WHITE PAPER

The stage-gate© model:

A value-driven approach to accelerate biomanufacturing



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INTRODUCTION

A large number of biopharmaceutical companies rely on CDMOs to efficiently move their product from discovery through to clinical and commercialization phases. According to BioPlan Associates' 2022 19th Annual Report and Survey of Biopharmaceutical Manufacturing Capacity and Production, about 87% of biopharma companies outsourced at least some activity to CDMOs.[1]

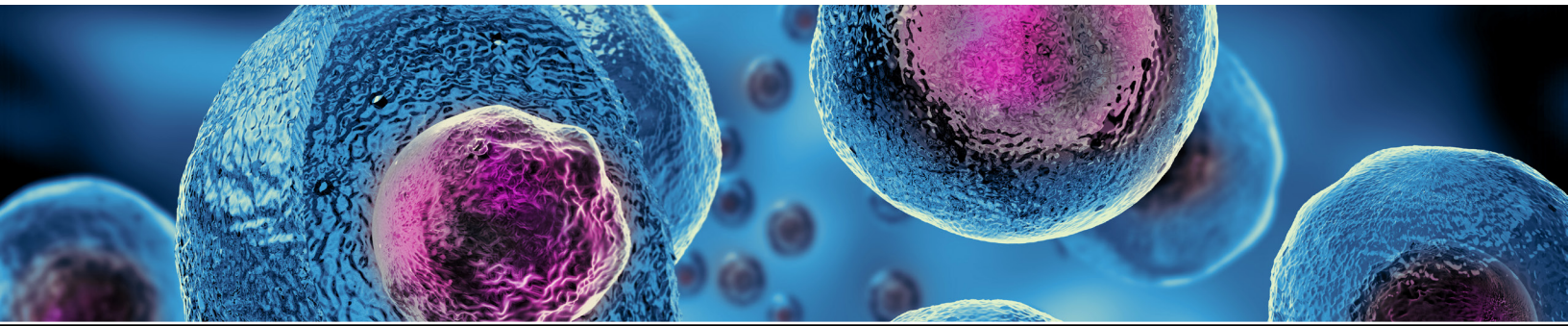
With the increase in outsourcing activities, successful technology transfer becomes even more integral to project success. The exchange of knowledge, expertise, and technology that occurs during transfer requires careful attention to detail. Given that biologics drugs cost 22 times more on average than small molecule drugs, the added expenses caused by tech transfer delays can wreak havoc on a development program.[2]

"A small biotech company could get great results in phase one with their drug, but may not have funding to run phase two," said Joseph Shultz, Vice President & Technical Head of Biologics and Vaccines for Resilience, a global development and manufacturing partner. "And they can't get more funding until they run a clinical study. If we can shorten the path from idea to IND by even a few months, it could mean millions of dollars the company can put toward its next clinical trial."

To help ensure lab processes and analytical methods transfer to the plant floor in a cost- and time-effective manner, it is paramount for an effective development and manufacturing partner to establish cross-functional teams and systematic processes to guide technology transfer. The stage-gate approach is one such process.

Originally developed for product innovation, the stage-gate approach has been used successfully across industries since the late 1980s.[3] Applying a customized version of this approach throughout the drug development lifecycle results in a highly flexible process that ensures critical activities from each stage are effectively delivered.

By performing a systematic review and quality check at various stages of the product and tech transfer lifecycle, it flows more smoothly and quickly while maintaining quality and compliance. In the end, drug developers benefit from shortened timelines, while patients receive earlier access to life-changing therapies.



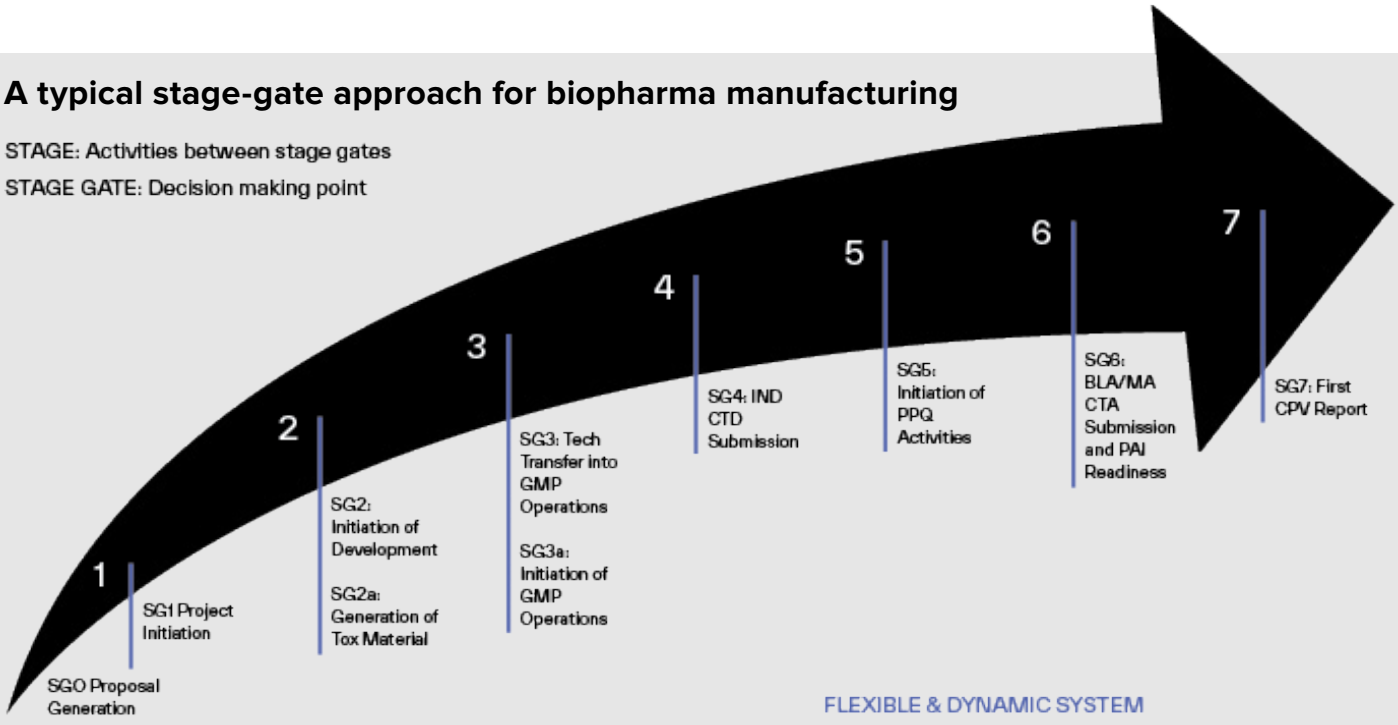
THE RESILIENCE STAGE-GATE APPROACH

A technique used by project managers primarily in product development, the stage-gate approach was designed for process improvement.[3] Using this approach, a large project is divided into stages. Gates between each stage serve as decision points. At each stage gate , decisionmakers come together to assess the previous stage. If all objectives from the previous stage have been met, the project moves to the next stage.

The Resilience stage-gate approach strives to transfer products and processes from sponsors into the development and manufacturing pipeline to enable effective biomanufacturing. To achieve this, the approach was developed to allow for rigor and velocity at each of the steps in the process through the establishment of cross-functional teams. An essential component of the stage-gate approach is stage-gate review, where critical stakeholders from different functions review deliverables from that particular stage and decide whether to move forward with the next set of activities. This is achieved by following a thoughtful risk mitigation approach.

Because the stage-gate approach is customizable, it provides a flexible process while ensuring the CDMO completes critical activities from each stage. “Two of our main objectives are rigor and velocity,” said Marta Papini, Director, Global MSAT, for Resilience. “We built the system in a way that allows us to focus on activities that are critical for that stage. But we also want to maintain the highest standard of compliance. We want to be agile, we want to have the velocity, but not at the expense of rigorous compliance.”

A typical stage-gate approach for biopharma manufacturing



WHAT ARE THE ADVANTAGES OF A STAGE-GATE APPROACH?

While shortening a tech transfer timeline by a month or more results in clear financial benefits due to labor hours and other resources saved, the advantages of an agile approach go much deeper.

Cost control. The faster the CDMO completes the process and/or executes the tech transfer, the sooner the client can get its therapy to patients. An earlier approval and commercial release mean more time on the market before the patent expires. In the pharmaceutical sector, companies can win (or lose) up to $13 million per drug per day.[4]

Time saved off one project may also enable biotech companies to initiate their next project sooner, causing a positive ripple effect in regulatory submissions and commercial launch timelines. “This level of efficiency expands their capacity to accomplish more with their existing resources, rather than constantly expanding their team in order to bring more molecules in their pipeline to clinic,” said Adriano D’Ambrosio, Director, Commercial Development for Biologics and Vaccines for Resilience. “If they’re spending extra time due to inefficient tech transfers, it becomes cost or resource prohibitive to move forward.”

Effective risk-mitigation approach. Working in predefined stages, with reviews at each stage, enables teams to determine whether a product is viable to proceed. It’s possible, upon reviewing stage activities, that a project should be paused, modified, or halted altogether to mitigate some of the risk identified.

Case study 1:

Platform model mAb tech transfer to full-scale demonstration run

Challenge: The client needed to fast-track late-stage development of a dual mAb program. Resilience needed to have sufficient process characterization and product development quality (PDQ) workflow at the beginning of this process.

Solution: Resilience worked from stage gates six and seven to manage risk and development workflows. Resilience reviewed existing process data, assessed process risks, and assigned risk scores for detectability, probability, and severity for all parameters in each unit operation. That process drove development of mitigation strategies for all high-risk items.

Result: The project is ongoing; however, to date all processes are proceeding according to plan. The client expects to file a BLA according to its initial timeline.

Regardless of the result, a methodical approach helps teams provide rapid response. “If you run a typical 30-day process, you may have to run another 30-day process to implement the change and another process to correct a downstream issue that wasn’t visible when the first issue presented,” said D’Ambrosio. “The ability to respond in real time, throughout the stage and at stage gates, allows us to troubleshoot and make adjustments early in development, which preserves resources.”

Patient access. The sooner a product reaches the market, the sooner patients benefit. Given biologics tend to treat rare and serious conditions, faster access has potentially life-saving implications.

“Patients are the ones ultimately benefiting sooner from a treatment,” said D’Ambrosio.

“In some cases, if the treatment isn’t available early enough, some patients may never get the opportunity to receive this specific treatment.”

With significant funds saved by shoring up processes, biologics companies can potentially maintain or reduce drug prices. An improvement in pricing is necessary to serve the global patient population.

About seven billion people globally do not have access to biologics, partly due to pricing.[5] “Every cost increment that allows for a lower cost per dose that we can subtract could add millions of patients worldwide,” Shultz said. “Ultimately, we’re about helping people. How many more companies could get their drug to the clinic? How many blockbuster drugs have died on the vine because we used up too much time?”

Case study 2:

Rapid tech transfer of vaccine product to cGMP

The case: A client needed a rapid tech transfer of a novel vaccine product to move quickly to GMP and to support an IND filing for first-in-human studies. The client had already developed the process and analytical methods.

Solution: Resilience used its advanced digital framework to comprehensively capture all client information. A collaborative Q&A tracker enabled the team to efficiently resolve outstanding queries. Additional optimization was needed to successfully scale upstream activities. All information was transferred to the Resilience platform to transfer into cGMP manufacturing and quality.

Result: This process, combined with close communication with the client, enabled Resilience to execute early GMP batches quickly and successfully and release the product so that the client could submit an IND submission on time.

STAGE-GATE CORE CONCEPTS

The Resilience stage-gate approach is based on three core concepts: velocity, flexibility and rigor. All three concepts work together as part of a well-orchestrated, cross-functional process.

Flexibility: Resilience has defined seven stages for biomanufacturing, however, not all stages are relevant to a client depending on where the client product sits in the lifecycle. Depending on the project, it may skip stages or start at a later stage. A project early in development may start at the beginning – stage one.

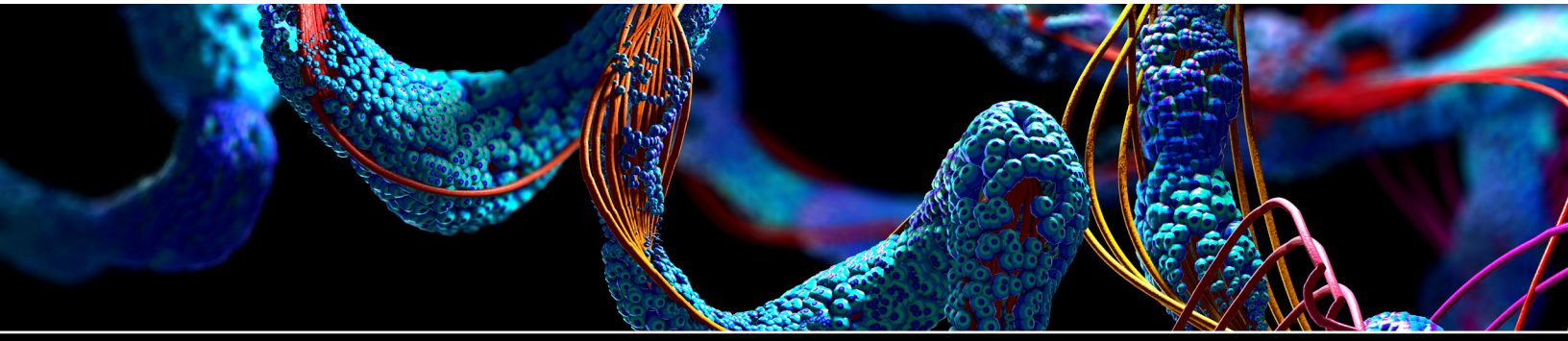
A project may also exit before stage seven. For example, Resilience may oversee a project through IND filing and then the project may move to another CDMO for commercial manufacture. Another may stay with Resilience throughout the product lifecycle.

Velocity. A flexible approach enables Resilience to move with agility and velocity. “Agility means proactively building technology transfer and integrated projects plans that encompass the appropriate transfer strategy for a client,” said Papini. “We focus on priority deliverables first while meeting safety and regulatory compliance.”

Velocity comes with diligent upfront planning, close communication, and industry expertise; with an emphasis on having a strong strategy ahead and being able to foresee if we are deviating from the path and being able to proactively redress. Each team member knows what needs to be done at each stage. With a solid plan in place, team members move through the stage efficiently. It’s a straight line rather than an obstacle course.

Rigor. Agility and flexibility cannot happen at the expense of rigor. Rigor refers to meeting or exceeding regulatory and quality requirements throughout a project’s lifecycle.

“Throughout the stages, teams regroup and review progress to ensure the right level of rigor is in place and the quality data looks as expected,” added D’Ambrosio. “A rigorous regulatory team is embedded into the process, which allows for oversight and guidance throughout the process. Should there be a need to course correct, we have input readily available from our subject matter experts and regulatory affairs.”



THE RESILIENCE DIFFERENCE

Resilience implemented a stage-gate approach as a way to accelerate biomanufacturing for established and emerging biologics. It developed processes and platforms to allow scientists to develop, transfer, and manufacture biotherapeutics faster, safer, and at scale. Through close partnerships and advanced technology, Resilience gives customers full visibility into their data and their product's progress.

A few things to know about Resilience:

- **With sites across 6 states in the US and one in Canada and over 2 million square feet of manufacturing capacity, Resilience has the capacity to manage virtually all aspects of biologic development.** The Resilience network includes sites that specialize in cell therapy, gene therapy, nucleic acids, vaccines, and other biologics. All sites use the same standardized processes for consistency and reliability across its network.
- **It's a technology company devoted to science.** Resilience uses advanced technology to enable end-to-end value chain connectivity and transparency. The company is working to automate rote tasks such as information intake and report generation to further boost efficiency. Live data viewing enables clients to track project activity in real time. The company also has its eye on advanced analytics for robust data analysis.
- **Resilience has capacity and equipment that span process and analytical development and GMP biomanufacturing, with the expertise to match.** A strong regulatory team covers everything from advising to preparing submissions. Many of the individuals on this team have worked for clinical trial sponsors, which gives them extensive experience collaborating with the FDA. To ensure all aspects of a project remain in compliance, Resilience regulatory experts consult on all stages of a project.

Since 2020

Over 25 *active technology transfers*

+

Over 20 *projects in process and analytical development*

CONCLUSION

Biologics and biotech companies invest years of time, money, and energy to develop molecules that have the potential to impact the lives of patients. Well-orchestrated technology transfers are paramount to moving these valuable products forward. A stage-gate approach mitigates risk throughout development and manufacturing by bringing in multiple stages of planning, review, and quality assessment.

By following this established methodology, biologics developers can realize efficiency gains that equate to significant cost savings, while enabling pipelines to reach their full potential. Patients are depending on it.

"Entire therapeutic industries could fall apart if we continue with cumbersome manufacturing processes," said Shultz. "Some of these therapies can be curative, but we have to empower the industry to make that happen."

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RESILIENCE

Resilience is a technology-focused biomanufacturing company dedicated to broadening access to complex medicines across a variety of therapeutic areas. Founded in 2020, the company is building a sustainable network of high-tech, end-to-end manufacturing solutions to ensure the treatments of today and tomorrow can be made quickly, safely and at scale. By continuously advancing the science of biopharmaceutical manufacturing and development, Resilience seeks to free its partners to focus on the discoveries that improve patients' lives and protect biopharmaceutical supply chains against future disruptions.