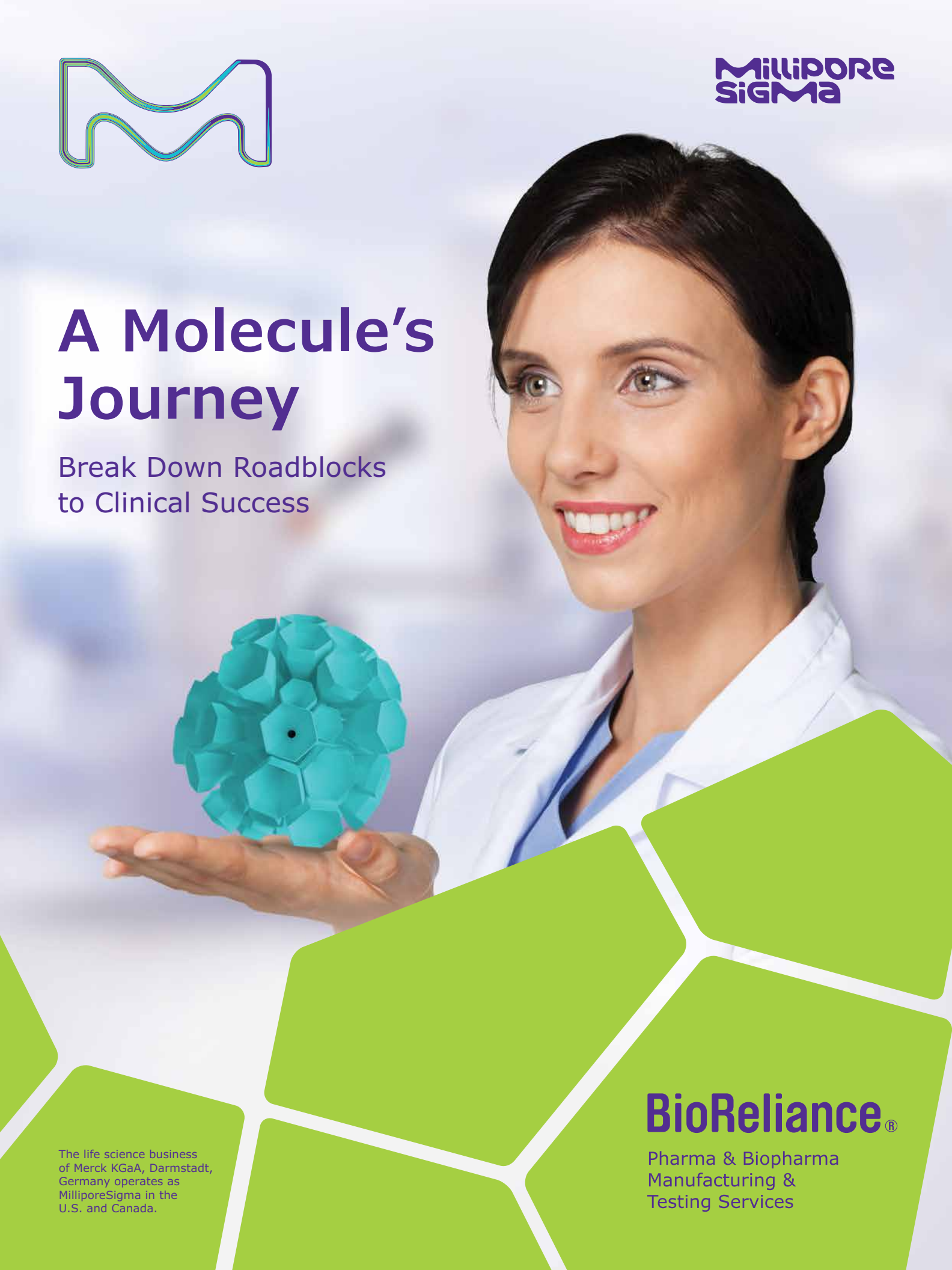

A Molecule's Journey

Break Down Roadblocks to Clinical Success

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BioReliance®

Pharma & Biopharma Manufacturing & Testing Services

A Molecule's Journey

Breaking Down Roadblocks to Clinical Success

A guidebook for today's biopharma executives seeking to navigate through the important considerations necessary to successfully bring a molecule to the clinic

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Every biopharma executive must make important decisions early in clinical development that will impact their molecule's journey – and ultimately the success of their commercial strategy.

The key to this success is to make the right decisions at the right time. In this guidebook, our experts share some key considerations to help biopharmaceutical companies successfully advance a molecule from the laboratory to the clinic as quickly as possible without sacrificing product quality, process efficiency, or patient safety. To achieve this goal, companies must navigate the complexities associated with business planning, cell line development, analytical development, process development, technology and technology transfer, and regulatory and risk assessment.

Business considerations

Speed to Clinic

Filing Strategy is Key to Commercial Success

Process Efficiency Over Speed

Speed to Clinic

For emerging biotech and small-to-medium sized companies in the earliest stages of clinical development, accessing the market as quickly as possible is of paramount importance because heavy investments are being made in research and development without revenue generation. This period of time can be particularly challenging as the financial health and viability of the molecule is usually linked to how fast the company is able to demonstrate clinical value and raise funds. To achieve this goal, companies typically choose one of a few strategies: out-license the molecule to a large biopharma company once the molecule has demonstrated clinical value; outsource manufacturing of the molecule to a contract manufacturing organization (CMO) to avoid making the necessary capital investments while maintaining the rights to the molecule; or become a manufacturer and invest in a biomanufacturing facility. A guidebook has been developed to help executives navigate through the important considerations necessary to successfully build their own GMP biomanufacturing facility. The guidebook can be accessed here: **EMDMillipore.com/molecule-journey-commercial**.

The right investment strategy for a biologic highly depends on whether the biologic is an originator or a biosimilar and which market is being targeted. For a biosimilar, the company will need to consider other molecules that are on the market, including the originator biologic and other biosimilars, before deciding on the best business strategy to move forward. For example, if the molecule is the first or second on the market, then it would make sense to go for a larger market; but if the molecule is the third or fourth on the market, then building a biomanufacturing facility and going after a larger market may not make business sense.

Filing Strategy is Key to Commercial Success

The drug filing strategy is critical for commercial success and can be either global or local. Each country has its own patient population and the size of this population will drive the market size and ultimately the revenue. Therefore, it is important to identify the right country to file the drug first in order to obtain access to the market quickly. Although strategies that target countries with the largest patient populations may appear to make business sense, these countries may also be more expensive and/or difficult to conduct clinical trials. On the other hand, it may take longer to obtain regulatory approval and gain market access in countries with a smaller patient population. All of these and many other nuances need to be taken into consideration when deciding on the best approach to drug filing.

Process Efficiency Over Speed

At the earliest stages of clinical development, it is not uncommon for companies to focus on getting to the clinic as quickly as possible at the expense of process development efficiency. This strategy is never recommended because a poorly developed process can backfire in the later stages of development when scale-up is necessary, particularly if inefficiency makes the drug too expensive to produce for the patient population. With scale-up, the process should be consistent and reliable and should be able to run with minimal resources so that it can deliver a cost of goods that is compatible with the market. For this reason, process efficiency should always be addressed at the earliest stages of clinical development.

When selecting a service provider for early stage development activities to help speed a molecule to the clinic, companies should seek a trusted partner because the viability of their company rests with these molecules. The right partner will have the right set of expertise and capabilities, as well as a proven track record within the industry. Moreover, the speed of the CMO should be taken into consideration as a company can be delayed from getting into the clinic quickly if the CMO cannot meet the timeline expectations.

Cell Line Development Considerations

Choose the Right Clone

Perform Robustness Studies

Ensure Genetic Stability

Choose the Right Clone

Cell line development is a critical first step in early stage process development. Key considerations when choosing a cell line include the cells' ability to produce the biologic of interest, and then generating a clone from that cell line that can produce the biologic at high productivity/titer and high protein quality. Protein quality is of particular concern for a biosimilar, which must demonstrate biosimilarity to the originator biologic. Once a clone has been identified that produces a quality protein at the target titer, a cell bank will then be established, which typically takes 28-30 days. This cell bank will then undergo safety testing, a regulatory requirement to ensure that there are no contaminants.

Perform Robustness Studies

Once a cell bank has been established from a single clone, the next challenge is to determine the ability of the cells to perform in scaled-up conditions. A best practice is to perform robustness studies that replicate the physical environment that the cell line will experience when scaled up in a bioprocessing environment. For example, a bench-top stirred-tank bioreactor can provide a good understanding of a cell's ability to withstand the challenges it will face when scaled up. Cells are under a lot of stress in a bioreactor and if they are not tested during the early stages of development, the company could have to start from scratch to seek out a more robust clone if the cells cannot withstand the pressures of a bioreactor.

Ensure Genetic Stability

Another consideration for cell line development is to select a clone that is not only of the highest productivity, but one that is also genetically stable. It is critical to choose a clone that will not change over time. Genetic stability testing is conducted empirically; the general rule is that if the productivity and protein quality remain stable after 60 generations of cells, the cells are considered genetically stable. This process takes between 60-120 days.

When choosing a partner for cell line development, it is important to identify a provider that not only possesses internally all the expertise for cell line development, but one who can produce the necessary clinical material. This means identifying the right clone within a pool of cells, demonstrating proof of concept, and conducting the requisite testing that is necessary to satisfy regulatory bodies. Moreover, some service providers are able to offer proprietary cell lines that are more conducive to producing high-producer clones with less development times than non-proprietary cell lines.

Analytical Development considerations

- Get an Early Start
- Future-Proof the Methods
- Leverage a Templated Approach

Get an Early Start

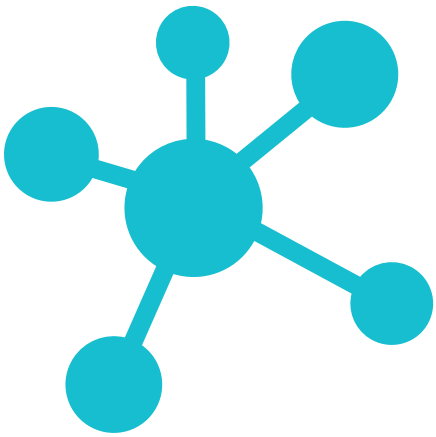
During upstream processes, analytical methods are applied to samples from the harvest in order to monitor the content and quality of the molecule and provide information such as the glycosylation pattern. Samples from each downstream purification step are monitored for purity and quality of the molecule and process contaminants. Because analytical methods are so integral to your entire workflow, establishing the right panel of methods and confirming performance and robustness should start early, at the time of process development.

Future-Proof the Methods

While development of analytical methods should start early in the process, always keep the future in mind. At some point the method will be used in a GMP setting or production support and likely be part of a technology transfer. A best practice is to not incorporate unusual or exotic reagents or unfamiliar suppliers for the analytical method. For example, a reagent that is difficult to supply will present an issue for the GMP step. An optimized method and a secure reagent supply will reduce the risk from the start, and protect the process when transferring to the validation method.

Leverage a Templated Approach

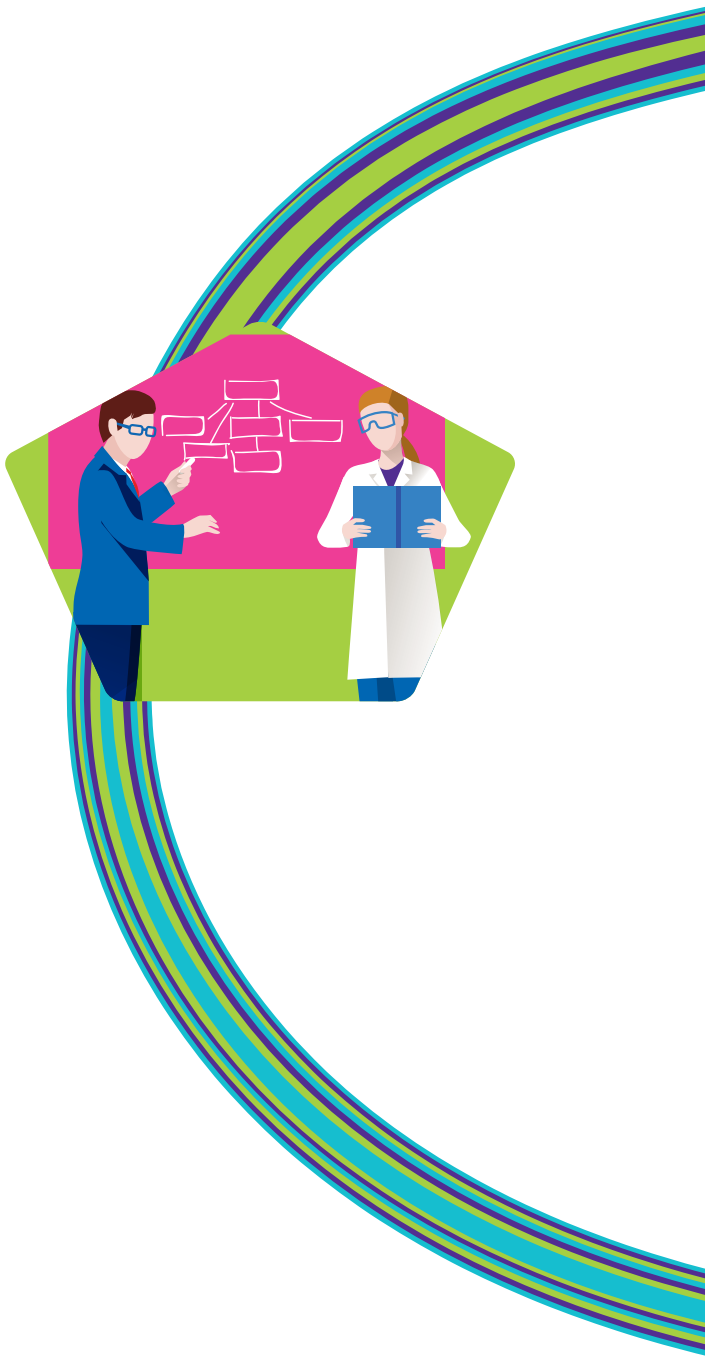
You don't have to start from scratch each time you need a new method. The process of analytical development can be accelerated with use of robust, generic methods and a templated approach to their evaluation and assessment- but still allow flexibility. Even if a specific, novel method is needed, the templated approach will save time as you can start with proven, foundational elements of the method and then integrate customized aspects tailored to each phase and project.



process development considerations

Ensure Process Efficiency and Viability

During the earliest stages of process development, it is important to ensure that the process is both efficient and viable in terms of tech transfer at later stages of clinical development. Engineering in process efficiency ensures favorable biomanufacturing costs by seeking to eliminate wasteful steps and optimizing multi-work area capacity utilization. The term *process viability* involves the ability of the process to be reliably reproducible through scale-up and tech transfer to another operation, where it can then be implemented and validated per its original intentions. Such viability is not only applied to the robustness of the engineered process, but also its ability to meet the economic goals of the project. The overall life cycle of the process should always be considered including commercial and regulatory issues along with ease of scalability.



Financial Viability Over Productivity

The best process is one that is also viable from a financial standpoint. Although productivity is a critical component of process development, if the cost of a molecule is $1,000/gram, then the process itself is not efficient, and is therefore not viable because the final drug product will not be financially viable. As mentioned above, a poorly developed, inefficient process could result in a drug product that is too expensive to produce for the patient population, thereby negatively impacting its commercial success.

Ensure Process Efficiency and Viability

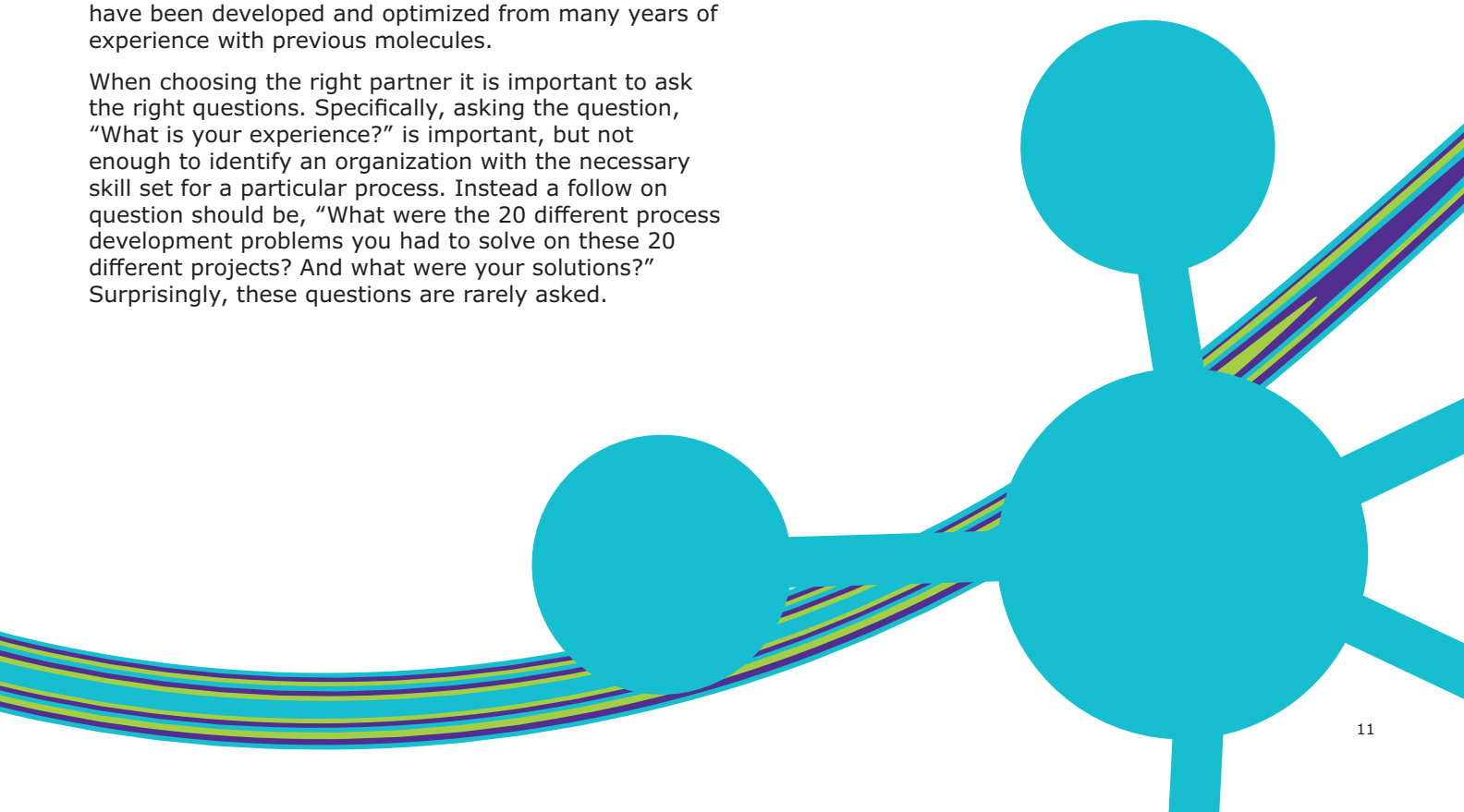
Financial Viability Over Productivity

Ask the Right Questions

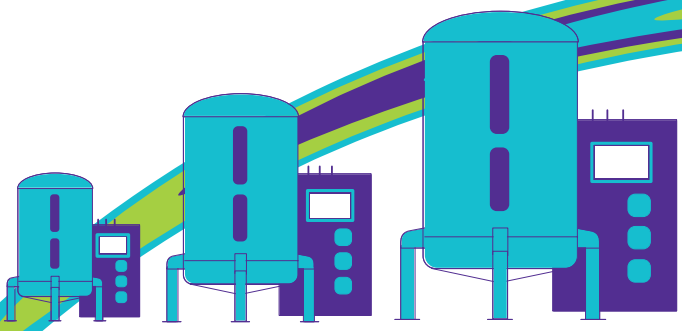
Ask the Right Questions

If a company does not have the requisite skills or resources necessary for process development, then it would make business sense to outsource this important component to a trusted partner. This approach can also reduce time and complexity as established drug manufacturers are able to use process templates that have been developed and optimized from many years of experience with previous molecules.

When choosing the right partner it is important to ask the right questions. Specifically, asking the question, “What is your experience?” is important, but not enough to identify an organization with the necessary skill set for a particular process. Instead a follow on question should be, “What were the 20 different process development problems you had to solve on these 20 different projects? And what were your solutions?” Surprisingly, these questions are rarely asked.



technology considerations



Flexibility Can Reduce the Cost of Goods

From a technology perspective, flexibility is key. Flexibility includes not only the templating of conventional unit operations to ensure process flexibility, but also equipment mobility. The ability to move equipment in and out of the production suite and to quickly and easily prepare for the next run will increase the available time for production. Gamma irradiated (pre sterilized) assemblies and in-process aseptic connection/disconnection technology have made this mobility possible, along with the potential for a closed process.

The trend towards single-use equipment allows for enhanced flexibility and the ability to template processes. Single-use systems provide overall savings through the elimination of Clean In Place (CIP)/Steam In Place (SIP) and associated chemical, energy and time requirements. Moreover, single use allows for shortened timelines to facility start up and rapid suite configuration and changeover. Overall, these benefits result in a reduced cost of goods.

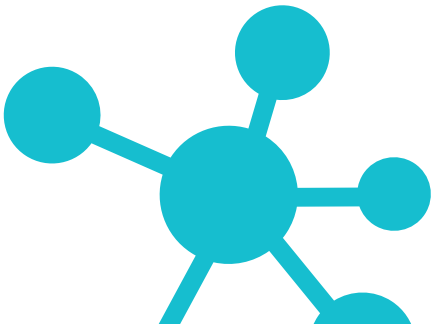
Scalability Is Key

Scalability is an important consideration when choosing technologies at the earliest stages of clinical development. For example, the ability to directly scale a bioreactor used for mammalian cell culture from 3L to 200L to 2,000L is a critical need. High throughput screening can be accomplished very efficiently using spin tubes or micro bioreactor formats. Once the top media and feed candidates are selected, they are tested in a 3L single use bioreactor format. The data obtained in the 3L bioreactor is directly scalable to the performance in the 200L and subsequently the 2000L single use bioreactor. The process is extremely efficient at screening candidates while simultaneously allowing predictability at production scale.

Evaluate for Ease of Use

Evaluating for ease-of-use is another important consideration when choosing technologies. Cost of Quality [i.e., failed batches/scrap] or process inefficiencies due to unnecessary complexities associated with processing equipment and their underlying technologies not only undermines the efforts of process development to deliver optimal systems but can impart longer-term negative consequences upon the bioproduction facility due to fixed installations and 'platform' choices that will be used for subsequent projects. Selecting technologies that exhibit a logical simplicity in use as well as flexibility in utility will likely pay collateral benefits beyond any single project. Examples of this include the use of pre assembled sterile process flow paths; connectors that allow for aseptic connection, disconnection and re connection while containing process fluids; and equipment designed with a single base unit capable of performing different unit operations with a simple adaptation.

While individuals might invoke different priorities when selecting process technologies, ultimately these priorities tend to coalesce around a total cost of ownership strategy. As such, reducing complexity and increasing flexibility can impart operating cost benefits over multiple processes, products, and facility utilization.



Flexibility Can Reduce the Cost of Goods

Scalability Is Key

Evaluate for Ease of Use

Reducing complexity and increasing flexibility can impart operating cost benefits over multiple processes, products, and facility utilization.

Technology Transfer Considerations

Work with an Experienced Partner

Begin with a Transfer in Mind

Be Thorough to Reduce Risk

Work with an Experienced Partner

It's inevitable. At some point, you will need to transfer a process either to another team for scale-up purposes or perhaps to another building, company or geography for manufacturing. Proactive planning for these events is essential as similar process conditions across different capacities and methods must be established.

One key to a successful tech transfer is experience. You need to know your equipment and set the tolerances and precisions of every operation and parameter in accordance with production capacities, leverage advanced tools for sizing and modeling and seamlessly manage people and planning. If this is your first tech transfer, don't go it alone – instead, partner with an expert who has done it many times and can optimize and accelerate the process while minimizing risk.

Begin with a Transfer in Mind

The ability to flawlessly execute and validate a tech transfer ensures robustness and applicability at higher scale. If problems arise, additional studies might be needed to understand and adapt the process, requiring extra time and money and putting key milestones in jeopardy.

As such, it is critical that every gap be managed as early as possible. Risks can be mitigated with use of pilot runs or via calculation tools for modeling and sizing. In a worst-case scenario, an unsuccessful tech transfer can result in loss of efficiency of the process such as a low titer or decrease of production yield, a loss of robustness in which GMP batches are not similar, or impact the quality of the molecule in terms of activity or charge profile.

Be Thorough to Reduce Risk

All data from development must be considered as potentially relevant and as key parameters for future tech transfer. A gap analysis should be completed between development and production and include methods, equipment, consumables and processes; everything that cannot be transferred directly “as is” must be assessed. This analysis details potential risks, the root cause, potential impact and informs the mitigation plan.

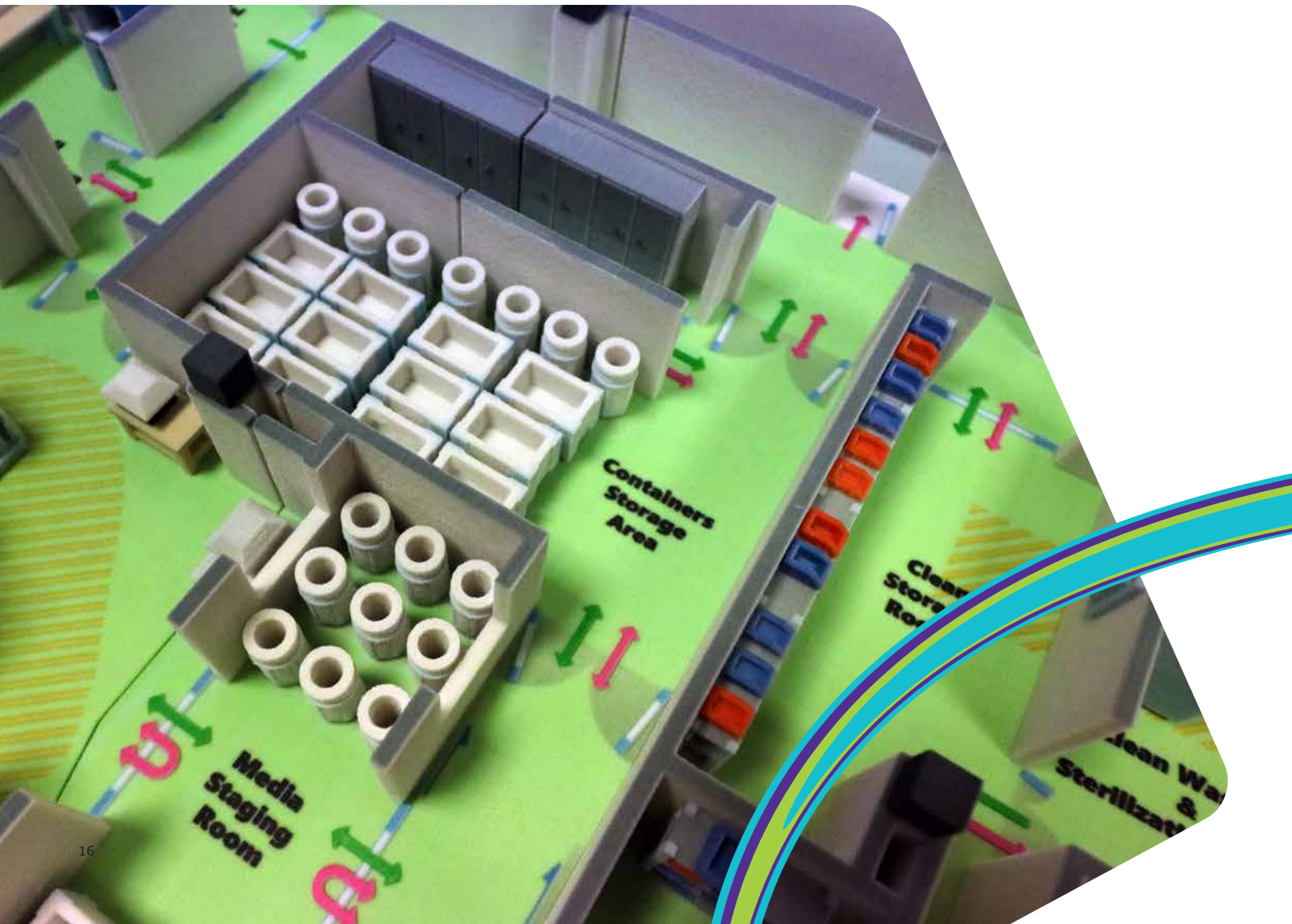
Keep in mind that every method and operation – even those considered the simplest – should be analyzed in detail as even a small difference can have a big impact. Any difference in methods, equipment performance and software represents a risk.

Regulatory & Risk Assessment considerations

Patient Safety is Always Priority

The main driver of regulations and risk assessment is to ensure patient safety. It is important to have milestones in place throughout clinical development that can assess for safety issues and product effectiveness, beginning as early as possible in development. Safety issues include not only contaminants, but also different product isoforms that may prove toxic to patients. Therefore, it is important to obtain deep knowledge of the product early in development in order to understand what potential safety issues to assess for throughout development.

From a contamination standpoint, it is important to demonstrate that logical product and personnel flows are in place, that work areas are properly sized and organized to prevent cross-contamination, and that measures are in place to mitigate risk (e.g., exposure to microbial contamination) to a minimum level.



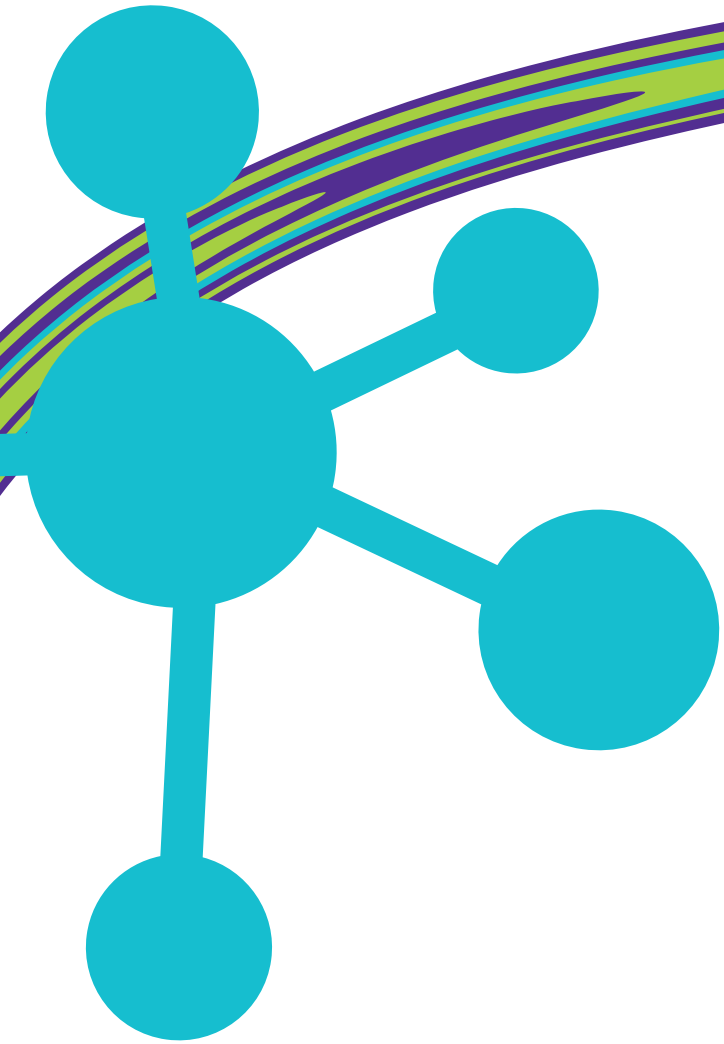
Patient Safety is Always Priority

Ensure Product Quality and Process Robustness

Engage Regulatory Authorities Throughout Development

Ensure Product Quality and Process Robustness

From the earliest stages of development, data supporting both product quality and process robustness will need to be collected and ultimately validated, and the analytics demonstrating each of these should be developed in parallel with process development. It should be demonstrated early that the process developed is robust enough to advance into later stages of clinical, and ultimately commercial development. With a focus on the established critical quality attributes, product quality should also be data-mined as early as possible prior to development of the first clinical batch, and then monitored closely after the first injection into patients.



Engage Regulatory Authorities Throughout Development

Understanding which countries a company intends to file will dictate which regulations they must adhere and which regulatory agencies will inspect the manufacturing facility. There are some differences in expectations among regulatory authorities on specific aspects of process validation and process controls, but they share some practices as well. There is a sharing of information between the European Union (EU) and the United States (US), and the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) guidelines are now finally becoming the worldwide basis for all countries.

From a regulatory perspective, a best practice is to have conversations with the regulatory authorities both up front and on a regular basis in order to validate the development approach, make sure that any assumptions made are correct, and ultimately to ensure that the company is going in the right direction. With regular engagement, more-informed decisions can be made to enhance the likelihood of commercial success.

Conclusion

When bringing a molecule from the bench to the clinic, there are many important considerations that biopharma executives must take into account throughout the journey that will impact the success of their commercial strategy. To safeguard against development setbacks and ultimately the viability of the drug candidate, every decision made should focus on getting to the clinic as quickly as possible, but never at the expense of product quality, process efficiency, or patient safety.

Companies that are in early stage clinical development but lack the requisite expertise and resources to navigate the complexities associated with business planning, cell line development, process development, analytical development, technology and technology transfer , and regulatory and risk assessment, should seek out a service provider to help break down roadblocks and improve the likelihood of commercial success. The right provider is one that has significant expertise bringing similar molecules to the clinic, has the right set of resources and capabilities, as well as a proven track record within the industry. Most importantly, companies should seek not only a service provider, but one that is also a trusted partner in the process, because the viability of the development program, and ultimately the company, relies on bringing these molecules to the clinic.

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