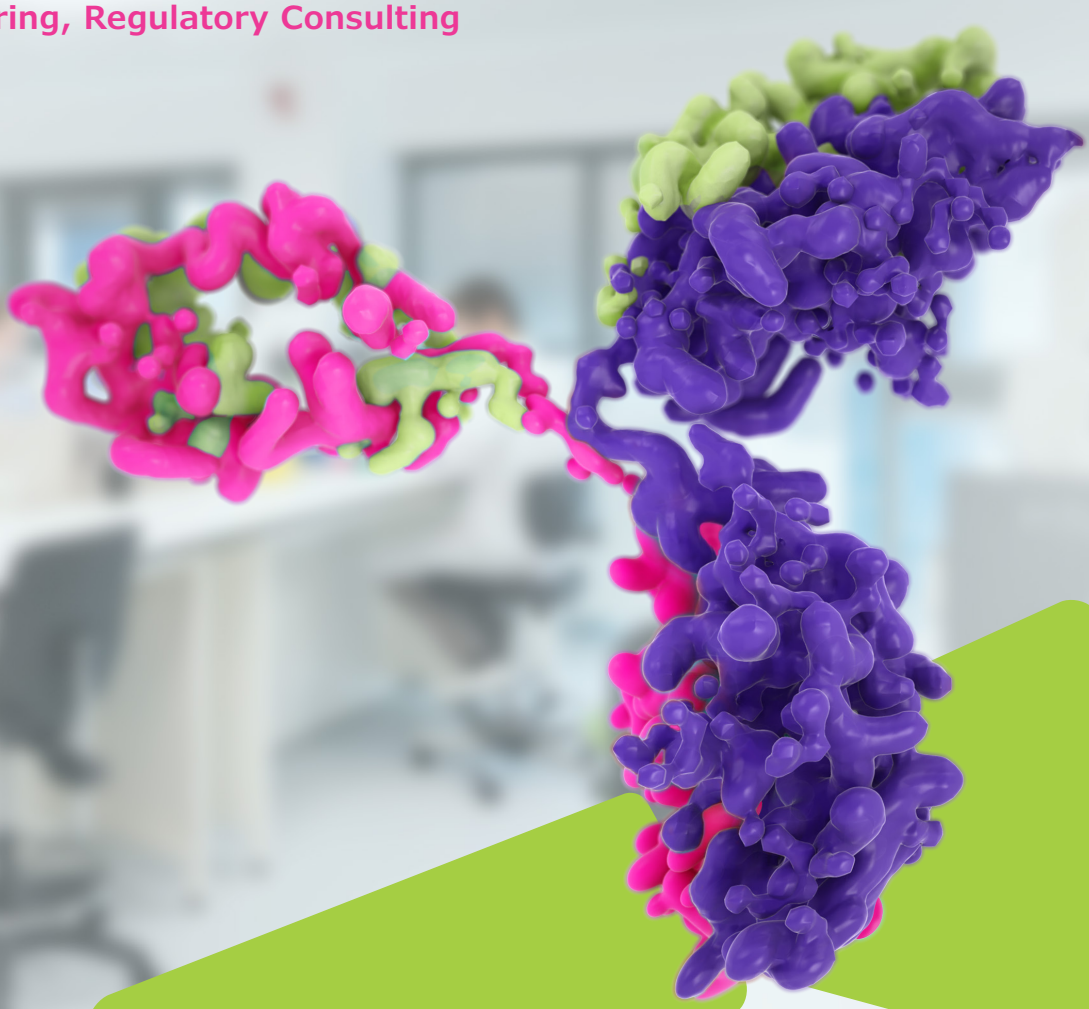
MilliporeSigma

Optimizing and Executing your Commercial Manufacturing Strategy

Process, Engineering, Regulatory Consulting & CDMO Services



BioReliance®

Pharma & Biopharma Manufacturing & Testing Services

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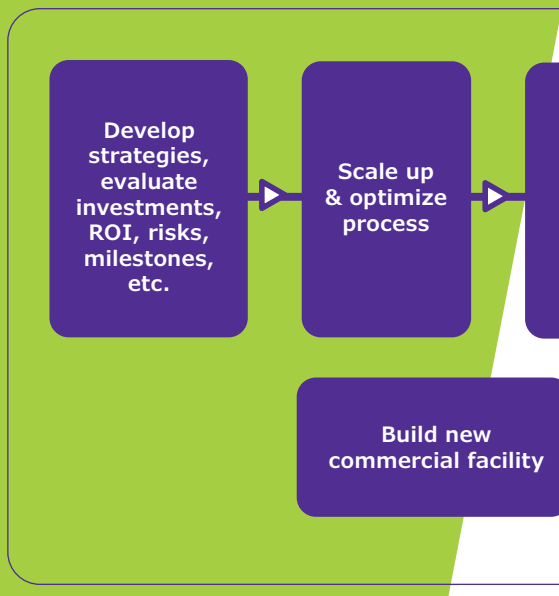

With a drug candidate in clinical development, you need to make important choices that will impact the success of the program, and perhaps the entire organization. One of the most critical decisions is definition of a long-term commercial manufacturing strategy.

Every therapeutic candidate and every company is different, and as such, there is no single, predefined commercial manufacturing strategy that will ensure success. Instead, development of customized strategy should be guided by answers to a set of mission-critical questions, considered well in advance of the need for large-scale GMP production:

- Is my clinical process scalable and viable to go commercial?
- Is my process and drug product well characterized?
- How do I ensure regulatory compliance?
- Do I have resources and expertise to optimize, scale and validate the process for GMP commercial operation?
- Should I subcontract GMP commercial operation or build my own GMP commercial facility?
- How should my facility be sized, designed and equipped for GMP commercial operation?

While the right strategy is one that is cost effective, accelerates time to market, reduces risk and meets regulatory expectations, there is more than one path to success **(Figure 1)**.

Figure 1. Defining and executing commercial production strategy for a biologic drug is complex and requires resources, experience and expertise in multiple areas including strategy, finance, process and analytical development and validation, as well as GMP commercial operations.

A Unique and Flexible Partner

As you advance towards commercialization, the BioReliance® End-to-End Solutions team is uniquely suited to help determine the best way forward and deploy the chosen strategy – no matter which approach is selected.

Our multi-disciplinary team has decades of experience with hundreds of biologics in the areas of process scale-up, optimization, validation for GMP commercial operation and production. We can provide the technology, equipment and expert counsel to support your internal teams in these critical steps or you can sub-contract these activities to us as your CDMO partner.

With either scenario, our highly experienced team will enable you to:

- Estimate required investments to support commercial scale production
- Evaluate and mitigate project risks
- Adapt, scale and validate manufacturing process to meet market demand
- Assure regulatory compliance for your drug GMP commercial operation
- Meet short project timelines with confidence

Our Difference is Your Advantage

Our unmatched breadth of expertise creates a competitive advantage for customers. In addition to being an industry leader in single-use technologies and equipment, we provide CDMO services at GMP facilities we conceptualized, built and have operated since 2012.

We also design GMP manufacturing facilities for our customers who wish to manufacture in-house. Our unique combination of leadership in single-use technology, CDMO capabilities and facility design expertise enables us to define, conceptualize and implement a commercial manufacturing strategy tailored to your exact needs and timing.

Whether you use our consulting services or select us as your CDMO partner, our team brings more than 33 years of experience in process development and more than 25 years in GMP production to your project. When you work with us, you benefit from our:

- Extensive experience in GMP operations using single-use technology
- Proven models for process scaling, optimization and validation
- Multi-disciplinary team with expertise in strategy, regulatory, GMP operations, process development, analytical, quality, EHS and engineering
- Willingness and transparency to collaborate with partners you bring into the project including consultants, A&E and technology providers
- Flexibility in the technical transfer of your GMP commercial production to our Biodevelopment Centers, to another CMO or to your own facility
    - Global network of Biodevelopment Centers to run bridge GMP manufacturing while your own facility is under construction

How We Work with You

As a first step in every customer engagement, we gather the information and documentation necessary to understand the state of your current manufacturing process and analytical testing methods.

This approach allows us to assess existing gaps and ensure that your process can be run at one of our Biodevelopment Centers for further process fitting, scaling and optimization activities as outlined in **Figure 2.**

Process scaling, fitting and optimization

Prior to starting any activity on the process, we ensure project viability and determine, in collaboration with our customers, the appropriate target for process efficiency and scale. Our extensive experience and breadth of expertise allow us to adapt and design fit-for-purpose solutions quickly, resolve any problems that may arise and accommodate unexpected changes, all while delivering against critical project timelines.

We accelerate and de-risk scale-up and tech transfer through use of pre-defined Upstream process/ Downstream process scale-up protocols and models using our own equipment and expertise with single-use technologies in GMP operations.

Below, we outline the steps following tech transfer of your process into our facility as we adapt your process to commercial operation.

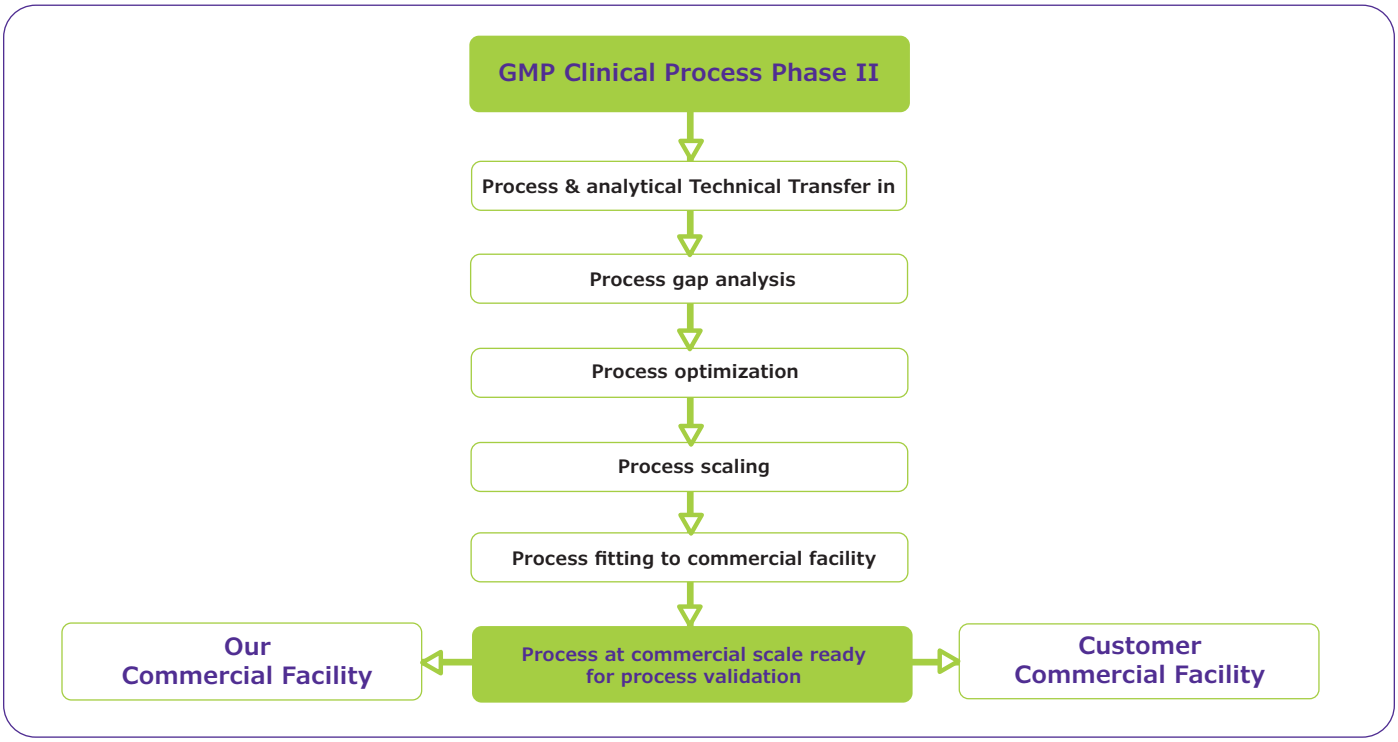

Figure 2. Several steps are undertaken following the initial tech transfer of your process to our facility to develop a commercial scale process ready for validation.

Process gap analysis

- Review, in collaboration with the customer, its commercial manufacturing strategy (drug market size and capacity needs, peak demand, clinical development and drug filing strategy) to determine the appropriate target for process optimization
- Review existing process including GMP requirements, quality, health and safety, regulatory, analytical and determine routes for process optimization
- Propose a path forward including recommendations for optimal scale, scale-up strategy, timing and process performance requirements

Process optimization

- Execute all necessary process and analytical development activities as defined by the process gap analysis
- Conduct pilot production (GMP or non-GMP) and reproducibility studies if needed as a result of process changes and associated risk assessment

Process scaling

- Execute all necessary adaptation to Upstream Process/Downstream Process to scale for GMP commercial production

Process fitting to commercial facility

- Ensure process is ready to be transferred to the facility where GMP commercial batches will be manufactured
- Adapt the process as required to fit within specific constraints due to existing non-critical equipment at the commercial facility

We accelerate and de-risk your process scale up with pre-defined Upstream/Downstream protocols and models we developed using our own single-use process equipment and technologies in our GMP production operations.

Process Validation

Process validation is a complex, yet critical, step in the transition to commercial scale manufacturing. The process must be frozen prior to starting process validation activities, and in many cases, limited information and data are available from the clinical stage.

Regulatory expertise is also required as the specific expectations of agencies around the world will depend on the nature of the project and the biologic drug. As such, the process validation strategy will be adapted as appropriate to ensure compliance.

During validation, process knowledge is developed and documented. Analytical method validation is also conducted to demonstrate the recommended approach is valid in the process range defined for each critical quality attribute (CQA).

Our experience with implementation of single-use technologies in GMP operation provides an advantage during process validation. These technologies offer benefits in terms of standardization of process equipment, simplified process validation due to reduced cleaning validation requirements and simplified technical transfers.

Below, we outline the steps included in process validation.

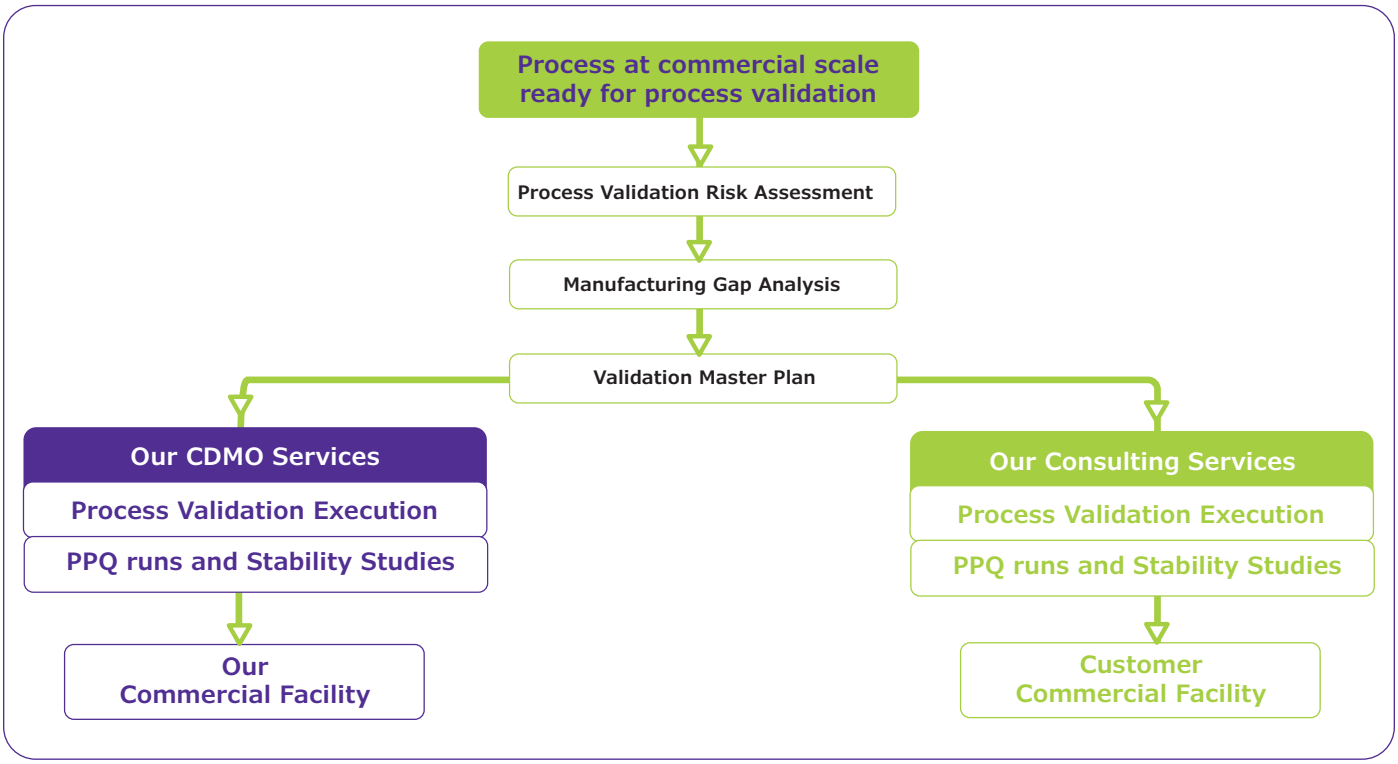

Figure 3. Process validation steps leading to the Validation Master Plan. Execution, PPQ runs and stability studies can take place at the customer site under the guidance of our consultants or at our Biodevelopment Centers and CDMO facility.

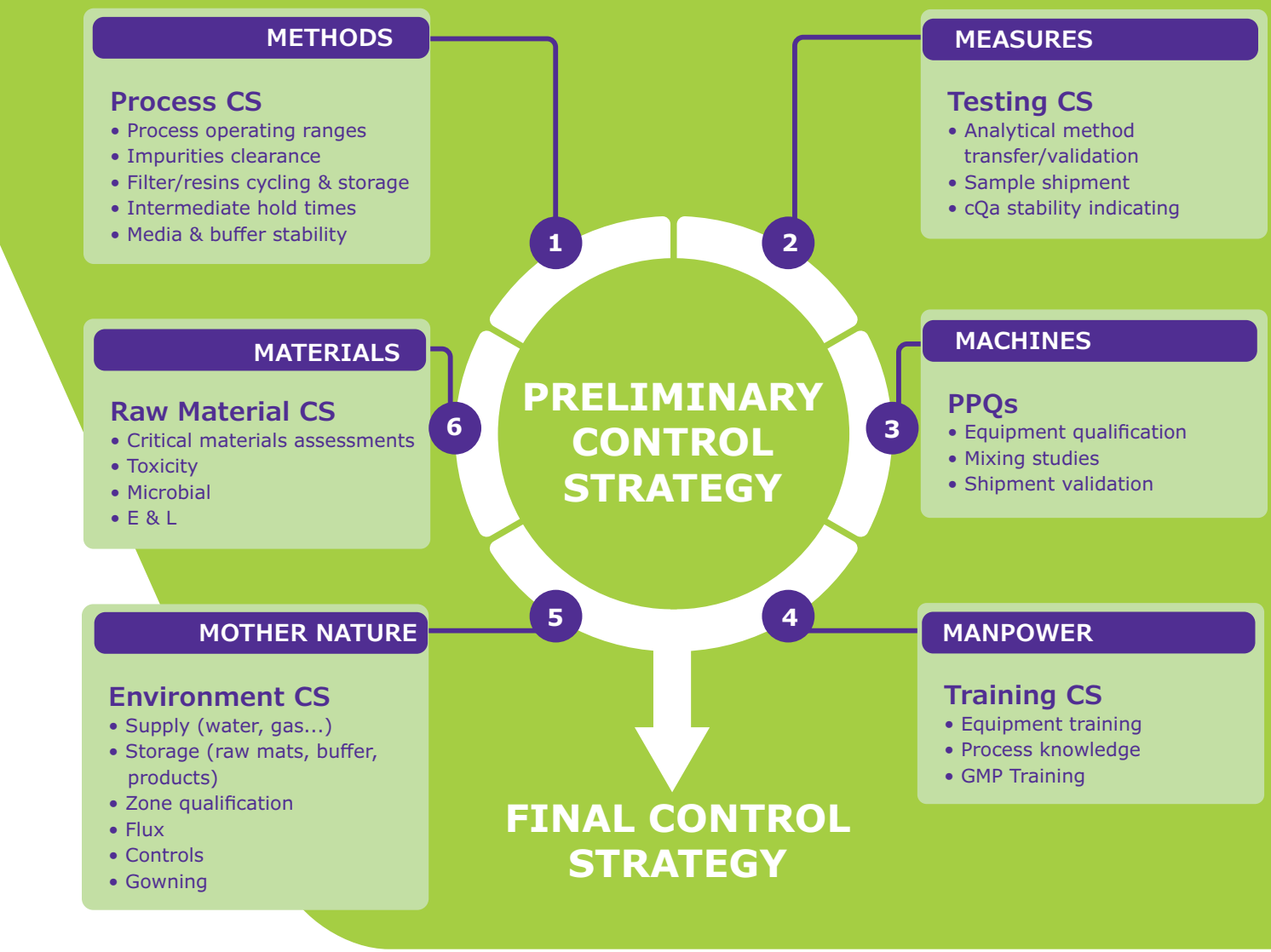

Figure 4. Six areas to be considered when defining process validation activities.

Process validation risk assessment & manufacturing gap analysis

- The determination of process validation needs is a documented risk-based approach to estimate the residual risk for the patient considering:

- Product knowledge (existing accumulated experience)
- Process knowledge and understanding (existing accumulated experience)
- Appropriateness of the control strategy

- The objective is to determine through a series of risk assessments and gap analysis, what is the appropriate quantity and type of data to demonstrate that the process delivers reproducibly a product that meets predetermined quality attributes.

Validation Master Plan

- Define validation activities to be performed to support the registration of the manufacturing process
- Write validation master plan, consolidating all information and including all studies and activities pertaining to the 6 M's **(Figure 4)**

Process Validation Execution

- Process validation can be fully executed at our Biodevelopment Centers, followed by the PPQ campaign at our GMP commercial facility
- Alternatively, our expert consultants can support customers executing process validation and PPQ campaign in their own facility, with some activities subcontracted to our global network of BioReliance® Validation Services laboratories as needed

Facility Engineering Services

We have operated our GMP clinical facility, now equipped with 100% single-use technology, since 2012.

Originally a stainless steel facility, we engineered its evolution into a complete single-use operation for production of monoclonal antibodies up to 2000L scale. Through this transformation, we acquired hands-on experience implementing and optimizing use of our own single-use technologies in GMP operation, which our customers can benefit from as they seek to design, equip and operate their own new facilities.

We can help our customers design their facilities with flexibility and efficiency in mind, accurately estimating CapEx and OpEx, and ensuring adherence to budget (Figure 5). In addition, customers also have access to our experts from all key functions of the GMP facility to ask questions, seek guidance and get counsel to help ensure success.

If you plan to invest in a new GMP production facility, we have designed a set of services and tailored programs to ensure your success. Our facility engineering services include manufacturing strategy development, facility feasibility studies, conceptual design and support for engineering, procurement, construction, management and validation (EPCMV) in conjunction with A&E organizations.

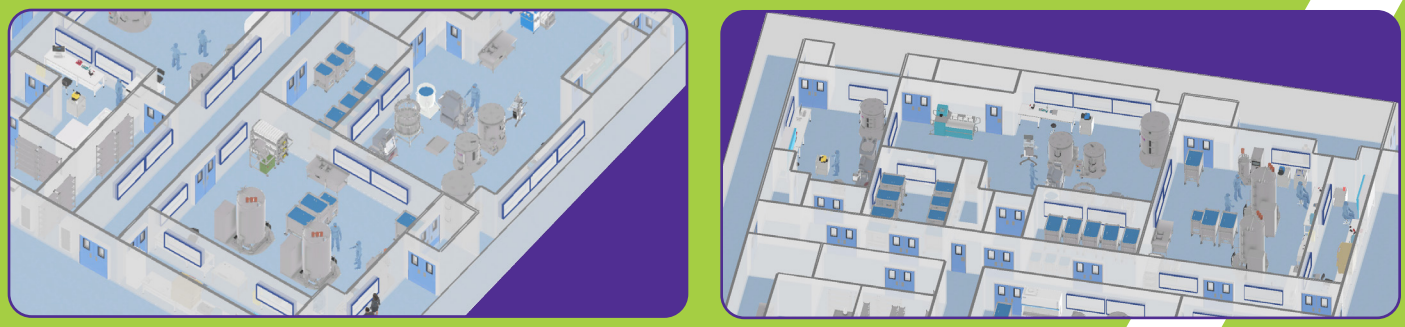

Figure 5. Key considerations when investing in a new facility

Image source: Hakobio

Manufacturing Strategy Development

- Provide all necessary information to adequately size investments required, measure and understand the risks vs. benefits and determine if the customer's manufacturing strategy is viable or not for further investment.
- Host customer team at our GMP facility for a session focused on key considerations affecting manufacturing strategy development and execution including:
  - Clinical phases and clinical material requirements with timing and costs associated
  - Clinical/commercial material manufacturing combination strategies based on the number of patients and what needs to be studied, market sizing vs. capacity needs and how to manage peak demand
- Host a workshop with our technical experts in GMP operation, process development, regulatory, facility engineering, quality, health & safety and analytical to further discuss your project and answer specific questions.

Facility Feasibility Study

- Review facility build up/expansion, facility fit or facility revamping projects with the customer team, taking into account process and facility engineering, GMP, quality, health, safety and regulatory requirements and evaluate potential pathways for project execution.

Facility Conceptual Design

- Design new facility based on the customer's commercial manufacturing strategy. Examples of deliverables, customized based on project scope and required level of detail, are provided in **Table 1.**

Facility engineering and construction – EPCMV collaboration

- Collaboration with the EPCMV partner you have chosen for your project, sharing our expertise of designing facilities and our experience of operating a single-use GMP facility

Activities	Deliverables
Process and Operation	- Facility operation strategy (assumptions on how the process will be operated in the facility) - Detailed process analysis (Volumes to produce depending on low & high titers assumption, manufacturing scale, batches/year...) - Process modeling and process flow diagrams - Creation of mass balance with low/high titer assumptions - Calculation of solution volumes and liquids handling strategy - Detailed equipment list with sizing (including storage vessels) with associated CapEx +/- 15% - List of process consumables - Assessment of the manning requirement for future operation
Facility	- Definition of facility concept: Area diagram and room table with footprint - Buffer and media volume and associated storage areas calculations - Facility layout in customer project environment - 3D modeling & visualization - Facility layouts with process, waste, people, material flows - Room classifications, AHU (HVAC concepts) - High level sizing utilities (production & distribution strategy), waste disposal strategy, automation strategy (process & facility) - Estimate facility CapEx +/-30%, FTEs estimate with organization of process operations, OpEx estimate +/-30%, estimated timeline
Regulatory	- Definition of the regulatory framework (list of guidelines/reference applicable) - High level regulatory strategy concept (gowning strategy, room classification...) - Facility regulatory risk assessment performed by our GMP site regulatory expert

Table 1. Example of facility conceptual design deliverables.

Regulatory Compliance Services

Your drug filing strategy will dictate how your process should be developed and validated as well as who will inspect the facility. We can support all aspects of regulatory compliance from file writing to post-approval. We have extensive experience with regulatory agencies around the world. We can evaluate regulatory expectations and according to your project needs, translate into proven risk assessment and risk mitigation methodologies. We have experience writing documents for IND/ IMPD/BLA/MAA submissions.

Our activities include:

Regulatory and GMP Documentation Review for Due Diligence

CMC Regulatory Support

- Interact with regulatory authorities both upfront and on a regular basis
- Support you in developing your regulatory strategy
- Gain authorities' expert advice regarding your forthcoming submission
- Obtain insight into possible post-submission regulatory questions

CMC Clinical and Commercial Content Writing

- Formatting of information to the Common Technical Document (CTD) to build the Chemistry, Manufacturing, and Controls (CMC) for the drug substances that will be submitted to support your clinical or commercial application

Support for IND/IMPD/BLA/MAA Submission

- Submission experience in multiple countries
- Support for meetings with regulatory agencies

Experience, Resources and Expertise to Ensure your Success

Integrated Project Management with a Single Point of Contact

In order to most effectively support each project and ensure timely progress against key milestones, we use a robust, detailed and thorough approach to project planning. Each customer has an integrated project management team with a single point of contact for all activities. This structured and proven approach ensures consistency and adaptability as the project evolves, along with complete and transparent communication.

GMP Biodevelopment Center

We gained significant experience through the design, build and ongoing operations of our GMP Biodevelopment Center. The facility houses five state-of-the-art GMP suites for therapeutic protein production and was one of the first to attain GMP compliance utilizing single use equipment for each unit operation from upstream through downstream. The facility was also designed to lower its environmental impact, including a significant decrease in water usage.

Our Experience

33
Years in Process Development

250+
Biologics
(Antibodies, hormones, fc-fusions, Recombinant Proteins)

75+
GMP Drug Substance Batches
Released since 2012 using single-use technology

Global Network

No matter where you are located, you can access the power of BioReliance® End-to-End Solutions and our expert counsel to advance from clinical to commercial scale manufacturing. Our global network includes Biodevelopment Centers, biosafety testing sites and validation service sites.

World-Class Experts

We have assembled an unmatched team of experts to help ensure your success as you transition to commercial manufacturing. Our team represents all aspects of manufacturing strategy development, process scale-up, optimization and validation, technology transfer, GMP production, regulatory compliance and facility concept design.

Meet some of our world-class experts:

Sébastien Ribault
Vice President and Head of BioReliance® End-to-End Solutions

Sébastien joined us in 2005 and is vice president and head of BioReliance® End-to-End Solutions and the managing director of the Biodevelopment Center located in Martillac, France, where he leads the CDMO branch dedicated to large molecules within MilliporeSigma. Sébastien also supports the development of new and innovative biomanufacturing technologies and solutions in collaboration with the company's process development team.

Prior to joining us, he was a gene therapy development scientist at Transgene and was head of the R&D laboratory and member of the board of directors at Hemosystem, an *in vitro* diagnostics company. Sébastien received his microbiology engineer degree from the Engineer School of Luminy, Marseille, France and his Ph.D. in molecular and cellular biology from the University of Strasbourg.

Peter Bell
Head Global Delivery of BioReliance® End-to-End Solutions

Peter is a maintenance engineer with more than 30 years of experience in the biopharmaceutical industry. He has held roles with increasing responsibilities in the areas of industrial maintenance, project engineering and corporate engineering functions at EMD Serono and GSK Vaccines. His prior experience includes time as the head of operations for Stallergenes Greer and as head of European Capex Portfolio Management for the biologics division of Lonza.

Laure Valognes
Head of Operations of BioReliance® End-to-End Solutions

Laure is a biotechnology engineer and has been with us for nearly 20 years. As head of operations, she is centrally involved in the coordination of activities related to process development, technical transfer and scale-up for GMP manufacturing. With deep expertise and more than 15 years of experience with GMP manufacturing requirements in the biotechnology setting, she is able to ensure the high quality of deliverables for customers.

Muriel Richard
Regulatory Expert of BioReliance® End-to-End Solutions

Muriel has 30 years of experience in the biopharmaceutical Industry, working across a wide range of functions including R&D, clinical production and quality. Muriel has more than 20 years of experience in regulatory compliance and is currently supporting customer projects within BioReliance® End-to-End Solutions. She has successfully led customers through numerous IND filings and BLA submissions and has filing experience with regulatory authorities in several countries and has regular conversations with these organizations.

Jérôme Pionchon
Engineering Consultant of BioReliance® End-to-End Solutions

Jerome is a mechanical engineer and has been with us for 20 years. He has held several positions from industrial and organizational projects to management in production, engineering and maintenance. In 2012, he became head of the technical department in the Martillac BioDevelopment Center and now provides engineering consulting services to customers within BioReliance® End-to-End Solutions.

About BioReliance®
End-to-End Solutions

We are an integrated contract development and manufacturing partner, offering adaptive solutions for small and mid-sized biotechs needing to develop and commercialize biologics.

We do this by balancing speed, risk and cost through custom solutions, by leveraging our bioprocessing technologies and process development expertise, and by allowing our clients to transfer their process and knowledge to their end point at any step of the way. With more than 33 years' experience, more than 250 biomolecules and numerous GMP clinical DS batches, we can build strong working relationships around you.

To learn more, please visit
EMDMillipore.com/adaptive-CDMO

BioReliance®

Pharma & Biopharma
Manufacturing &
Testing Services

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