sponsor's project, such as customized and digital labeling, serialization, and tamper-evident packaging options.

ARTICLE

PCI clinicalSMART™: A SMART Solution to Clinical Supply Management

Additionally, clinical trials involving cell-based therapies are becoming more and more common. Whilst many are manufactured and delivered straight to the patient for autologous use and are labeled at source, other heterologous products are emerging that are stored in vapour phase nitrogen and are cross matched to patients. These products need to be individually labeled and 'kitted' for the patient on demand, without thawing the materials. Therefore, operational and QP models that support the fast turnaround of these materials need to exist. The duration from receipt of order to packaging, QP certification and despatch sometimes occurs quickly, in as little as a few days.

It almost goes without saying, but regulatory compliance will continue to be a critical aspect for the industry. To operate at the highest level, CDMOs should ensure they are up-to-date with local and international regulatory requirements, are successfully audited by leading global regulatory bodies, and consistently adhere to Good Manufacturing Practices (GMP). By focusing on being audit-ready at all times, CDMOs are well-prepared for potential regulatory changes and are agile in their approach to adapt their internal processes and procedures to comply with any new regulations.

To operate at the highest level, CDMOs should ensure they are up-to-date with local and international regulatory requirements, are successfully audited by leading global regulatory bodies, and consistently adhere to Good Manufacturing Practices (GMP).

It is, therefore, clear that CDMOs need to continue to evolve and adapt, without losing focus on enhancing their quality control and assurance processes to ensure their products meet the highest quality standards. Alongside this, other core concepts remain integral to success, including investment in staff training, equipment, and infrastructure, to ensure their processes remain efficient, effective, and ahead of the curve.

Capabilities, Experience, Expertise

A broad yet in-depth range of capabilities, experience, and expertise is crucial for an industry-leading CDMO in the clinical supply arena. This includes packaging design and development, regulatory understanding, robust quality oversight, strong procurement, technical expertise, innovative technologies, and the flexibility and agility to support clinical and packaging operations effectively.

With the expectation from clients that their CDMO has leading speed to market capabilities, technology is paramount to that realization. Speed cannot compromise patient safety and regulatory compliance; technology will be foundational to that success. Smart and reactive inventory management solutions, late-stage labelling and packaging customization, and effective digital project management tools are all great examples of solutions that will drive this effort.

Excellent communication between the clients, project managers, and operations is essential, and digital platforms that enable access to real-time supply chain data provide an additional benefit (where such systems are available). For example, PCI has developed an in-house digital supply chain management platform; **pci | bridge™**, which allows clients access to this crucial data in real-time. As most projects are global, providing clients with this platform irrespective of time zone has proven highly valuable.

Being able to offer a wide range of storage temperatures and packaging at cold and frozen temperatures is a requirement, as a greater number of vaccines and gene therapies are being subjected to clinical trials. This capability is best supported by a strong global distribution network that includes depot partners for regions not directly supported by sites within the CDMO's network. It's also important to note that global distribution services incur a carbon footprint; it is becoming increasingly important to reduce this where possible—to recommend storage and distribution options and shipping systems that reduce the overall carbon footprint whilst maintaining product integrity.

Common Challenges and Strategies to Ensure Success

When supplying clinical trial materials, the most complicated packaging solutions occur when the clinical trial is blinded but the Investigational Medicinal Product (IMP) has not been manufactured to match the material it is blinded against. The complexity may vary, from the manufacturer printing the batch number onto a vial closure that has to be removed before packaging; over encapsulation of tablets and capsules to hide the differences between dosage form and strength; different coloured caps or crimps used on vial or bottle closures compared to the comparators; or different vial sizes used for the IMP compared to the comparator. Ultimately, the blinding solutions must be fit for purpose.

Other common challenges with clinical packaging include:

- **Moisture and Contamination:** If the packaging material is not sealed properly or is not moisture resistant it can lead to drug degradation, with the client's life-changing therapy becoming less effective, or even contaminated. Moisture can also cause the packaging material to deteriorate, which can lead to the loss of the drug's potency.
- **Compatibility Issues:** These may arise if the packaging material is not compatible with the drug's chemical composition. Again, this can lead to drug degradation, loss of potency, or even toxic reactions. It is, therefore, vital to ensure that the right packaging material is chosen based on the drug's properties.
- **Labeling Errors:** Clear, accurate, and legible labeling is critical. Labeling that is unclear, illegible, or incomplete can lead to confusion about the drug's dosage, administration, and potential adverse events. This can be a substantial challenge with small vials and in scenarios where cold chain packaging is required.

Any problems encountered ultimately result in delays to the project's clinical and commercial timelines. There are several key strategies that sponsors may consider, which can help overcome such issues.

- **Collaborating closely with packaging suppliers** ensures that the packaging materials are designed and manufactured to meet the specific needs of their drug products. This can help avoid compatibility issues, reduce the risk of contamination, and improve efficiency in the supply chain.
- **Investing in innovative packaging technologies**, such as smart packaging, can help to improve the safety, efficacy, and convenience of drug products. Smart packaging can also help to reduce costs and improve efficiency in the supply chain.
- To ensure the quality and safety of drug products, sponsors should **conduct thorough testing of packaging materials and processes**. This can include testing for compatibility, stability, and moisture resistance, as well as conducting validation studies to ensure the packaging meets regulatory requirements.
- **Sufficient stability data** is vital to enable packaging to take place with minor temperature excursions. This will speed up QP release of product, as there would not be delays where investigations into the excursions are required.
- Where possible, clients should strive to **establish product stability at temperatures that are routinely commercially available**. For example, routine frozen storage temperature is -15°C to -25°C. Products requiring storage below -20°C cannot be stored in the same variable freezers, instead requiring the purchase and validation of individual storage units. It's not unusual for this situation to potentially add months onto the start date for storage and packaging activities.
- **Consider commercial pack design earlier in the drug development process**. This is usually left until the last minute, with third-party design agencies brought in to design a commercial pack. Whereas the third-party design may tick the boxes in terms of branding, it often won't fit on the CDMO's equipment trains, resulting in expensive capital expenditure purchases or the need to redesign the pack to fit on the commercial lines. Partnering with a CDMO capable of designing prototype packs during clinical phases is the ideal solution here, saving huge amounts of time and money in the process.
- Lastly, sponsors can **prioritize sustainability** by choosing eco-friendly packaging materials and promoting responsible disposal practices. This helps to reduce the environmental impact of pharmaceutical packaging and improve the company's reputation among consumers and investors.

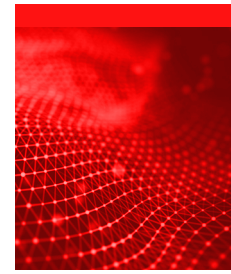
Case Studies

It's not uncommon for clinical trial start dates to be missed due to improper trade compliance planning, as clients are caught off-guard by the requirements for importing products into the US for study start-up. It is crucially important to consider the FDA

requirements for IND approval before the drug product is imported for clinical use in humans, including the FDA end use, which must be classified correctly to avoid unnecessary customs holds. Choosing a manufacturer that is located within the country of study start-up is a clear solution but, admittedly, this is not always attainable.

One solution is to use a site in Canada (or within the country of manufacture) for pre-IND support to prepare the drug product for clinical use, which can shave valuable time off study start-up and FPI target deadlines. For example, a CDMO with a presence in Canada would be able to pack the drug product whilst awaiting FDA approval, with the product then ready to ship once approval is received. On many occasions, we have seen clients set targets for study start-up that prove impossible to achieve, solely due to the inability to import the drug product into the country where the study is destined to start. Working closely with your supply chain partner and trade compliance experts will allow sponsors to avoid this costly mistake.

Given the ever-increasing number of clinical trials around the globe and the growing demand for speed to clinic and to market, the need to partner with the right CDMO is becoming more significant.



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Another specific example includes a client whose injectable material was manufactured to match the United States version of the comparator drug. In the EU, it is a requirement that any comparators used are sourced from within the EU. However, in this instance, the EU version of the comparator had a different vial size to the US version. As such, a drug carton had to be designed that contained an internal shelf to lift up the comparator product so it appeared to be the same size as the IMP. A window was also built into the designed carton to allow the material to be extracted via syringe, whilst ensuring it didn't compromise the blinding of the products. The packaging also needed to be robust enough so the drug product could not be removed easily at the site.

The time and cost of this carton design was an expensive and complicated process and proved challenging, adding significant time to the packing runs that, therefore, resulted in increased packaging costs. As it was possible to use the EU drug in the US, the IMP would have been blinded to the correct EU comparator, significantly reducing the time and costs involved.

Summary

Given the ever-increasing number of clinical trials around the globe and the growing demand for speed to clinic and to market, the need to partner with the right CDMO is becoming more significant. Sponsors should conduct their due diligence with care, asking the right questions of their prospective CDMO partners, and should establish an open, honest, and collaborative relationship with the aim of avoiding costly mistakes and hitting those vital clinical and ultimately commercial deadlines.

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Commercial launch is the critical endpoint of the drug development journey, and industry-leading CDMOs know first-hand what it takes to ensure it is achieved as seamlessly as possible.

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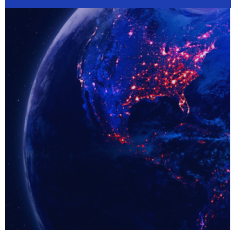
All roads in pharmaceutical outsourcing lead to one destination: commercial launch. It can take many years to get there, and a recent Deloitte study indicated that the average cost of developing a new drug candidate can exceed $2 billion[1]. Not only does the drug development process require vast amounts of money, but there are also patients around the globe who desperately need your drug product to improve their lives and alleviate symptoms or even cure their disease. Commercial launch is, therefore, the critical end-point of the drug development journey, and industry-

leading CDMOs know first-hand what it takes to ensure it is achieved as seamlessly as possible.

Trends and Challenges in Commercial Packaging

According to a recent report by IQVIA , oncology is recognized as as the fastest-growing driver of drug development, representing around 38% of the R&D pipeline, or a 10.5% CAGR over the last five years[2]. Avancements in science and technology, alongside a better understanding of the biology, immunology, and genetics of cancer, has lead to the development and approval of powerful targeted therapies that are capable of causing the complete durable elimination of tumours.

Precision oncology is transforming the way patients are treated. Many patient are receiving precision targeted immunotherapies that are tailored specifically to their disease. By their nature, targeted cancer therapies are more complex than conventional chemotherapies, often classified as being highly potent and requiring more specialized formulation develpoment techniques. As such, they require specialized facilities, equipment, and contained processing technologies, both in terms of commercial manufacturing and packaging.



RESOURCES

Package Design Solutions: Ensuring Speed to Market

The growing complexity of commercial pharmaceutical packaging places greater demands on CDMOs to meet the requirements of the end user and the nature of the drug product itself. The reasons for this increased complexity include, but are not limited to:

1. Protection and preservation of the drug product;
2. Safety concerns (such as child-resistant/ senior-friendly/tamper-evident packaging);
3. A drive towards reducing the overall environmental impact of packaging operations;
4. The need to deliver increasingly complex therapies to patients;
5. A shift towards ‘new to market’ products in injectable formulations, moving away from the Oral Solid Dose bias (although OSD remains a large driver of commercial market growth);
6. Ability of the CDMO to scale up manufacturing and packaging from clinical to commercial scale to meet launches and ongoing demand forecasts;
7. and creating an efficient end-user experience, particularly for patients administering the drug product themselves.

Self-administration of injectable or combination therapies, in and of itself, creates unique challenges in commercial pharma packaging, especially alongside the other trends listed above. When it comes to self-administration, the aim is to make

things as clear and simple as possible for the patient, which usually means a much more complex design process for the commercial pack. This is due to many factors, including device protection, thermal impact on the drug product, disposal of the packaging into multiple green channels, and clear direction of use for the patient's self-administration.

Thermal stability requirements mean that cold- and ultra-cold chain storage conditions are a necessity, particularly for live vaccines. Drug products stored in frozen conditions, usually between -20°C and -80°C, and packaged at refrigerated or ambient conditions require close monitoring. As a result, space becomes a vital factor in commercial pharmaceutical packaging. Not only are the processes for packaging biologics a lot larger and more complex than classic OSD blistering and bottling lines, but they often require storage temperatures between -20°C and -80°C for both bulk and finished products. Therefore, the space required for cold chain storage cannot be underestimated.

Not only are the processes for packaging biologics a lot larger and more complex than classic OSD blistering and bottling lines, but they often require storage temperatures between -20°C and -80°C for both bulk and finished products.

When selecting your CDMO partner, you might ask whether they are able to perform semi-automated frozen packaging solutions for vial products that cannot exceed 0°C, with typical temperatures between -20°C and -80°C. Such a process requires a specialized vial labeller that retains ultra-cold conditions, prior to operators manually placing the vials into the final carton. The benefits of semi-automated frozen packaging are:

- Higher operational efficiency;
- Lower quality risks, and;
- Lower safety risks.

The second and third benefits listed above are critical when it comes to the packaging and storage of high-value frozen drug products. Ideally, your CDMO would have their semi-automated commercial frozen packaging processes adjacent to their clinical packaging processes, as this simplifies the supply chain and mitigates the risk of the drug product being exposed to ambient temperatures.

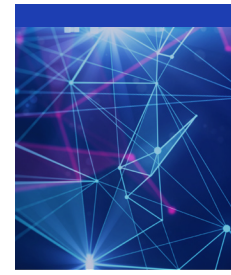
The demand for increased complexity coexists alongside industry pressure to lower dosage costs, provide resilience in the supply chain, and reduce overall time to market. These opposing forces are driving a technology and mind-set shift within the CDMO space and is something that will continue into the foreseeable future. But there's a solution to this inevitable bottleneck, which, though apparently simple, involves a mind-set shift within sponsor organizations.

Go Early and Go Deep

Early commercial engagement in the drug product lifecycle is becoming an increasingly important factor in a successful, timely commercial launch. The core message here, therefore, is 'go early and go deep'. By engaging the advice, expertise, and services of your chosen commercial CDMO partner early—ideally during Phase II to III—you ensure that processes involving long lead-times are factored in, alongside adequate research into the drug delivery platforms and their specific technical requirements. However, the hidden message here is to partner with a CDMO that is able to scale their processes from clinical to commercial supply early; all too often, sponsors partner with smaller CDMOs during early phase clinical supply, only to establish processes that need re-engineering at a later stage, increasing costs, delaying timelines, and adding a layer of complexity and risk to the drug development process.

Successful commercial packaging relies on the harmonization of *materials*, *design*, and *process*. If these three elements do not complement each other, the road ahead for both the CDMO and the sponsor organization will almost certainly be rough. Within each element there are hundreds of questions and considerations to discuss in order to find the optimum balance, and that is only achievable via strong collaboration with a CDMO partner that has adequate experience in commercial supply.

Sponsor organizations regularly work in isolation with design agencies for their commercial pack designs, without the input or knowledge of their CDMO partner. The core issue here is that, whereas the pack might tick the boxes in terms of branding and general 'look', there is little or no thought of how that pack will be manufactured, the protection it will provide, or the end-of-use disposal. The result: a clever, novel design that requires hand-packaging at a much greater cost, because automation costs are prohibitive when the product is not provided with the level of protection it needs.



WHITE PAPER

Optimizing Your Clinical Trial to Commercialization Journey

Case Study #1: Short-Term Solutions, Long-Term Loss

During the early clinical phases of a sponsor's drug product lifecycle, their CDMO partner of the time advised them to use stock tooling to blister pack their oral solid dosage form to place on stability. The reason was simple enough: they wanted to save money. However, whereas this is understandable to a degree, the cost savings at the time was only around £2,000. The sponsor went ahead with the stock tooling, which created a blister cavity that was oversized in comparison to the drug

product. They placed the blister pack on stability in cold form only, and the product eventually received Fast Track approval from the FDA.

Later, when the sponsor engaged with PCI to establish a commercial packaging process ahead of their drug product's launch, the pressure was on. Due to the Fast Track approval, and the suboptimal blister packaging process established with the previous CDMO partner, PCI was handcuffed to the same process. When packaging the drug product into this large, oversized cold form cavity, it naturally resulted in a large blister pack. The result was a maximum of two blister packs per cycle, and a lower output alongside the pack being too large for a standard cartoner ultimately resulted with a higher Cost of Goods (COGs) for the client.

Had the sponsor engaged with PCI during Phase II to III, a Value Engineering Program would have been conducted to produce an optimized blister pocket. This would have resulted in PCI being able to produce an additional blister pack per cycle for the sponsor and a higher CPM with the added benefit of automated cartoning. By making these changes, the sponsor would have benefited from:

1. Reduced lead times;
2. Reduced costs of goods, and;
3. Reduced environmental impact of their overall commercial packaging process.

Case Study #2: Dual Sourcing with an Integrated CDMO

Sponsors benefit hugely when partnering with a CDMO that is able to integrate commercial packaging and manufacturing services, particularly when it comes to establishing a dual sourcing strategy for a commercial drug product. The FDA draft guidance released in 2022 recommends that "stakeholders develop, maintain, and implement risk management plans (RMPs) to proactively assist in the prevention of human drug product and biological product shortages. RMPs can provide stakeholders with a framework to proactively identify, prioritize, and implement strategies to mitigate hazards that can cause a supply disruption. Such a supply disruption may lead to a drug shortage."[3]

Sponsors benefit hugely when partnering with a CDMO that is able to integrate commercial packaging and manufacturing services, particularly when it comes to establishing a dual sourcing strategy for a commercial drug product.

A global biopharma company approached PCI to secure the supply of a high value, highly potent drug product. It was emphasised that an integrated solution was an essential part of their risk mitigation strategy, with the dual sourcing partner

required to absorb up to 100% of their annual demand. A key consideration was PCI's UK-based Contained Manufacturing Facility (CMF), which is able to handle potent products to an OEL of 0.01 µg/m^3. The combination of potent manufacturing capabilities and the global network of commercial packaging sites was fundamental to the sponsor's needs, with the complexity of vendor management reduced by selecting a single dual sourcing partner.

Through their due diligence, and through PCI's integrated outsourcing solutions, the sponsor benefitted in a number of ways, such as:

- **Risk mitigation**, via immediate continuity of supply for their high value, life-saving therapy.
- **Agility and flexibility of supply**, as a second source provides additional capacity to absorb any unexpected increases in demand.
- **Geopolitical benefits**, with additional manufacturing and packaging locations leading to more local supply, therefore reducing distribution costs and carbon footprint.
- **Added product value**. in the event a drug product is out-licensed, or sold to another owner, a robust dual sourcing strategy adds significant value to that drug product.

Elements of Successful CDMO Partnership

There are three main aspects to a successful partnership between the sponsor company and their CDMO partner:

1. Working with one CDMO throughout the drug product life cycle ensures a deep understanding of the product and maintains the necessary level of knowledge and experience. Transferring between CDMOs is not a straightforward task. Working together to deliver an end-to-end solution and navigate challenges along the way leads to success.
2. The process by which a CDMO is chosen is also critical. The assessment criteria should not only take into account the CDMO's technical capabilities, but also the more subjective factors, such as how the company communicates, how they approach a problem, their proactivity, and the emphasis placed on building a true partnership, whereby the CDMO becomes a seamless extension of the sponsor team.
3. Thirdly, the continual education of employees about the nature of the actual drug product is more vital than ever. It elevates care and ownership to a different level, as it encourages staff to truly understand the impact of their role within the CDMO in human terms (i.e. improving or even saving lives).

Sponsors should view their CDMO partner as a travel companion—someone they'll journey with throughout the drug product's lifecycle. Challenges are inevitable, but partnering with the right CDMO, at the right time, ensures that challenges are met with industry-leading technology, experience, and expertise. It is, therefore, strongly advisable to find the right CDMO partner for your needs, and take the right care to consider the broader aspects of how a CDMO operates.

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Support Services & the Holistic Approach to the RFP Decision Making Process

The provision of non-core support services is what differentiates the good from the great, and sponsors should consider the impact of such services when developing their RFPs.

AUTHOR:

Justin Schroeder
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PCI Pharma Services

In the current pharmaceutical landscape, CDMOs are ubiquitous. But until the CDMO boom in the 1990s, this wasn't the case. What began in the 1980s as an industrial stopgap to fulfil capacity needs is now conservatively projected to become a $170+ billion-dollar market in 2032.[1] Naturally, when an industry grows so quickly, so does the evolution of service offerings, such as the ability to handle multiple dosage forms, scalability from early clinical supply to commercial launch, and the continued investment in, and expansion of, industry-leading technology and facilities.

However, whereas reports estimate that over 500 CDMOs are currently operating around the globe,[2] only a small percentage are able to serve in a consultative capacity and perform non-core, value-added functions alongside the core functions of development and manufacture, clinical trial supply, and commercial packaging. The provision of non-core support services is what differentiates the good from the great, and sponsors should consider the impact of such services when developing their RFPs.

Package Design for Manufacturability (DFM)

Whereas the core services of D&M, clinical supply, and commercial packaging remain the core drivers of On Time, In Full (OTIF) delivery, there are a range of support services that a CDMO may offer that can help streamline the overall drug product journey. Package design is one example.

Traditionally, these services have been outsourced to third-party agencies that produce a design based on the dosage form and the sponsor's branding requirements. On paper, this process can produce a slick, branded package that is suitable for the selected dosage form. However, when package design is not performed with *manufacturability* in mind, it can cause significant challenges that may add both cost and time when it comes to manufacturing the commercial pack at the selected CDMO.

VIDEO

Discussing Advancements in Oncology With Tim Roberts

For example, if the design specifications do not fit the CDMOs packaging equipment, it must either be re-designed or the sponsor must consider purchasing suitable equipment for the required specifications. Combine this with the fact that the package design is often regarded as an afterthought, only to be considered at the very latest stages of drug development, and the result is a significant cost- and time-loss implication at a crucial stage of the drug development journey.

The solutions here are twofold:

1. Sponsors should consider package design much earlier in the drug development process. Whereas not all drug products will reach the market, good preparation is strongly advised to avoid costly launch delays.
2. Sponsors can partner with a CDMO that is able to offer package development and design services in-house. By doing so, sponsors avoid complicating their supply chain by outsourcing additional services, are able to review sample commercial packs during the clinical stages, and can save time and money in the process.

Taking a meticulous approach to package design ensures a much smoother road to commercial launch, particularly where the CDMO can provide in-house expertise and help support and design services from an earlier stage in the drug development journey.

The same is true for artwork services. Identifying a CDMO able to offer a full suite of services related to packaging services including in-house artwork services can, again, reduce vendor management complexity and drive efficiencies.

Supply Chain Management Solutions

Not all sponsor organizations have the resources or expertise to manage every aspect of their supply chain. Without dedicating internal resources, or recruiting additional staff, it becomes operationally complex and often unachievable within clinical and commercial timelines, especially when unforeseen difficulties emerge and threaten said timelines.

Imagine, for example, that a clinical trial has started, but it is discovered that the quantity of drug product packaged and supplied to trial sites is not sufficient to support ongoing site re-supplies to the end of the treatment period. Or, during the planning of a complex global clinical trial involving multiple dosage forms and inventory items, that the sponsor's internal Clinical Supply Manager resigns, creating a gap in support. In these situations, project delivery can depend on the ability of the CDMO to support their sponsors with immediate resources and expertise in the form of embedded personnel.

Releasing a drug product within the US requires a single stock keeping unit (SKU), but not all markets allow this level of simplicity. For example, releasing a drug into Europe involves producing artwork in many different languages, and potentially holding stock within each individual market awaiting commercial orders. The potential waste involved with pre-printing artwork for multiple SKUs is another negative, in what used to be the normal way of doing things. However, some CDMOs have moved towards HAPA digital printing as a way to achieve Late-Stage Customization (LSC), which revolutionizes the way drug products are commercially supplied across complex markets.

By producing commercial drug products in bulk and storing as brite stock, various markets can be supplied via a Just in Time model by utilizing HAPA digital printers and shipping the required order quantity without overstocking or wasting resources on excess materials and shipping fees. The ultimate benefit is a greater speed to market, whilst maximizing the use of product with short expiry dates and the reduction of line clearance activities.

ARTICLE

Pharmaceutical Research, Development, and Launches Can Save Lives — and the Earth

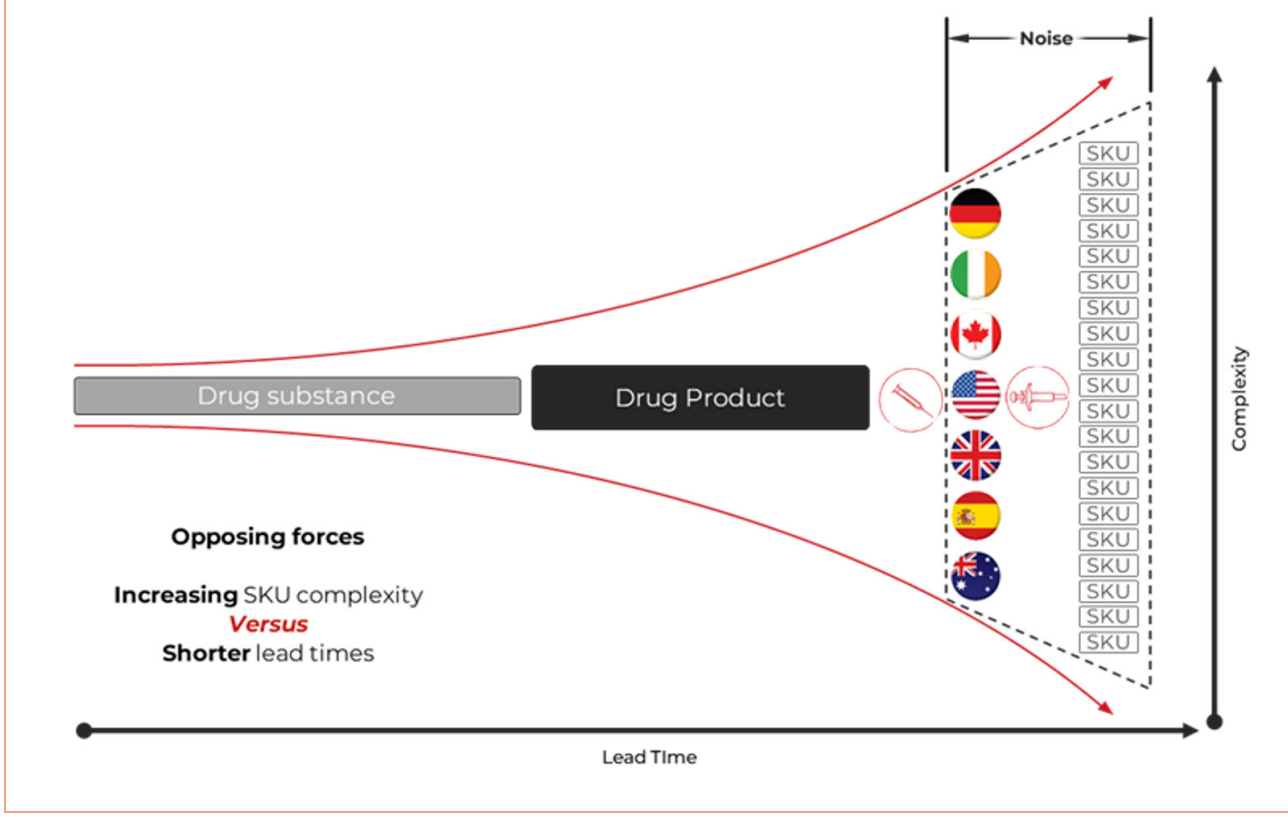
FIGURE 1 demonstrates a visualization of the 'Trumpet Effect', wherein a single drug product requires packaging into multiple SKUs for a multi-market destination, such as EU and RoW countries. Using LSC as a commercial packaging strategy reduces the overall complexity of the drug manufacturing and packaging process, resulting in shorter lead times and a quicker route to market for your drug product.

Partnering with a CDMO that is able to provide robust and varied supply chain management solutions is hugely beneficial. It ensures a lower-risk and more efficient supply chain, access to established expertise in a range of essential non-core services, and ultimately achieves greater speed to study and market for your drug product.

CDMO Selection

Due diligence is essential when selecting a CDMO partner. The RFP process often focuses on the core services and processes alone. Whereas many CDMOs can fulfil these requirements, the RFP may not involve a wider consideration of the full scope of what the CDMO is able to offer along the way to deliver a seamless solution and reduce vendor management complexity.

FIGURE 1: Visualization of the Trumpet Effect for Drug Manufacturing and Packaging



The following questionnaire aims to guide sponsors who are approaching or are actively participating in their CDMO selection process. Alongside the usual questions around core capabilities, this list also considers the wider scope of CDMO services that may help a sponsor achieve greater speed to clinic and, ultimately, market launch. The list covers three broad categories: Drug Development and Manufacturing; Packaging, Storage, and Distribution; and Support Services and Collaborative Flexibility.

PART 1

The RFP Questionnaire

Drug Development and Manufacturing

1	Does the CDMO have the development capabilities to perform any additional work that may be required?
2	Does the CDMO provide full in-house analytical services to support development and manufacturing activities?
3	Is the CDMO capable of scalable manufacturing processes, from early phase clinical supply to commercial launch?
4	Does the CDMO have the required *capacity* to scale alongside your product throughout the drug development lifecycle, and through commercial launch?
5	If your product requires lyophilization to ensure stability, does your CDMO have the experience and equipment to develop an efficient but robust lyophilization cycle?
6	What is the CDMO's track record in terms of solving complex formulation challenges, and are they able to provide case studies to outline any relevant examples?
7	If your product is an OSD containing a highly potent API, can your CDMO safely handle the molecule to ensure operator safety and product integrity?
8	Is the CDMO able to manufacture liquid formulations, in the event that your drug product requires a paediatric alternative in accordance with FDA guidelines?
9	Is the CDMO experienced with drug products, medical devices, and combination products relevant to your project needs?
10	What level of experience does the CDMO have, and are they able to provide relevant case studies outlining their problem-solving abilities?

Continued on next page >

PART 2

The RFP Questionnaire

Clinical and Commercial Packaging, Storage and Distribution

1	Is the CDMO able to provide artwork services to support your packaging needs?
2	Can the CDMO provide clients with real-time supply chain data via digital platforms?
3	Is the CDMO able to offer a wide range of storage temperatures relevant to your drug product needs?
4	Does the CDMO have the appropriate capacity to support cold- and ultra-cold chain storage of your drug product if required?
5	Is the CDMO able to provide semi-automated frozen packaging services?
6	Does the CDMO have a strong global distribution network, including depot partners, for regions not directly supported by the sites within the CDMO's immediate global network?
7	Is the CDMO capable of supporting the supply of multiple products globally?
8	What is the CDMO's record in terms of achieving successful commercial launch?
9	Can the CDMO offer an appropriate level of capacity to support commercial forecasts and potential increase in demand?
10	Is the CDMO willing to consider strategic investments to support large-scale, long-term commercial supply?

Continued on next page >

PART 3

The RFP Questionnaire

Support Services and Collaborative Flexibility

1	To what extent does the CDMO offer cross-functional support to clients?
2	Can the CDMO provide customizable solutions that are tailored to your specific project needs?
3	Does the CDMO offer in-house analytical support, including the transfer and development of analytical methods, as well as full release testing relevant to your specific project requirements?
4	Does the CDMO offer in-house Quality and Regulatory Support services for clinical and commercial supply?
5	How strong is the CDMO's regulatory inspection history?
6	Is the CDMO committed to embracing new technologies as the industry and your requirements evolve?
7	Do the CDMO's manufacturing and packaging facilities offer flexibility when accommodating new projects?
8	Is the CDMO able to provide, where needed, embedded or consultative support for clinical trial supply?
9	What is the CDMO's approach to continuous employee education and training?
10	Is the CDMO able to provide relevant case studies showing how they approached certain challenges?

The aim of the RFP questionnaire is to draw attention to the nuances of core service provision in pharmaceutical outsourcing and key considerations, as well as to the non-core service offerings that can help to de-risk your supply chain and maximise the efficiency of your drug product journey. It is inspired by decades of experience in a wide range of outsourcing activities, including thousands of successful clinical trials supported and hundreds of successful commercial launches. By raising awareness of the wider scope of pharmaceutical outsourcing, sponsors may experience greater success not only in their selection of the right CDMO partner, but throughout their journey from early phase development to commercial launch, and beyond.

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- **Are you eyeing a local market or seeking to conquer the global stage?**
- **How do you prioritize quality and regulatory compliance in your supply chain?**
- **What scale and volume requirements do you anticipate for your projects?**
- **Are you seeking end-to-end solutions or specific services?**
- **What's your ideal timeline for project initiation and completion?**
- **Does sustainability play a significant role in your outsourcing decision?**

Share these insights with our dedicated team, and together, we'll create a dynamic partnership that leads your business to unprecedented achievements. **Experience the power of tailored CDMO solutions** – contact us today!

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