PERSPECTIVES ON:

Trends in Outsourcing the Development and Manufacturing of Biologics

MilliporeSigma is the U.S. and Canada Life Science business of Merck KGaA, Darmstadt, Germany.

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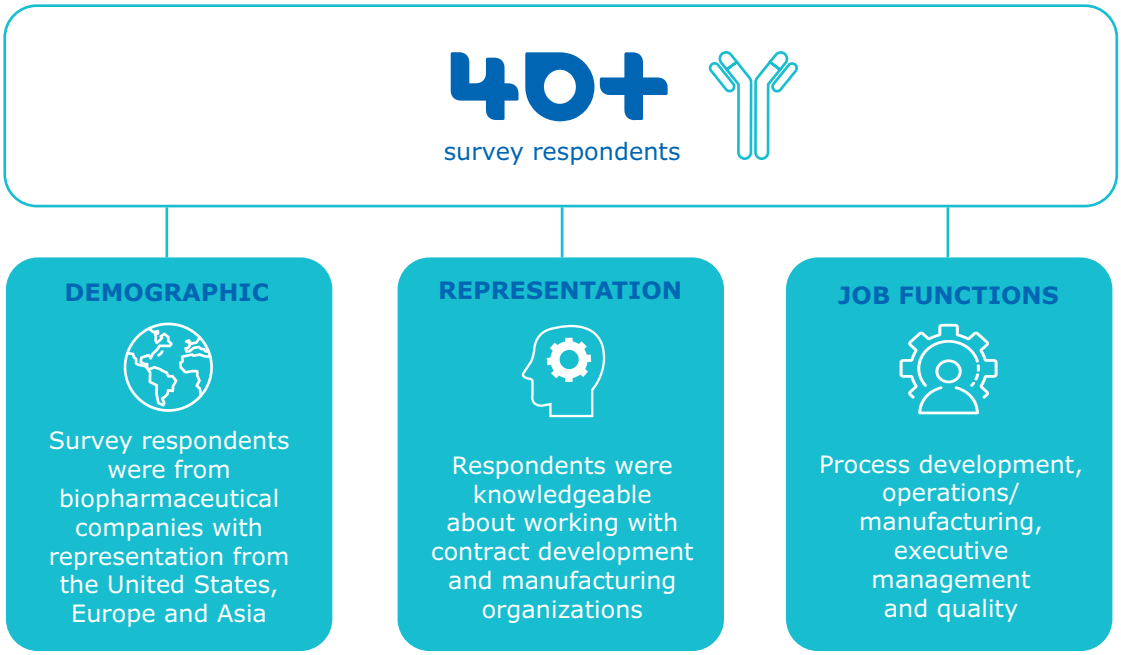
CTDMO Services

Many factors must be considered when determining the best approach for development and manufacturing of a biopharmaceutical. The right strategy must align with organizational objectives, accelerate progress toward key milestones within regulatory expectations, and ensure quality and patient safety. Risk is always present and must be identified and weighed against the need to move quickly and remain compliant.

In many cases, a company will engage a contract development and manufacturing organization (CDMO). Outsourcing to an experienced CTDMO can offer significant advantages in terms of speed, flexibility and risk mitigation. Use of an external partner can also reduce risk and provide flexibility when the timing of regulatory approval across multiple geographies is uncertain or delayed.

In this whitepaper, we share highlights from a global market research survey of small, mid-sized and large biopharmaceutical companies on trends related to outsourcing. Members of our team, working with the Millipore® CTDMO Services portfolio, then offer their perspectives on the survey results.

Research Methodology

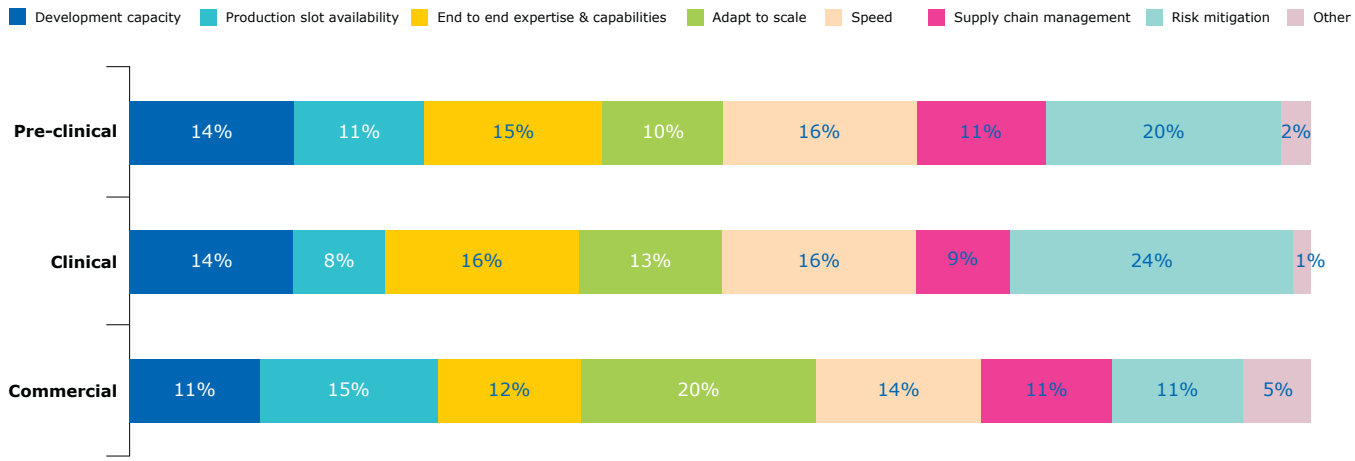


Key Findings

1. What We Heard:

Risk Mitigation, Speed and End-to-End Capabilities Drive Outsourcing During Pre-Clinical and Clinical Phases; Adapting to Scale and Production Slot Availability are Drivers at the Commercial Phase

Main Reasons for Outsourcing Drug Development and/or Manufacturing to a CDMO



Our Perspective

When customers leverage our Contract Testing, Development, and Manufacturing Organization (CTDMO) services in pre-clinical or early clinical phases, a critical objective is to advance projects in a timely manner while identifying and mitigating risks. This need was clearly reflected in the survey responses.

In situations where timelines must be further accelerated, such as with Fast Track designations, we always consider available options to condense timelines safely and within regulatory expectations. We have brought hundreds of projects into clinical manufacturing, and that experience, coupled with expertise across many molecules types, cell lines and processes, allow us to select the technical options best able to accelerate timelines. Based on available data, for example, we may recommend going directly to scale-up before small-scale development is complete and defer the confirmation studies to a later time. This flexibility is beneficial, especially when a process must be adapted to an evolving regulatory framework linked to a fast track designation.

Survey respondents also noted the importance of access to end-to-end expertise and capabilities. Development and manufacturing programs are highly complex, starting from cell line, process and analytical development through clinical and commercial scale production. The advantage of having all of these activities within a CTDMO offers advantages in terms of speed, control of the project and intellectual property, and simplified project management.

We believe expertise and experience in process development are also critical at commercial scale. When moving into the commercial stage, the existing clinical process must be adapted to a robust commercial process for routine production with consistent drug product quality. In many cases, the clinical process was developed with speed in mind, and as a result, the process and product may not be well-characterized and there is little experience with production (i.e., one or two clinical batches have been produced). This situation requires a highly qualified CTDMO to identify critical quality attributes (CQAs) and associated critical process parameters (CPPs) early, fully characterize the process and apply the appropriate process validation strategy. The validation strategy can vary depending on the therapeutic indication, drug filing strategy and whether there is a fast track designation for the drug. In the case of fast track designation, some process validation activities may be postponed until after approval of the new drug application (NDA). We have extensive experience in these situations and the ability to flawlessly manage rolling NDA submissions and interactions with regulatory authorities.

Takeaway #1:
Choose a partner with extensive regulatory experience and in-house analytical capabilities.

We agree that adapting to scale and production slot availability are main drivers for outsourcing at the commercial phase. Both aspects require the CTDMO to be flexible in terms of the scale of production and the ability to respond to changes in market demand, which can be quite unpredictable. During the first years of commercialization, the market is not yet fully established and many parameters impact demand. Among these factors are local healthcare system reimbursement, variation in dosage, the presence of new competitors and the prescribing habits of physicians.

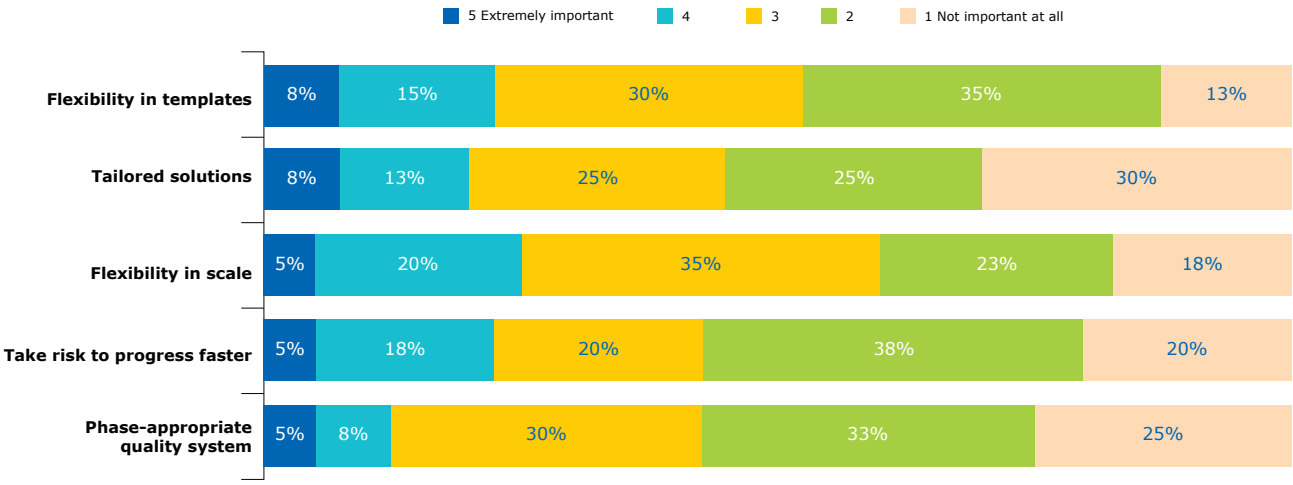
Once the drug has been on the market for some time, demand becomes more predictable and forecasts more accurate. At this stage, customer priorities typically evolve from flexibility to efficiency and cost savings. The focus turns to reducing the cost per gram of drug product and the most effective way to do this is through increasing the scale of production – referred to in the survey as “adapt to scale”.

Our single-use commercial production suites support both 200L and 2000L scales, offering the flexibility needed to respond to forecast unpredictability at launch and in the first few years following approval. As demand increases or decreases, a “scale out” approach can be applied by simply adding or removing 2000L single-use bioreactors. In doing so, production capacity is scaled in either direction very quickly, without the need for a change in production scale and associated process validation and BLA (Biologic License Application) re-filing. This approach is enabled by our global network of facilities, an agile team, extensive experience with tech transfer between sites and the same scale, equipment, technologies templates, procedures, and quality systems across sites. The benefit to the drug manufacturer is the opportunity to delay the decision of scaling up a process with associated costs and regulatory risks, to the time when commercial supply is easier to predict, and forecast accuracy is higher. Once demand is predictable, production can be scaled to reduce the cost per gram of antibody produced. At this time, we can support scale-up and transfer of the process to a scale larger than 2000L.

2. What We Heard:

Drug Developers with Molecules in Pre-Clinical Phases want Flexibility from their CDMO

Important Aspects at Each Phase: Pre-Clinical



Our Perspective

During preclinical process development, it is common for CTDMOs to apply a pre-defined template which can streamline workflows. The ability to leverage a templated approach is essential, but equally important is the ability to tailor that template to meet the needs of a specific molecule or timeline. The overall approach must also remain flexible in the case where regulatory requirements might be evolving or streamlined, as was the case with therapeutics targeting SARS-CoV-2.

While templated approaches can offer flexibility, there are many cases in which a completely custom solution is required. For example, a difficult to express molecule may necessitate a tailored balance of speed, risk and cost.

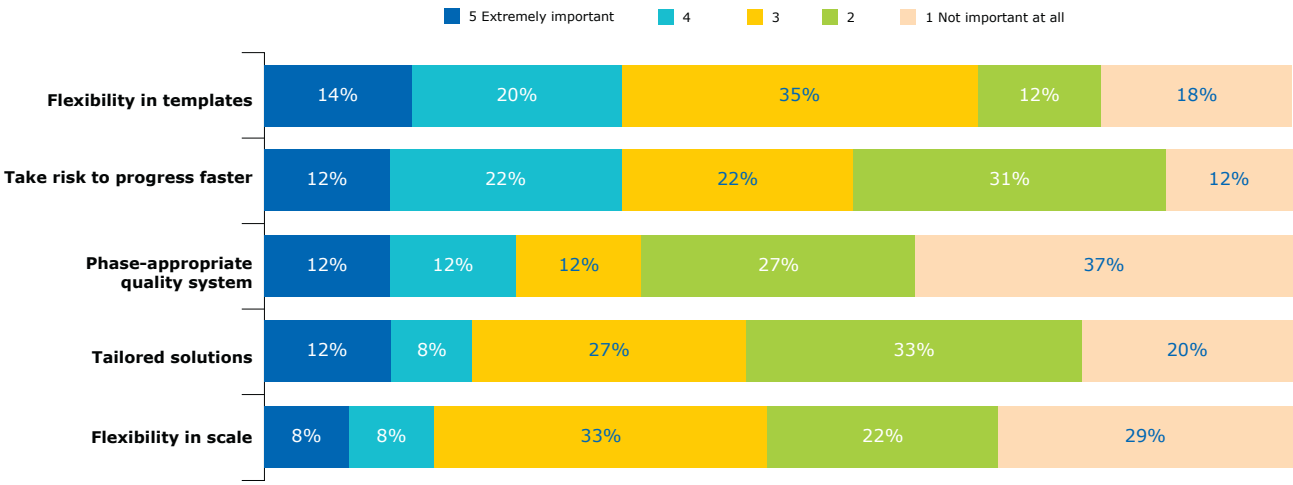
The concept of taking risks to advance more rapidly is also an important consideration at this stage and a frequent conversation we have with customers. Risks related to the process or business can be considered but must be balanced with the need to move rapidly through early stages. When exploring where timelines can be compressed, we apply our deep expertise and broad experience to offer viable options. Different scenarios are evaluated in close collaboration with the customer; any approaches that may potentially compromise patient safety, however, are never considered.

At the clinical stage, another consideration is flexibility, which is needed for the clinical batch production scale. Additional slots may be required as forecasting the quantity of drug substance required for clinical trials is not an exact science.

Takeaway #2:
Choose a partner who offers flexibility in process templates and tailored risk mitigation strategies.

3. What We Heard:
Flexibility of the CDMO and Measured Risk Taking Remain Important during the Commercial Phase

Important Aspects at Each Phase: Commercial



Our Perspective

By the time late clinical and early commercial stages are reached, some level of understanding of the process and the molecule is achieved. At this point, the CTDMO partner should take that knowledge and experience into consideration and adapt process fitting, characterization and validation studies accordingly.

Our role as the contract manufacturer is to take that process, adapt it to our facility capabilities, scale it, validate it for commercial production and produce the drug product. This requires flexibility to effectively and efficiently integrate the process, the client's knowledge of that process, and characterization of the molecule, and apply our institutional knowledge and expertise to appropriately adapt a manufacturing template.

Drug manufacturers should be aware that some CTDMOs may not leverage the knowledge accumulated by their customers during earlier stages, preferring to start from scratch. This approach adds time and risk to the process and thus careful selection of the CTDMO partner is critical.

Taking risks to progress faster was also cited as being important in commercial stages. In our experience, there is an opportunity to accelerate timelines during process validation, while ensuring the larger process meets quality criteria, is controlled and reproducible from batch to batch. We are often asked by clients to what extent this step can be streamlined. As an experienced CTDMO, we define what is possible, delineate the appropriate boundaries and put risk mitigation plans in place.

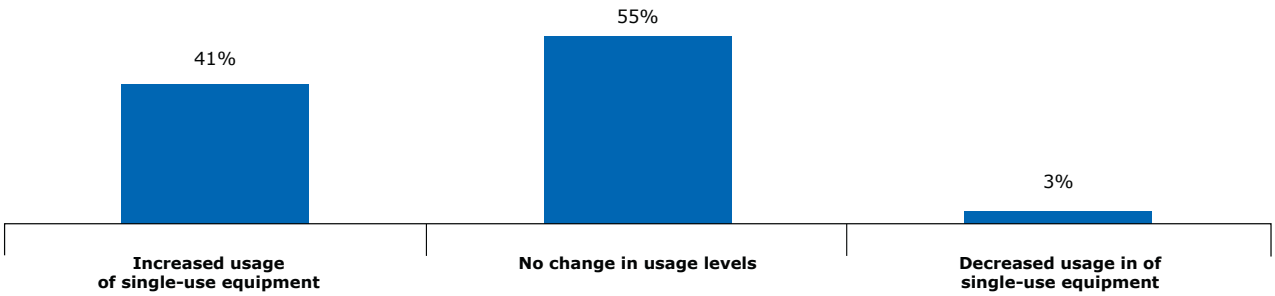
The approach used for process validation will vary depending on whether the molecule is a first-in-class drug, a biosimilar or has a Fast Track designation. We provide guidance based on what must be completed and when, if the desire is to accelerate the time to market. The key question to be asked is what absolutely must be completed in terms of process validation for the BLA and what is a "nice to have". With a Fast Track designation for example, the BLA is a rolling submission process in that the BLA can be granted and the drug marketed with limited process validation data compared to the standard submission process. Ultimately, however, the same level of validation must be achieved, which can include studies that are completed post BLA approval.

Takeaway #3:
Choose a partner who takes your past experience into account and builds on it.

4. What We Heard:

Single-use Technology is Preferred for Monoclonal Antibody Processes and Offers Greater Flexibility than Stainless Steel

Single-Use Equipment in a mAb Process



Our Perspective

Single-use technologies offer many benefits for biopharmaceutical manufacturing. A CTDMO with proven expertise and broad experience with these technologies across clinical and commercial manufacturing is best suited to derive the greatest value for a customer.

As noted above, an important benefit of single-use is flexibility in terms of scale. While manufacturers cannot control or always predict the evolution of demand for a therapeutic over time, single-use technology allows the CTDMO to be fast, flexible and responsive to change, important considerations over what may be decades of commercial manufacturing.

Single-use technology enables standardization of equipment and less complex operation, thus facilitating the tech transfer process. The transfer might be from the CTDMO back to the innovator's manufacturing network or the drug might be out-licensed or acquired by another company. Regardless of the scenario, the transfer must be seamless and efficient and enable the manufacturing process to run at the receiving site with no or minimal changes from the original process.

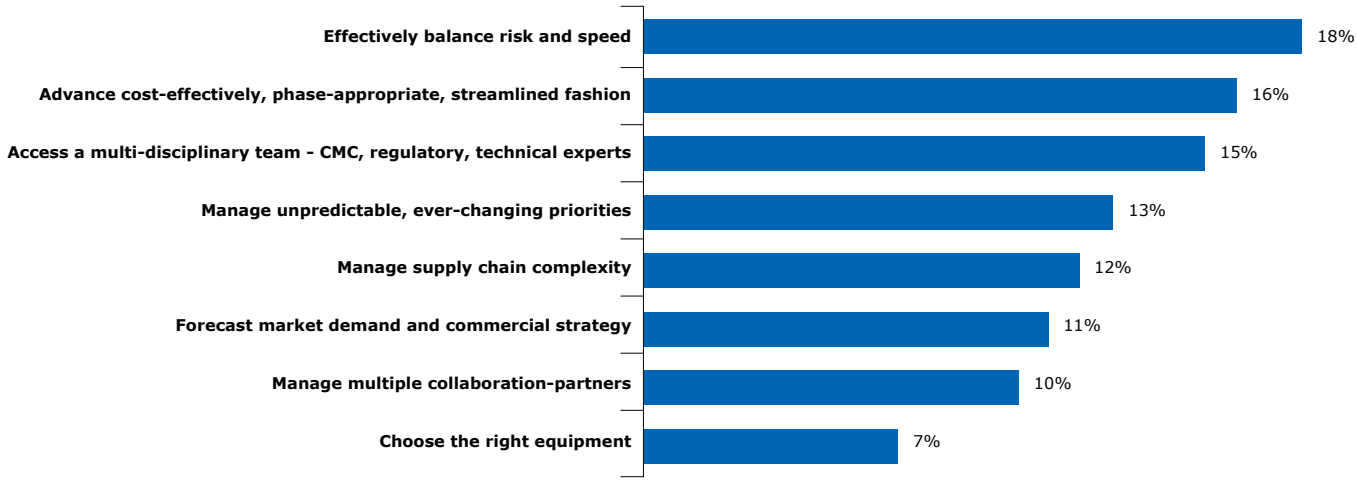
We use standard equipment across different suites in different sites for clinical and commercial production; this offers more flexibility and speed when adapting to customer needs. Because manufacturing suites are virtually identical, process fittings are eliminated, tech transfers are simplified and de-risked, and process validations are simplified and possibly reduced to comparability studies only. In addition, because we manufacture the single-use technology that is used in our global locations, if a customer decides to take drug production in-house, we can supply the same equipment used in our CTDMO operation which simplifies and accelerates tech transfer to the customer's facility.

Takeaway #4:
Choose a partner with proven expertise and broad experience in single-use technology.

5. What We Heard:

Drug Developers and Manufacturers want their CDMO to Effectively Balance Speed and Risks

Overcoming Major Hurdles with a CDMO Partnership



Our Perspective

Balancing risk and speed is a hurdle drug manufacturer look to their CTDMO to address. The ability to do this is closely aligned with the ability to manage unpredictable and shifting priorities. Success amid this uncertainty is dependent on the technical expertise and experience of the CTDMO, as well as a multi-disciplinary team and world-class project management capabilities.

Our cross-functional teams include representatives from upstream and downstream development, regulatory, quality systems, manufacturing, analytics, and project management. Teams work closely to ensure rapid and transparent communication both internally and with our clients. With these skillsets, we apply the most advanced technologies, identify risks, find solutions and drive projects forward in a proactive manner.

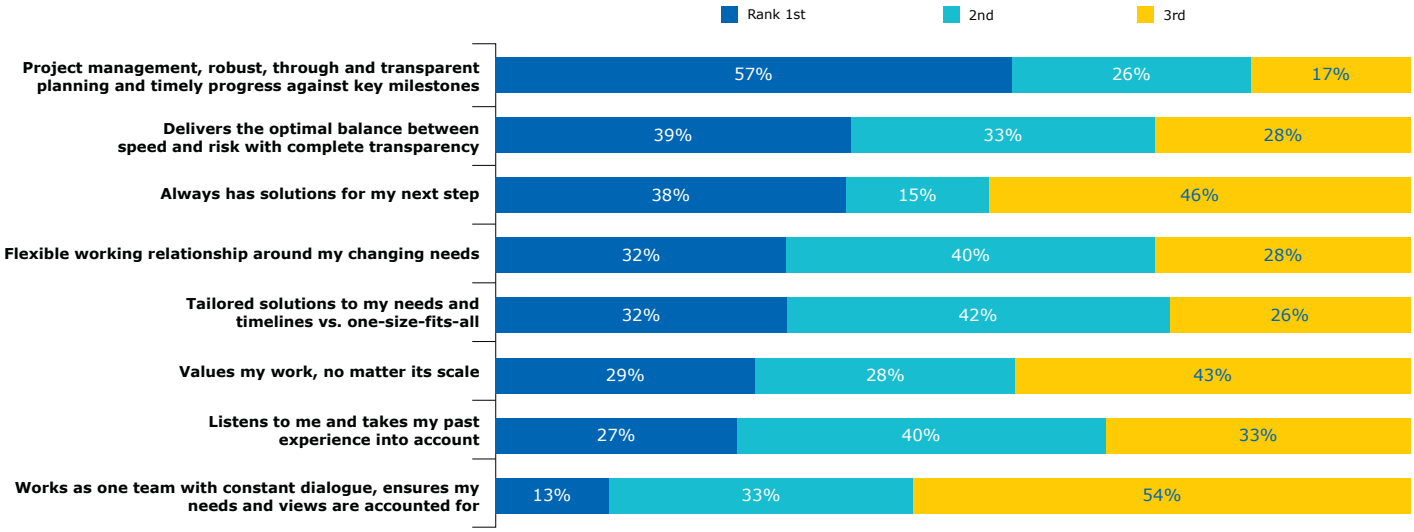
While managing supply chain complexity ranked somewhat lower in the survey, we believe it is a critically important role of the CTDMO. Managing supply chain complexity is increasingly important given the impact of disruptions created by the pandemic. On-time commercial supply is of upmost importance to ensure access of much-needed medications to patients and the CTDMO plays a significant role. The CTDMO must identify critical raw materials required for drug production and ensure these raw materials are available on time to avoid delay in commercial production.

As we manufacture many of the critical raw materials used in drug production, we implement safety stocks for these materials. This allows us to better secure GMP clinical and commercial production slots for our customers.

Takeaway #5:
Choose a partner with an integrated supply chain of critical raw materials.

6. What We Heard:
Project Management is Among the Most Important Elements of the CDMO Partnership

Most Important Elements of a CDMO Partner



Our Perspective

We agree that robust and responsive project management is one of the most important aspects of a CTDMO partner. It sets the stage for success and influences all other elements touched upon in this survey. A dedicated project manager from our team works closely with all members of the multidisciplinary team and is the point person for the client, ensuring timely and transparent communication, managing complexity and providing the client a comprehensive view of the project and any associated risks that may arise.

The project manager also serves as the customer's advocate, gathering their business needs, constraints, and additional knowledge about the molecule and transferring this to the internal team on a consistent basis. In addition to communications overseen by the project manager, there are regular scientific and technical discussions and direct interface with specialists from different teams engaging directly with the client.

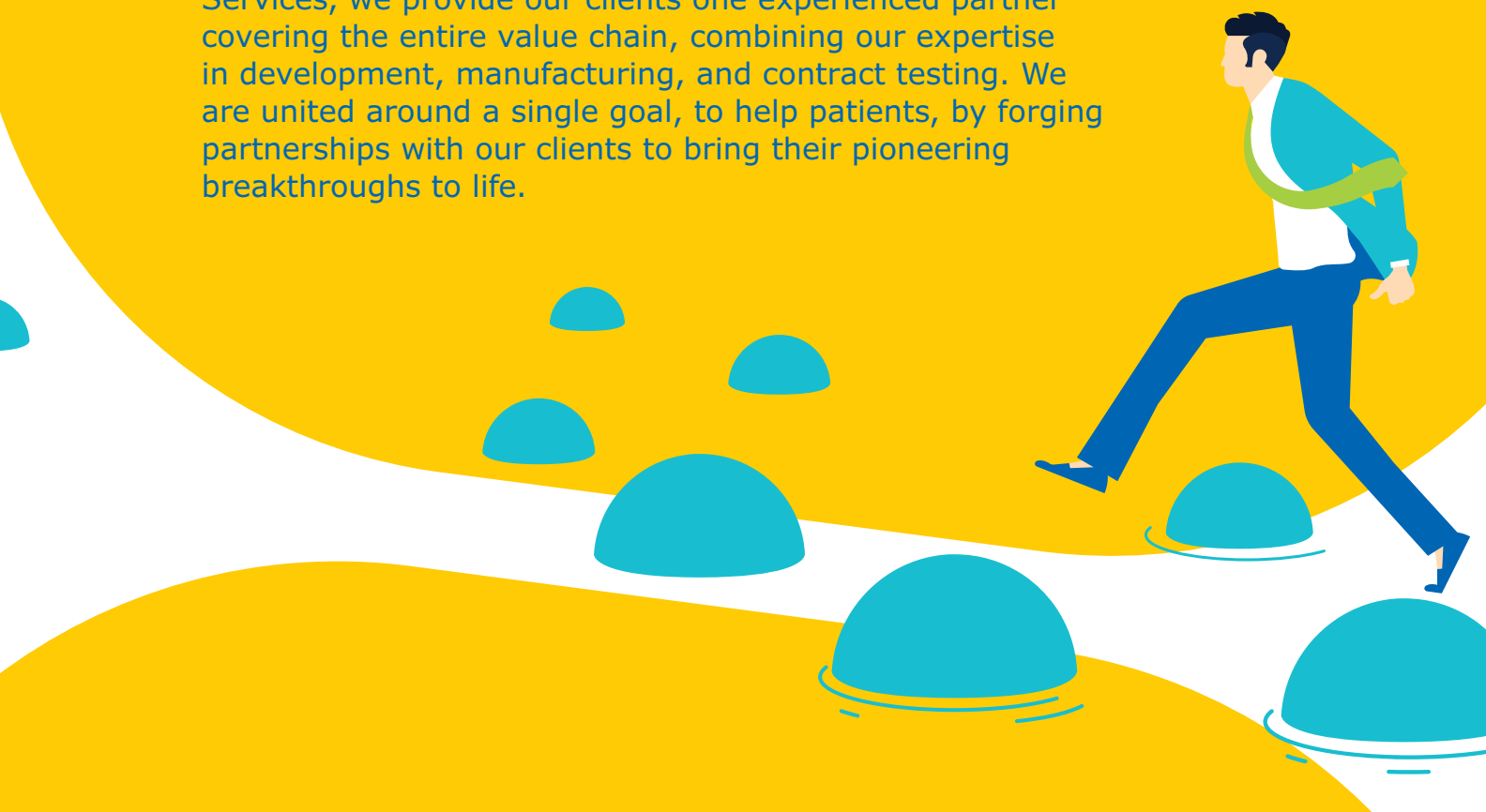
Takeaway #6:
Choose a partner with first-class project managers who put customers in the center.

Conclusion

Advancing a biopharmaceutical from process development through commercial manufacturing is highly complex, risky, and time consuming. It requires decision making in the face of uncertainty, balancing speed with the need to remain aligned with regulatory requirements and, in many cases, selecting the right CTDMO partner.

These survey results define the attributes of an outsourcing partner that are sought by developers and manufacturers of biopharmaceuticals. A CTDMO should offer the depth of expertise, broad experience and flexibility necessary to navigate complexities and mitigate risk from the earliest stages of development through manufacturing. The right CTDMO will also understand all aspects of the process from development through commercial production, apply the most advanced technologies, and offer a range of options suited to the company, molecule, timelines and appetite for risk.

Companies that are advancing a clinical candidate for the first time, as well as those that have navigated this route before, will benefit from the knowledge and counsel of a trusted CTDMO with a proven track record. With Millipore® CTDMO Services, we provide our clients one experienced partner covering the entire value chain, combining our expertise in development, manufacturing, and contract testing. We are united around a single goal, to help patients, by forging partnerships with our clients to bring their pioneering breakthroughs to life.



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About Millipore® CTDMO Services

For clients seeking an outsourcing partner, we provide a streamlined experience to cover the entire value chain from pre-clinical to commercial phases. Our integrated Millipore® CTDMO Services offering combines our expertise in contract testing, development, and manufacturing to accelerate solutions for clients and patients. Our technical leadership, regulatory know-how, testing services and manufacturing expertise are tightly aligned with our supply network to offer total solutions for our clients. We leverage 30+ years of global success with dedicated sites around the world. We are the industry's experienced choice, built to serve pioneers.

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