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Accelerate your pipeline with CDMO collaboration

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Introduction

The opportunity – and challenge – of biomanufacturing

Innovative biotherapeutics are transforming the lives of patients around the world every day. They offer a powerful defense against serious medical conditions such as cancer, diabetes, and rheumatoid arthritis. Manufacturers are challenged to develop and deliver these products in a dynamic, ever-changing environment where speed and efficiency are critical.

While monoclonal antibodies have proven themselves for many years as a therapeutic modality for a wide range of human diseases, a growing focus on niche drugs for smaller patient populations has created a tremendous amount of change in the biopharma industry. Investing in a large facility for a single product is no longer a sustainable business model. Instead, pharma companies are looking to collaborate with CDMOs to augment their capacity and expertise, refine their processes, and ultimately shorten their time to market.

Choosing to work with a CDMO creates a new set of factors to consider. This e-book is designed to help you determine if working with a CDMO is right for you – and if so, you'll discover the best practices that make working with a CDMO as efficient as possible. You'll answer questions such as:

- Do we have the right in-house resources to do this work on our own?
- If we decide to build our own facility, can a CDMO help us to keep our molecule on track until the new facility is online?
- What do we have to gain by working with a CDMO? And what are the risks?
- What can I do to ensure a smooth tech transfer to the CDMO?
- What will the CDMO do to protect my intellectual property?

Companies who can adapt to this new paradigm of flexibility and agility in biomanufacturing will be the ones who succeed as the industry continues to evolve. And for every success, there's another group of patients in the world whose lives will be dramatically improved.

About the authors

Patrick Guertin, Global Technical Manager
Cytiva

Patrick Guertin is a Global Technical Manager for Cytiva's Fast Trak biomanufacturing team. With 30 years of experience in upstream process development and process optimization, he has helped develop and drive the application of single-use bioprocessing. His areas of focus include pilot plant operations, technology transfer and cGMP manufacturing of recombinant therapeutic molecules, monoclonal antibodies and vaccines. He has also been involved in new product initiatives, market support, and providing technical guidance for colleagues and clients.

Edward S. Hines, Global Technical Manager
Cytiva

Edward S. Hines is a Global Technical Manager for Cytiva's Fast Trak biomanufacturing team. With over 30 years of downstream process development experience, he has helped develop hundreds of purification strategies for recombinant therapeutic molecules, monoclonal antibodies and vaccines. His skills include HPLC and Electrophoresis methods, viral clearance study design, process modeling, downstream unit operations, cGMP regulations and membrane manufacturing. He has also been involved in new product initiatives, market support, and providing technical guidance for colleagues and clients.

Joseph Makowiecki, Director of Business Development
Enterprise Solutions, Cytiva

Joe has been in the Bioprocess industry for 24 years and has held management, senior management and director positions within Process Development, Pilot Plant, cGMP Manufacturing and Enterprise Solutions organizations. As Cytiva's Director of Business Development for Enterprise Solutions, his responsibilities include product management of the FlexFactory (single-use, flexible and deployable biomanufacturing platforms), strategy for both the FlexFactory and KUBio (modular facility solutions) offerings, new technology identification and integration, and commercial activation.

Joe's expertise and experience includes downstream process development, scale up, cGMP manufacturing, process technical transfer, manufacturing site operations, contract manufacturing services, bioprocess solution selling and business development. He has been involved with the development, technical transfer, scale-up and manufacture of multiple diagnostic, vaccine and bio therapeutic products from mammalian, microbial and insect expression systems.

Patrick McMahon, Global Business Development Manager
Fast Trak CDMO Services, Cytiva

Patrick McMahon is the Global Business Development Manager for Cytiva's Fast Trak biomanufacturing team. With 25 years of experience in business development, product management, and project management, he has helped bring several projects through to commercialization including Cinquil, Soliris, and Rituximab. His areas of expertise include process development, process transfer, operations and formulation/aseptic filling. He is experienced in supporting global regulatory and process validation requirements, managing biologics bulk drug manufacturing sites in the US and China.

Fast Trak CDMO Services

Supporting your biomanufacturing journey

Whether you're looking to manufacture toxicology batches or cGMP material for clinical trials, Cytiva's global Fast Trak™ team will help you expedite your molecules to clinic with full transparency. We deliver proven expertise to accelerate your pipeline:

- Cell culture medium development and optimization
- Process development and optimization for upstream and downstream
- Pre-clinical non-cGMP and cGMP clinical batch manufacturing, phase I and II
- Analytical development and QA/QC/Regulatory support
- Technology and process transfer

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Is not using a CDMO slowing down your process development?

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In today's biomanufacturing industry, drug manufacturers must navigate a changing landscape that is more diverse than ever before. Advances in science to address previously unmet needs are paving a new course in patient treatment while also challenging how drugs have traditionally been developed and manufactured. New technologies to increase efficiency and flexibility in small batch production, such as high-throughput technologies, modular equipment and single-use technology (SUT), combined with automated solutions create novel ways to produce drugs faster with better quality and safety oversight.

As a result, many companies are considering creative ways to expedite not only their timelines but also their knowledge and technical capabilities. And while adding capacity and expertise can help you remain competitive, so too can partnering with a CDMO to create and optimize biomanufacturing processes that can improve yield and reduce production costs. Doing so also allows you to delay any major financial decisions on your molecule until you see how it performs in the clinic. So, as you think about your internal strategies and what your next best step is, consider what process development capabilities you have versus what you could possibly gain from working with a CDMO to not only be successful but also improve your chances of getting to market sooner.

What you can gain from a CDMO

Infrastructure, experience, and expertise are key variables in achieving the time-saving efficiencies needed to get ahead. If your facility is still equipped with traditional or older technologies, you are already at a disadvantage. A CDMO can offer automated systems, such as those that can execute either the designs of experiment (DoE) or create the design space, allowing you to save time by generating meaningful process data using a scientific approach rather than guesswork. It is also important to establish a platform approach, whether it is bench scale, high throughput, or large-scale manufacturing, as well as the analytical capabilities that will not just support where you are now but also where you want to be in the future. If you do not already have these resources, you will need to increase your capital expenditures to obtain them, as well as the skilled staff to run them.

Using a CDMO with the capacity and advanced equipment you need and the large-scale experience necessary to utilize them properly and efficiently helps make the process more economical. Experience, in general, is important for a CDMO but having experience with a wide range of cell types and molecules is also beneficial, as working on various types of projects may help them anticipate what problems you might encounter and which solutions to use to address them quickly. Another benefit of working with an experienced CDMO is the knowledge and experience your staff will gain by working with a seasoned partner. This includes process development and cGMP manufacturing. For example, relative to cGMP manufacturing, each phase of clinical trials brings new demands for your product and your team. Knowing what information to provide to regulators and when can help expedite your clinical trial process, facilitating product approval and market entry. And as you continue through each phase, scale-up needs increase, particularly when you get into human clinical trials. Many companies lack the large-scale capabilities in-house, so having a CDMO on hand to help as the demands of your clinical trials change helps avoid major delays.

Finally, you not only benefit from expedited work and support along with a broad background of experience, but you are also strengthening your internal team through this experience. This support is especially important for companies working on multiple initiatives where prioritization becomes important. As your staff improves their base of knowledge and transfers some of their work to a CDMO, they also free up some time, which can then be dedicated to the areas where they are more skilled or focused, such as upstream or downstream. This creates more flexibility in decision making and where they ultimately dedicate their time. A company may even decide to outsource only those areas for which they lack the necessary resources, rather than the entire process development process, which is an option you can explore with the CDMO you choose.

What are the risks of working with a CDMO?

There are many benefits you can gain from partnering for process development, but it can be intimidating to share your product and your knowledge about it with a company that is offering the same services to your competitors. One of the biggest perceived risks of doing so is the loss of intellectual property (IP) rights when working with a CDMO. Companies want to know how their IP will be protected by their partner, which includes key components such as equipment, resins, etc. A nondisclosure agreement is also always implemented at the earliest stages and helps to ease the mind of the customer. At Cytiva, the goal is to build long-term relationships with customers rather than one and done transactions. That is why, if something is developed jointly with Cytiva, a customer is given a royalty-free license for that in perpetuity.

Another concern of many customers considering outsourcing as an option is that they will lose their decision-making capabilities. While some organizations may be rigid and uncompromising in their ability to collaborate with customers, it is important that a CDMO is flexible and operates in a collaborative way. The communication style and transparency of a partner are important factors when selecting your future CDMO. Look for one that has worked with a wide spectrum of customers, from large pharma companies to small virtual companies and even startups. This shows they have the willingness and ability to adjust to the needs of different customers, regardless of size and/or experience.

It is difficult to know in early stages what path you eventually want to take with your product (whether you manufacture it yourself, transfer to a different manufacturer, or eventually sell it to someone else), so you want a partner that empowers and enables you by developing a process that can be easily transferred to other organizations. They should maintain open lines of communication with you throughout the duration of the project, such as regular meetings to discuss the most recent data and the status of the development process compared to timelines and expectations. This allows the customer to stay in the loop and retain their decision-making ability and, if necessary, change the direction of the project or provide input that might be helpful.

How to evaluate your CDMO options

Determining the right CDMO for your project is often dependent on the scope of capabilities of your service provider. Do they perform process development through cGMP manufacturing and, if so, to what stage? Another very important consideration are your end goal(s). For example, if you do not want to invest in manufacturing capacity, then you will want to look at what the CDMO's capabilities are in terms of commercial supply. Do they have what you will need to meet your commercial needs? Will they be able to fit you into their schedule? Look for a CDMO that has flexible manufacturing solutions to fit your end goal. If you want to have your own manufacturing capabilities, choose a CDMO that can perform a reliable technology transfer of the process back to you as well as offer you solutions that fit your future capacity needs, such as a modular facility.

Use a high-level checklist with input from all relevant team members/departments to evaluate your partnering options. A site visit is also an important activity as you can not only view the site but also review the facility infrastructure, including equipment and building. This will give you a chance to interact face to face with the scientific and managerial team members who will be assigned to your project. When doing so, make sure there will be a dedicated project manager who will act as the main point of contact but allow direct communication between the respective subject matter experts from each team. Look for any red flags that may indicate potential issues down the road, such as a history of failed FDA audits or a refusal to let customers onsite during process steps.

Overall, find a CDMO that aligns with your desired outcomes for each stage and the milestones you need to achieve your end goal. Process development is an iterative stepwise process striving for process reliability and product safety, ideally resulting in robust cGMP manufacturing. If you struggle with buy-in from others within your company, help them understand this is a multifaceted initiative, ultimately allowing you to save time and money while also achieving the highest level of product quality.

Pulse check: How to assess your in-house biomanufacturing capabilities

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In the business world, the mantra "fail fast" is often used to describe an approach where success can be achieved by knowing what to do and when to do it. In that model, risk takers have to be willing to embrace their failures, as a way to determine the path forward quickly. However, applying this model in the pharmaceutical industry can be far too costly when it comes to achieving first-to-market goals. Any delays that slow progress, impact a company's bottom line, or have regulatory ramifications are going to result in projects that may not make it to market before any competitors' products, if at all.

Therefore, rather than failing fast, you must figure out a way to succeed as quickly as possible. This requires a comprehensive assessment of your company and its capabilities. In some cases, you may find your company has the in-house resources necessary to do it on your own. In others, though, achieving your goals could require tapping into external expertise that helps save time and gain speed to market.

By checking the pulse of your organization first, it is possible to identify any gaps and develop a plan for how to address them, so you can make the right decisions at the right time. Knowing which path is best for your company and choosing the right partner (when necessary) mitigates risk and accelerates outcomes, moving you faster and further in this highly competitive environment.

Does your business strategy align with your capabilities?

When assessing your organization's capabilities, you must be brutally honest about its resources and technical and capacity capabilities. Overcommitting in any of these areas can become a liability when you overextend. For example, you may have the technical capabilities but not the resources or the infrastructure, which could ultimately cause bottlenecks. External expertise in certain manufacturing strategies may also be required, such as in single-use technologies.

Capacity and capital: Are you prepared?

One major risk to a company's supply chain is demand volatility. Underestimating the demand of a product can lead to a drug shortage, preventing patients from receiving what can sometimes be life-saving medication. However, overestimating demand is just as risky, as this can lead to wasted inventory and even lost jobs. Nevertheless, a company must have enough capacity for its drug demand. The decision then becomes: Do you have the capacity and/or capital to control your own manufacturing destiny on your own, or do you need to engage the help of a contract development and manufacturing organization (CDMO)?

If you do not have the financial budget to support building a biomanufacturing facility or a bioprocess train, partnering with another company early can delay any CAPEX investments. Choosing a single-source partner that has access to not only end-to-end biomanufacturing capabilities but also to product development and innovations in biomanufacturing equipment, cell culture media, resins, and single-use devices can increase efficiency and speed to market

In-house expertise: Are you covered?

In addition, while small to midsize biotech companies may possess an arsenal of brilliant minds, they must have a full wing-to-wing understanding of media development, from discovery through commercialization and scale up. If that knowledge is not available in the early phases, the company will likely spend far too much time and money repeating experimentation. There could be issues later, too, if analytical assessments are not completed properly and the focus is on something like titer instead of on product quality attributes. With the right expertise, you can move forward very quickly with the design of your biomanufacturing process and then dovetail into other critical factors, such as cost of goods and availability of raw materials during scale up.

A thorough understanding of the availability of raw materials is also necessary, or you could find yourself in a situation where you are missing a critical component of your process. This triggers regulatory considerations, which may require additional clinical work to determine the impact. Having products and services in one place with a single-source provider can facilitate troubleshooting any raw material supply issues. There are various types of requirements for import and export, as well as trade barriers in some regions of the world that could affect availability.

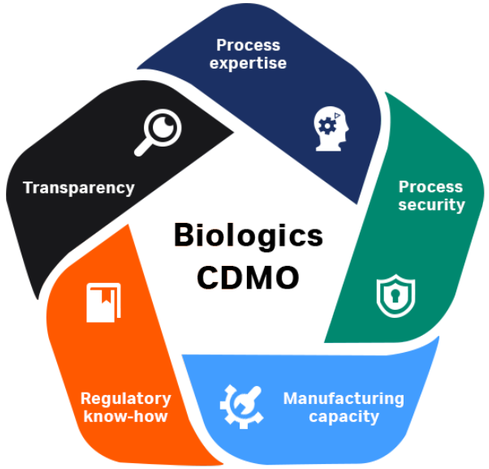
Regulatory considerations: Are you compliant?

The nuances between regulatory bodies across the world are often overlooked when determining a company's ability to work on its own. A formulation has to not only be scalable but also accepted (and approved) by the country's governing body, whether that be in the U.S. or in an emerging market, such as China. The latter is a particularly challenging area, as it does not allow clinical data to be leveraged globally. Instead, it must be performed again within the country, which can add three to six years of work. You must understand the impact any changes during development can have on not just the final formulation for your drug but also its eventual approval. Compliance should be considered as early as drug discovery, especially in biologic products, as the first-to-market company is the one that ultimately ends up owning that market space. Other companies that follow are at a disadvantage and must then adopt a new strategy, such as discounting their product, in order to be successful.

Overall, it is important to be honest about what internal capabilities exist and whether the necessary skills and resources are available in-house to deliver the intended outcome in a timely manner. If they are not, it makes smart business sense to engage a CDMO, in order to avoid any major failures and/or a longer lead time to market. But what benefits should be expected from this relationship and how do you choose a partner that is right for it?

Considerations for choosing a CDMO

The experience and expertise of a well-established CDMO can offer many benefits, especially if your business strategy is to ultimately control your own manufacturing destiny. Partnering with a CDMO can offer the training necessary to prepare you for that independence. This requires openness and collaboration with teams working openly side by side. If this happens, a CDMO's team is not just developing the process with you but also sharing the reasons why it is being done a specific way.



Transparency: Does the CDMO foster an open partnership?

An open partnership depends on how the CDMO manages its customer on-site. It is up to you to vet any potential CDMOs and find out how open they are willing to be over the course of the relationship. Ask questions, such as does the CDMO allow both teams to work openly in a pilot plant, or is your team allowed only in specific areas of the building during processing steps? Also, find out what the CDMO intends to provide at the end of the project. Does it provide

documentation, such as analytical testing requirements and SOPs, and will it speak openly with you to support it on an ongoing basis, even after the service work is rendered?

Regulatory experience: Is the CDMO prepared for the challenges of global manufacturing?

When it comes to regulatory expertise, a CDMO should have the knowledge necessary to successfully deal with local authorities, particularly in emerging markets. It may even lean on established relationships with regulatory agencies. For example, when developing a process globally, work has to be done very early in the developmental setting to meet the needs of the market in which a company wants to enter. Having an understanding of what level of acceptance there is from the local regulatory agency is imperative. There are different challenges in various regions of the world that expose some of the IP associated with the molecule or the process itself.

Intellectual property: How will the CDMO protect your critical IP?

Additionally, a CDMO should be able to help build a strategy around protecting and preserving that critical intellectual property. It may use a well-established entity to do so. This includes establishing terms and conditions of an agreement all the way through the engineering modifications required to protect any electronic data generated during the process or even security in the laboratory to protect the cell line, such as cameras, physical locks on the bioreactors, and restricted access to cell line storage/cultivation. Another strategy would be to use a black-box approach, where the CDMO does not know what the molecule is, or it may not perform the testing itself. It provides only the development work and then sends the samples back to the customer for any testing. Having a plan to protect IT is especially critical in emerging markets, where there is the potential for differences in legal requirements to leave vital information dangerously vulnerable.

In the end, leveraging service support externally can lessen the risks associated with drug development, such as building an infrastructure, especially if your strategy is based on unpredictable demand. This tightens up cash flow internally prior to having a commitment that a drug product will meet approval in the market space. A single-source partner that is both a service provider and a product developer can give you optimal results in a drug development setting through access to early product innovations and a holistic understanding of the process and equipment requirements. By receiving this kind of insight in advance, you reap the benefits of both worlds, which help you not only go faster to market but also further.

Doubling up for speed: Using parallel operations in biopharma manufacturing

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Drug development is inherently risky. The high stakes associated with producing a lifesaving drug can weigh on a manufacturer. Every decision can make or break a project, and, unfortunately, many are made long before anyone knows if the drug will make it to market. This is compounded by the fact that so much of the work that goes into drug development is done in silos, weakening the potential for vital cross-functional communication and collaboration.

Parallel operations for speed to market

One solution to drug development challenges is adopting a parallel operations business model. This approach affords the opportunity to develop a process or to perform cGMP manufacturing in a parallel path using the resources of an external contract development and manufacturing organization (CDMO) while simultaneously establishing your manufacturing capabilities. In the end, you can mitigate the risks of drug development, reduce your capital costs, and get ahead of your competition by increasing your speed to market. This article provides several recommendations for how parallel operations can be leveraged in your biomanufacturing strategy.

1. Marry up your process and facility design

When it comes to expanding biomanufacturing capacity with a new manufacturing platform or facility, often two separate teams support those efforts. On one side, a group of experts focuses on the engineering perspective, heading up the facility design itself and overseeing capital costs. The other team performs process development, looking at the molecule and creating an effective, scalable formulation. These two teams are seldom married. Therefore, a facility or manufacturing train could end up being designed in a way that does not meet the technical needs of the project, setting up the company and the product for failure. This issue goes beyond just selecting the right bioreactors and chromatography columns; it also includes other important factors, such as knowing what the throughput of the facility should be, an appropriate size and footprint, and the number of people needed to support operations.

Working with an external CDMO process development (PD) team can help bridge the communication from PD to manufacturing by ensuring that your process can be optimized to the scale of your new facility. It can also help mitigate common tech transfer pitfalls that can occur. Using this business model, you can then bring that knowledge back in-house and transplant the process to your internal engineering group, ensuring a smooth handover of operations into your newly built facility.

If you have already designed a platform process and later found it did not meet your demand forecast, parallel processing can offer benefits retrospectively. While this may require additional capital investment, it is still useful to look at an existing process and identify what is not working to future-proof your facility design. An external CDMO can help you scale your process in real time so that you can quickly adjust your biomanufacturing strategy.

2. Keep the pace during capacity expansion

When speed to market is critical, you want to avoid wasting valuable time in progressing your molecule to clinic. Outsourcing process steps to a partner who fills the gaps in your organization and enhances, rather than replaces, your internal expertise is critical. This type of collaboration strengthens your organization through a holistic approach that gives you the wide range of tools necessary to ultimately control your own manufacturing destiny.

If there are any reservations about maintaining a product's titer and analytical comparability while preparing a new single-use or hybrid manufacturing facility, parallel processing can support proof-of-concept runs. This allows you to experience any anomalies that could occur during the developmental optimization or transfer work and then adjust your plan accordingly on a parallel path. Through a parallel operations business model, you could also consider outsourcing cGMP manufacturing with an external partner that is using the same equipment that will be installed in your facility. The process and knowledge can then be transplanted into your newly installed facility with minimum tech transfer issues. This will ensure a successful handover of operations back to your internal manufacturing team.

By considering these options, you can avoid having a facility sitting empty for several years while a product goes through clinical trials. CDMO services help you defer capital equipment costs until commercial manufacturing is ready to begin and the molecule can start generating revenue.

3. Seek help when entering a new or unknown market

The fierce competition driving speed to market is very palpable in the biosimilar arena. Taking advantage of the expired/expiring patents of some of pharma's biggest blockbuster drugs means a new opportunity to cut drug costs for both manufacturers and consumers. However, any organization testing these waters faces considerable challenges, especially if they intend to target global markets. For example, developing a drug in China can become especially arduous when you are not familiar with the China Food and Drug Administration (CFDA) requirements for Phase 3 clinical trials. Specifically, the clinical trial application (CTA) lots for the product being pursued must be tested not just within China but also in the facility where the biosimilar would be manufactured.

If you are entering this market for the first time, you face the prospect of building a new facility for your drug before you even conduct clinical trials. But what happens to your investment if the drug is not approved? And what would the biosimilar competition in China be like by the time your facility is finally built years later? These are just some of the questions you would need to consider if you take the risk of building a facility before you know the future of your drug.

Rather than take these risks, there is the option to work with a local CDMO who has experience navigating these complex processes. They can help progress your molecule through clinic in parallel while you consider your long-term biomanufacturing options.

Buy down the risks of drug development with parallel operations

Regardless of the type of molecule you pursue, the fear of the unknown can be one of the most crippling barriers a manufacturer faces. It is difficult to visualize the obstacles you might encounter over the average 12-year timeline it takes to bring a drug to market. Millions of dollars are invested in designing and validating a facility while there is still so much to be determined about the drug's development process, such as throughput, molecule performance, and scale. If surprises down the road force you back into the design phase, it may require significant amounts of validation work for the facility, the utilities, and the equipment. The delays this work would cause could mean the difference between delivering an innovative first-to-market product and just another "me-too" drug. Overall, delaying investment decisions until you know how your molecule will perform can help save significant dollars and avoid risk. Parallel processing gives you the option to work with a CDMO and delay the decision of which biomanufacturing solution might work best. This gives you time to choose from a variety of solutions depending on your demand forecast. In the end, collaboration with the right CDMO on a parallel path can ensure process security, transparency, intellectual property (IP) protection, and significant cost savings.

Best practices for a successful bioprocess technology transfer

Joseph Makowiecki, Director of Business Development, Enterprise Solutions, Cytiva

A well-executed bioprocess technology transfer (tech transfer) is critical to ensure smooth knowledge transfer and optimal process reproducibility. If not executed properly, you risk reducing the quality and efficiency of your process. Waste time trouble shooting, and you may delay your time to market. In today's global markets effective tech transfer is critical.

What is tech transfer, and when does it happen?

Technology transfer is a formalized process for moving the manufacture of a drug from one facility, one scale or one drug life cycle phase to another.

Tech transfer occurs multiple times during the life cycle of a drug as it progresses from lab to commercial production. At each stage, changes in equipment, methods, and materials may require process optimization or redevelopment, and the new production team will need training. Changes in materials or scale can result in process variability, and critical process parameters may need to be optimized, or the entire process may need to be redeveloped.

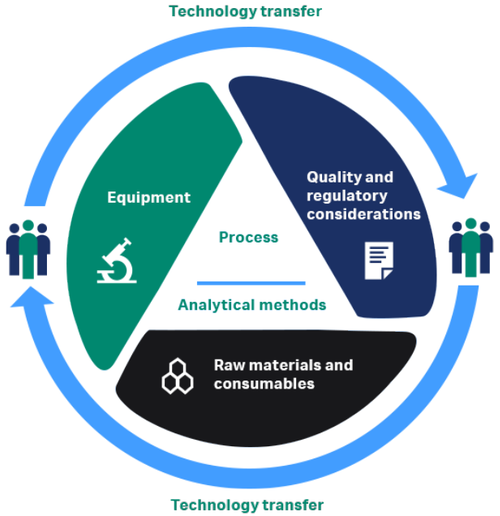
Whether you are a well-established biopharma company or a small start-up, smooth tech transfer is critical to the success and speed to market of your drug. A successful tech transfer requires diligent planning, proper documentation and procedures, and experienced experts who can guide the process and avoid the pitfalls.

For a large biopharma company, tech transfer may also occur when they want to add capacity by bringing an additional facility on-line, or wish to transfer production to another site, or even to another country.
Small companies that are developing a new drug and do not yet have manufacturing capabilities may wish to work with a contract manufacturing organization (CMO) or contract development manufacturing organization (CDMO).Established companies with many drugs in the pipeline may also turn to CMOs for manufacturing capacity in the pre-clinical and clinical phases. If the drug is approved and enters the market, companies may then wish to transfer manufacture back in-house or to new facilities.

All of these situations involve technology transfer. There are always risks involved: careful planning and documentation, understanding of critical quality attributes, and attention to detail at every step of the process, are of paramount importance.

Elements of technology transfer

Let's look at a stripped-down model of technology transfer and see what it entails.



Knowledge transfer is the heart of technology transfer. Who will be on the receiving team? Do they have the necessary expertise? What training will be required to complete the tech transfer successfully?

- **Equipment:** It is unlikely that the target facility will have exactly the same equipment and models as the transferring facility. How will these differences affect the process? Will process changes be necessary?
- **Raw materials and consumables:** If your target facility uses different equipment, are your raw materials and consumables compatible? If you are moving the process to another country, will a secure supply of your media, buffers and resins be available? Are the materials that you are currently using compliant with local regulatory requirements in the new location? If you must substitute, what and how much process re-development will be necessary?
- **Regulatory considerations:** You may need to re-validate your process you are running on different equipment. If you are transferring to a different country, you may need to re-validate not only your process, but also your analytical methods to comply with local regulations.

TIP: Remember that tech transfer must also encompass your analytical methods, including characterization testing, release testing and comparability.

But it's not that simple...

A start-up biopharma company at the late research stage or clinical stage will face additional complicating factors.

- Scaling up from lab-scale to clinical production will entail development work to translate the process. How deeply do you understand your process and mechanism of action (MoA)? What can be transferred directly, what can benefit from a scale transfer function, and what needs to be redeveloped de-novo? The more that you know and share, the smoother the tech transfer is likely to be.
- A lean start-up organization is often lacking in-house expertise in tech transfer and bioprocess manufacturing. You will need expertise "on your side" to ensure that all your bases are covered, and you have oversight from bioprocess quality, business and legal perspectives.
- If outsourcing, CMO selection and relationship will be critical to the success of your tech transfer, your therapy and your business.

TIP: Ensure that key expertise in the critical process and manufacturing attributes is retained in your organization to help guide tech transfer.

The top five essential factors for efficient tech transfer

Technology transfer is a significant step along the way to your end goals for your drug or therapy. Make sure these essential factors are in place and aligned with your goals to maximize tech transfer efficiency and success.

- A comprehensive tech transfer document reflecting deep product understanding and includes all the important parameters of your bioprocess, analytical procedures and critical quality attributes (MoA, CQAs etc.)
- CMO capabilities aligned with your requirements and goals
- Clear goals setting up front
- Timelines, costs and deliverables meet your needs
- Expertise and quality oversight in the specific applications required
- Capacity
- Communication – open and often
- Transparency
- Contract SOP embodying a robust plan
- Clearly defined roles and responsibilities
- Process and facility map
- Analytics transfer
- Process development as necessary
- Demonstrated equivalence at the starting scale/process
- Proof of concept engineering runs at scale prior to GMP
- Clear, frequent and transparent communication.
- CMO transparency—being able to go into the plant to see how the process is run, and being able to bring the process back in-house, (including reverse knowledge transfer).

Document, document, document

Documentation is not an event, but a best practice to be implemented, and referred to, at every step along the way. Templated standard operating procedures and documents, approved by the quality team, will increase the speed, efficiency, effectiveness and quality of technical transfer. Rigorous documentation of deviations along with root cause analysis and corrective/preventative actions will help ensure consistent process execution.

The technology transfer document

From the technology and bioprocess standpoint, the tech transfer document is the all-important roadmap to implementing your process in the CMO's environment. It will contain all the information and parameters pertaining to the process and the product, including materials and analytical methods. The more that you have nailed down regarding your process, and your effectiveness in documenting this knowledge, the smoother will be your technology transfer and any ensuing redevelopment.

The technology transfer SOP

Since technology transfer is core to the business of a CMO, you can expect your CMO or CDMO to work within the framework of a clearly-defined methodology, documented as a standard operating procedure (SOP). The goal of the technology transfer SOP is to improve the effectiveness, efficiency, quality and compliance of the biomanufacturing technology transfer process. A thorough, reliable tech transfer methodology will go a long way towards ensuring success in both the technical aspects and in building the business relationship.
Expect a technology transfer documented SOP based off a standard methodology and templates, tailored to the specific project. A well-designed SOP will include:

- Defining the goals, scope and steps involved
- Defining roles and responsibilities
- Utilization of template documents
- Increasing the level of control through process control, document control, communication, decision and sign-off controls
- Increasing the level of quality through quality team involvement and oversight

If your tech transfer is to a CMO, the contract with the CMO will be driven by SOP and the technology transfer document, so be sure the SOP is detailed and robust.

CMO or CDMO selection: key considerations

Selecting your CMO or CDMO, and crafting your contract with them, is one of the most critical and complex business decisions for your company. You will be sharing your intellectual property with them, and they, in turn, will be creating significant intellectual property as they scale up your drug and continue its development. Be sure to include reputation, as well as capabilities, in your selection criteria. How can you prepare in advance to avoid typical pitfalls?

TIP: Hire an experienced expert who can guide you through vendor selection and contracting, who knows what to look for, and what to look out for. It is well worth the investment.

Here are some of the key factors that go into framing your vendor selection and contract.

- Timelines: do they have capacity to meet your timelines? Can you secure additional runs if demand exceeds forecast?
- Equipment: how similar, or different, is their equipment to what you are currently using? Is their equipment in line with your long-term plans? For example, if you foresee eventual commercial production with single-use equipment, is their current equipment aligned?
- Expertise: Do they have experience working with similar drugs?
- What do they bring to the table for analytical procedures? If you later transfer production, will you have access to their methods and SOPs for both analytical and manufacturing?
- Regulatory considerations: what do they bring to the table, and what do you need? Can they meet clinical regulatory requirements, and can they go beyond that to provide guidance for you?

Understanding where you are, and where you are going

Planning a successful tech transfer requires understanding what both sides (sending and receiving) have for process and equipment, the differences, and what redevelopment might be required.

TIP: Consider the definition of your end-point carefully. While you may be moving from lab to scale-up for pre-clinical production or Phase I trials, is that really your end-point? Choices (e.g. equipment, consumables) at any stage may simplify or add complexity to future tech transfers, scale up and redevelopment activities.

Intellectual property considerations

For a small bio-pharma start-up, especially one spun out of a research lab, hiring a consultant with experience in negotiating successful biomanufacturing outsourcing contracts will be a wise investment. Framing all of the aspects of the business relationship, the contract will help set expectations and avoid future pitfalls.

Don't overlook the intellectual property that will be developed or supplied by the CMO. This may include analytical methods, cell lines that must be licensed, documentation of their process and methods. Should you wish to bring manufacturing in-house, or transfer to a different or additional CMO in the future, will this IP be available to you? What costs will be associated with it?

TIP: Remember that when working with a CMO or a CDMO, not only will you be sharing your IP with them, but they, also, may integrate their own IP into the manufacture (and testing) of your drug, as well as potentially develop new IP. Plan for this eventuality.

Engineering runs

The engineering run is a non-GMP trial run which tests your process, equipment and automation to confirm that your process is outlined correctly, as well as confirming that the staff is properly trained to run the process. During an engineering run, your process will be run at scale, or close to at scale, on the CMO equipment prior to transitioning to GMP production. While this can be quite costly, it is worth the expense. During this run, any differences in the process resulting from scale, materials or equipment differences will be exposed. Identified critical process parameters may need to be adjusted. The learnings gained during an engineering run will help drive a lot of risk out of the transition to a GMP manufacturing process. If you go straight into GMP manufacturing and run into any issues, trouble-shooting can be much costlier—in time and money—than the engineering runs.

Transparency

Technology transfer is a complex undertaking that requires communication, and even collaboration, between the biopharma company and the CMO. Transparency is a key factor, so understand your CMO's style up front to set clear expectations. For example, what is their policy and preference regarding a "person-on-the-floor" from the client side? Will you be able to go into plant to see how the process is run? This is especially important if you plan to bring the process back in-house.

TIP: A relationship is a two-way street. Build trust with clear expectations, communications and transparency.

Best practices: wrap it up

It may be tempting to think of technology transfer as a "send and receive" process, with the sending organization transferring technology to the receiving organization. It will be more helpful, and set you up for success, to understand tech transfer in the framework of a relationship, whether between the biopharma company and their CMO, or between different teams internally.

When working with a CMO, the tech transfer, while a major milestone, is not just a hand-off—it is the beginning of an ongoing relationship. It is important to establish a strong, cooperative rapport with the CMO's alliance manager, and to maintain quality oversight on an ongoing basis. Throughout the tech transfer process, you will be defining, establishing and building this relationship. For a start-up or emerging pharma company, this is a bet-your-business prospect.

- Utilize consultant(s) to guide you through.
- Plan for contingencies, plan for success. Early planning prevents later grief.
- Cover all the bases, including supply chain, equipment, regulatory and intellectual property.
- Manage the vendor selection criteria and process with expert help.
- Document tech transfer in depth:
- Technology transfer document from the SENDING side
- Technology transfer standard operation procedure (SOP) from the RECEIVING side, adapted to the specific instance
- Contract, from both sides

As in the bioprocess lab, in tech transfer the devil is in the details. Nail down as much as possible up front, but communications and transparency are necessary to deal effectively with the many issues that may arise along the way.

The transparent CDMO: Maintaining autonomy in your biomanufacturing partnership

Patrick Guertin, Global Technical Manager, Cytiva

The complexities of today's biologics and intensifying competition in the industry are making it more important than ever to develop a successful first-to-market strategy. Collaboration with a contract development and manufacturing organization (CDMO) can make it possible to bring your drug to market — and to patients — faster, as additional resources allow your operations to run more smoothly, and you can react faster when problems arise. Nonetheless, handing over vital information about your product can understandably feel like you are giving up, or even losing power over, your own project.

That is why it is important to find a partner who can help alleviate the risks associated with drug development but also understands how to work in a fashion that protects your intellectual property (IP). Complete transparency and open communication are key factors in doing so. But how do you know your CDMO is prepared to offer that type of commitment to your project, and what business practices should you look for to ensure they can?

1. Lay a strong project foundation

In the beginning of your project, a CDMO will want to complete exploratory work to determine any optimization opportunities that can create the most efficient process. The more information you include in your request for proposal (RFP), the better, so the CDMO has the information they need to propose the most effective changes. Your organizations must then work together to define the goals of the project and clearly outline how the CDMO's knowledge and expertise can help execute your business strategy as well as how information will be transferred between your teams. Not only does this encourage better collaboration, but it also facilities the handover process in the end. Identifying and outlining goals using documentation rigor and project management, both in terms of technology transfer as well as standard operating procedures for the respective equipment and platform technologies, is critical for establishing individual roles and responsibilities.

With each stage of work that is identified, milestones and deliverables should be identified in conjunction with the timeline. You can then track the pace of the project to make sure it is staying consistent with expectations. It also prevents you from over- or under-committing scope, which can cause misunderstandings of deliverables. Template documents, such as for batch records, process records, etc., can lay a foundation for the project but should be revised in accordance with the project needs. This offers the benefit of efficiency while still capturing the unique features of your specific technical details. Although there is a minimum criterion a cGMP manufacturing facility must abide by, the templates allow a CDMO to accommodate enhanced testing or quality evaluations, such as additional analytical test methods for a particular molecule.

Through close collaboration and discussion early on, your needs can be addressed and project deliverables are created that fulfill your expectations. Being adaptable and willing to negotiate creates trust and drives teamwork, ultimately ensuring the molecule is successful in clinic.

2. Establish effective communication: Build bridges, don't burn them

Clear and effective communication is essential. Project management and oversight is a full-scope component from the earliest stages of the project to its completion. As part of that project management, project teams must be identified with their emails, phone numbers, and any other forms of communication. People should be introduced right away, so everyone is familiar with whom their technical and non-technical counterpart is and can build bridges among those teams (i.e., upstream, downstream, quality, analytical, etc.). This not only creates the initial connection between the appropriate departments, but it also helps build a larger and more cohesive team.

By closing any potential gaps in communication, you eliminate delays and/or misunderstandings that often create frustration and opportunities for error. When vetting CDMOs for your project, inquire about its communication structure by asking questions like:

- How accessible are the people in the respective areas?
- Will they be clearly identified?
- What's the communication policy with respect to meeting frequency or updates?

Ideally, they should offer a clear pathway for communication that provides you with outlets where you can reach out and ask questions at any point in the project. If the CDMO does not outline a plan for effective communication, it can have a lasting effect on the strength and cohesiveness of your teams.

3. Operate as "one team"

Like any successful relationship, the importance of trust and respect cannot be understated, and valuing each other's expertise is a crucial part of forming a strong business partnership. Often, this mutual respect occurs by working side-by-side to understand how the services of a CDMO are supplementing the expertise within your organization rather than replacing it. Essentially, you and your CDMO should function as one team, working to foster your relationship and facilitate knowledge transfer.

For example, a transparent CDMO that values close collaboration will allow a "person in plant" during optimization of the development process as well as manufacturing to observe in-plant activities. This provides you with the opportunity to view processing firsthand as well as see the progression of the process first hand and completion of the respective steps. By asking questions and hearing the logic behind all of the decisions being made, you can gain a deeper understanding of the process in real time. Additionally, it gives your experts a chance to jump in when critical or even non-critical decisions need to be made, as well as to help troubleshoot.

As this happens, the two teams strengthen their relationship and establish comfort and trust between each organization, so it can be a positive experience if subsequent support is needed later. Training also occurs throughout the project, so less time is spent doing so in the end. This transparency gives you the ability to be autonomous when you return to your facility or when the process is taken back to the lab.

4. Define how your CDMO will protect your IP: Are they willing to work "inside the box?"

Allowing a CDMO with knowledge and expertise to support you means sharing valuable knowledge and data about your product and process. Ownership of the molecule itself almost always resides with the customer. However, defining whether there will be co-ownership or exclusive ownership of the techniques, process, and platform technologies should be identified up front. Certain items of work might be done exclusively by the client, so processes would need to be defined on how that information is to be handed back and forth across the two teams and by whom.

You may even want some information blinded in a black box approach, which essentially protects the critical quality attributes (CQAs) of your product. A CDMO using this method receives samples from the customer to test and has an open relationship about the CQAs without ever knowing what they are. Some CDMOs may not want to work this way because it makes process development more difficult or they want a long-term relationship where, in the end, they manufacture your commercial product. If they do not have the internal capability to execute this type of approach, it should raise red flags about whether they are the right fit for your project. In addition, they should have a legal understanding of how to preserve IP for a particular entity, so both sides can move forward without any constraints.

An open partnership depends on how the CDMO manages its customer on-site. It is up to you to vet any potential CDMOs and find out how open they are willing to be over the course of the relationship. Ask questions, such as does the CDMO allow both teams to work openly in a pilot plant, or is your team allowed only in specific areas of the building during processing steps? Also, find out what the CDMO intends to provide at the end of the project. Does it provide documentation, such as analytical testing requirements and SOPs, and will it speak openly with you to support it on an ongoing basis, even after the service work is rendered?

In the end, reaping the benefits of an experienced CDMO while protecting your process know-how and securing a successful transfer of knowledge can be challenging. The pace at which drug development moves also adds a layer of complexity and a sense of urgency. However, working with a CDMO that values transparency and open lines of communication is critical. You can not only gain expertise and experience but also valuable independence, giving you the security and longevity you need to achieve commercial success.

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