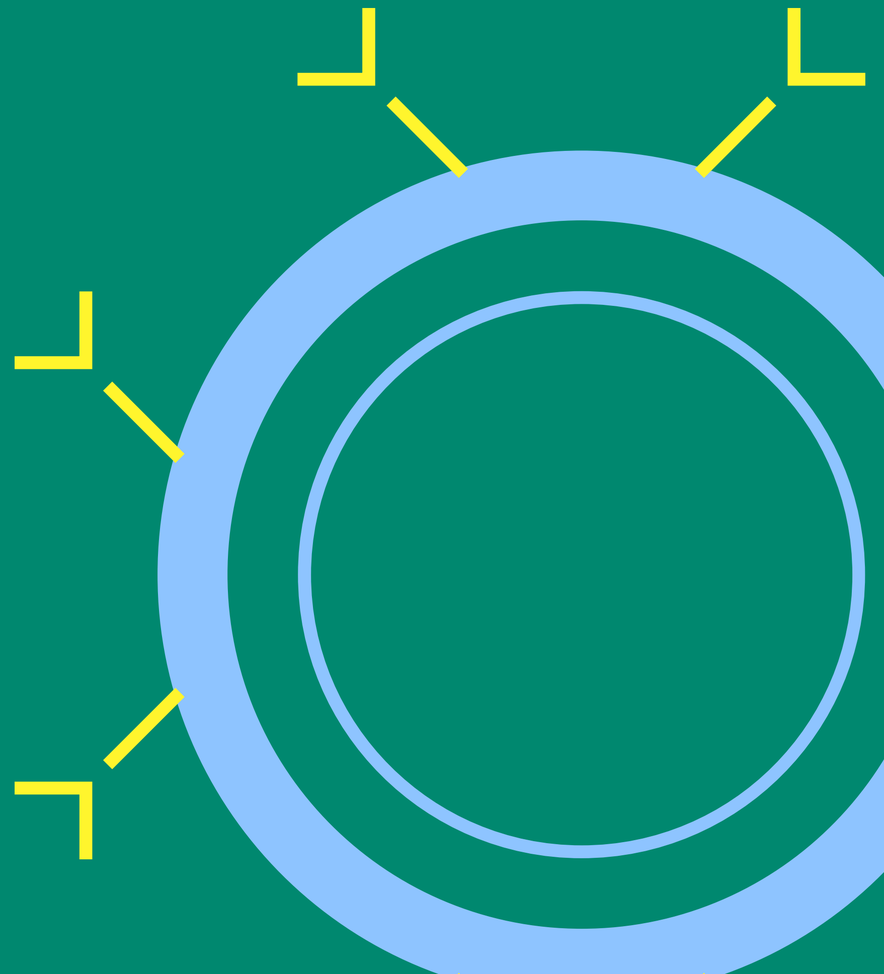
The top four challenges and solutions

Navigating cell therapy process development



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Process development for cell therapy manufacturing

Process development (PD) involves designing and creating an efficient, robust process, while keeping an eye on costs and overall effectiveness. While productivity takes center stage, you also need to think about factors like cost, revenue, material sourcing, and meeting regulatory requirements. As a cell therapy developer, PD is essential. It helps you establish a repeatable process that adheres to GMP standards, preparing you for clinical trials and eventually commercialization.

Considering cell therapy PD optimization before scaling up or out can make a significant difference on your path to commercial success. Overlooking this step might cause your inefficiencies to scale with you, leading to bigger challenges further down the line. In this eBook, we delve into the main obstacles and factors surrounding cell therapy process development, empowering you to make well-informed decisions throughout your journey.

Top PD challenges for cell therapy manufacturing

1. Addressing open and manual processes

Understand the risks and benefits associated with cell therapy workflows.

Navigating the cell therapy manufacturing landscape can be a complex journey, especially when open and manual processes come into play. Contamination is a significant risk factor in these cases and can directly impact the success of your therapies.

So, how do you optimize your workflow for both safety and efficiency? One way is to implement closed and automated systems. By doing so, you create a more secure environment. For example, during an open process, operators might have difficulty extracting cells for transfer to another system. This opportunity for human error can potentially lead to lost patient material and delays in treatment.

As an emerging biotech or start-up that's preparing for GMP manufacturing, it's crucial to reduce the number of touchpoints that may become sources of contamination or mistakes. By taking the initiative to lessen manual interactions and establish efficient automation, you're better able to safeguard your operations.

PD challenge	Solution
Open and manual processes carry a significant risk of contamination	Implement automated solutions to reduce the number of touchpoints

2. Tackling resource limitations

Scaling up or out can be a daunting task. But it doesn't need to be.

For many in the cell therapy manufacturing space, optimizing PD before scaling up or out can be a daunting task due to hurdles like lab space, personnel, and time constraints. Plus, when you're in the earlier stages of your cell therapy manufacturing journey, figuring out the necessary equipment for clinical and commercial manufacturing can be an additional challenge. As a start-up, you might have reached the pre-clinical stage, but lack the experience needed to successfully bring cell therapies to market. You may also need additional guidance regarding equipment and process requirements as well as optimizing the facility layout.

Moreover, start-ups often face shortages in essential resources for process development. This includes challenges such as not having access to a GMP-compliant lab, which is crucial for producing cell therapies. Validating equipment and processes to achieve GMP compliance also requires time and effort. Furthermore, completing experiments within tight timeframes can become a source of stress for smaller companies.

As a result, cell therapy manufacturers may consider outsourcing certain development tasks to overcome these gaps effectively. A project manager can help provide guidance to keep your projects on track and within budget. When exploring this option, it's essential to collaborate with a team that truly understands your process layout. That way, they can help streamline and optimize your workflow while ensuring GMP compliance in your cleanroom.

PD challenge	Solution
Resource limitations	Consider outsourcing certain development tasks or hiring a project manager

3. Creating a robust design

Enhancing efficiencies through standardization.

Creating repeatable processes: the ultimate goal of PD projects. If the manufacturing process isn't repeatable, it becomes highly inefficient and unprofitable.

But, in cell therapy manufacturing, established process standards are scarce compared to those in bioprocess. The bioprocess industry is significantly more mature, resulting in a greater number of process standards and increased efficiency. Cell therapy, on the other hand, deals with higher variability in cell sources and patient materials, making the process more complex to standardize.

Consistency and effectiveness are essential for successful cell therapies, no matter the cell type. If your expertise is in developing a particular therapeutic, such as CAR T, you might lack familiarity with different cell types like TILs. Therefore, you might need to make a trade-off decision on whether to specialize in a given therapeutic area or not.

Understanding cell doses is crucial for developers to determine annual production needs, equipment requirements, and other vital factors. However, with a potential gap in knowledge about various cell types, you might face challenges in deciding the best processing parameters and determining the right cell doses.

Overall, you want to minimize variables and create a dependable, efficient design that ensures consistent results without unnecessary waste. And to do so, you need to consider equipment that is flexible and scalable, right from the start of your journey. That way, should your strategy change, you're still set up for success.

Early on in developing your process, consider these key controls. Implementing them will enable you to create a repeatable and robust process for cell therapy development:

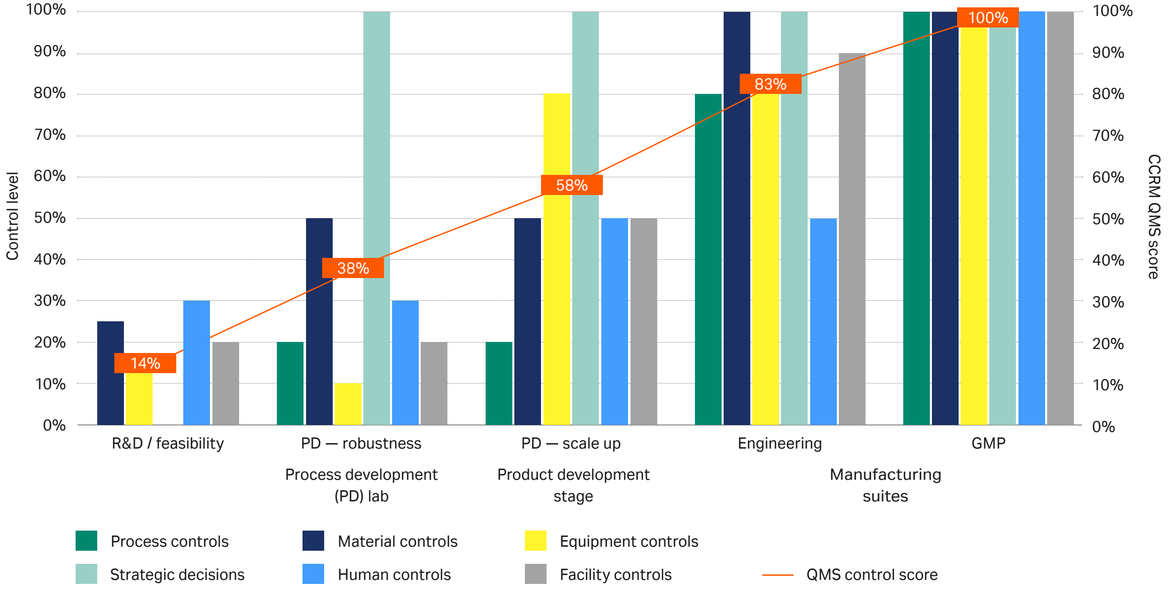
Control element	Description
Process controls	Protocol → SOP → Engineering batch record → GMP batch record Protocol → Developed test method (TM) → Qualified TM → Validated TM
Material controls	Materials selected → Materials qualified → USP <1043>
Equipment controls	Equipment selected → Equipment installed → Qualified equipment (IQ/OQ/PQ)
Strategic decisions	Open vs closed, type of bioreactor, type of purification and selection strategy, analytical methods
Human controls	Documented training of personnel from general to specific
Facility controls	Process development space → Pilot plant → Controlled manufacturing space

IQ – Installation qualification
OQ – Operational qualification
PQ – Performance qualification

PD challenge	Solution
Creating a robust design for a repeatable and scalable process	Invest in equipment that is flexible and scalable from the beginning

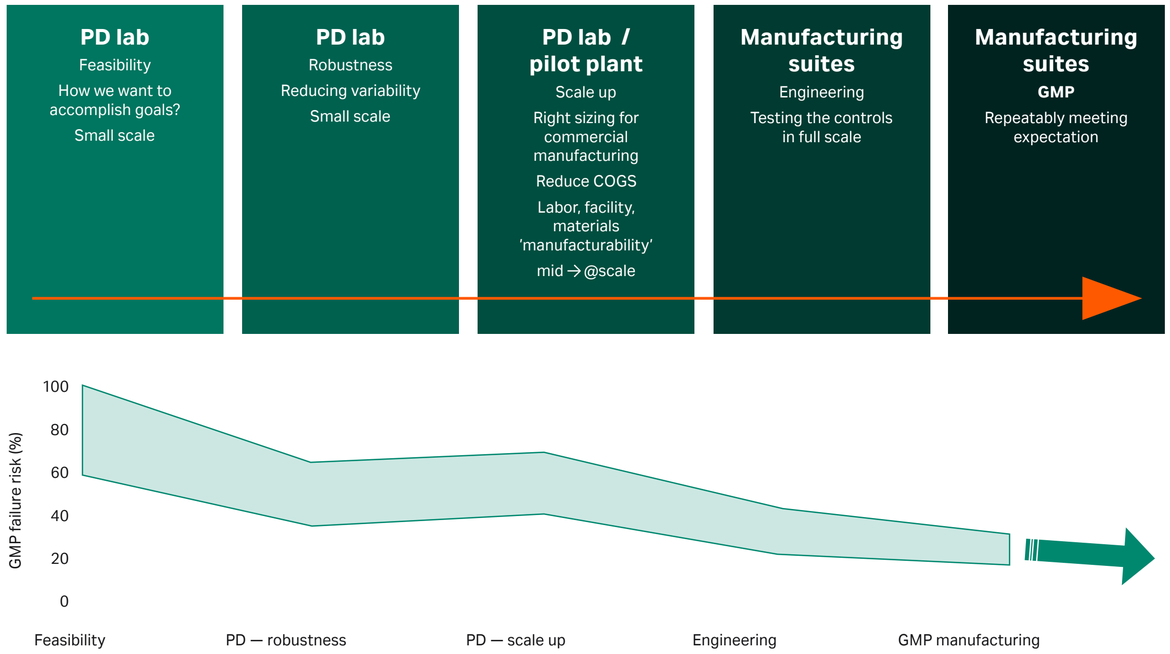
GMP product development

This chart illustrates the journey a therapy undergoes before reaching commercialization. You'll notice that the greatest room for creativity and exploration lies with the R&D team. They have the most opportunity to experiment, test various media, and discover the most effective solutions. As the therapy progresses towards commercialization — through scale-up, proof testing, and tech transfer — the process becomes increasingly standardized. By the time you reach GMP, experimentation with media is no longer occurring; you have precisely honed in your methods to ensure both repeatability and optimal efficiency in your process by this stage.



Understanding robust design

As you progress through your PD process, you're effectively reducing the risk of process or therapy failure. Starting with the feasibility step, there's a higher failure risk, since you're still determining if the process will work. However, as you advance toward GMP manufacturing, the risk diminishes. This lower risk is achieved through careful evaluation of robustness, scale-up, and successful engineering runs, ensuring a consistently reliable process.



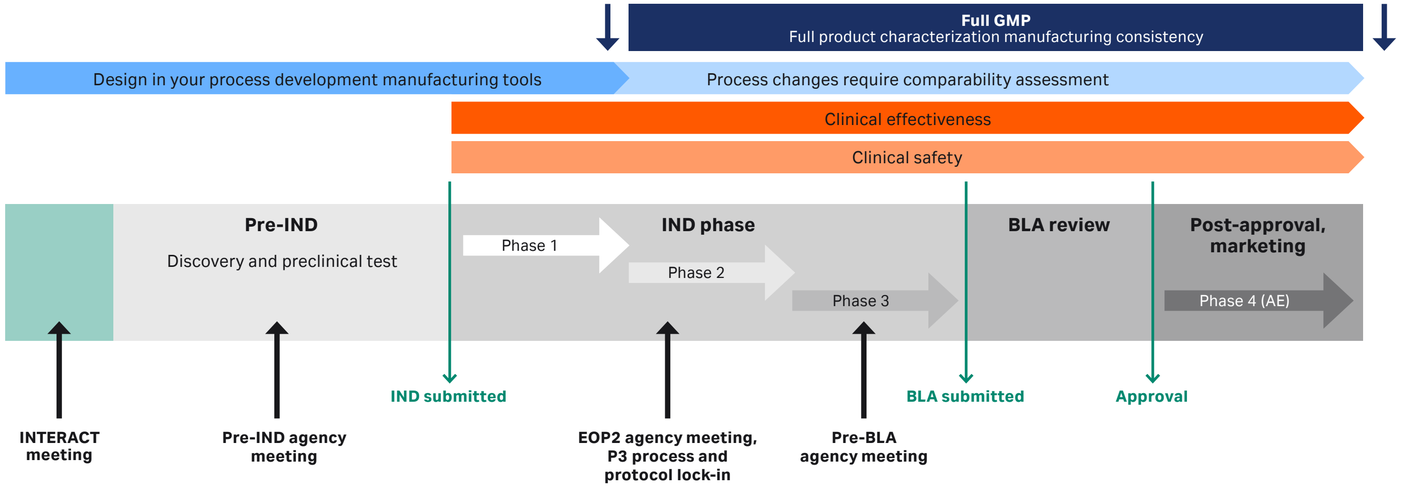
4. Navigating regulatory requirements

From pre-IND to post-approval

As you advance towards clinical trials and commercialization, there are rigorous standards that need to be met while preparing for GMP manufacturing. In such a closely regulated industry, it's vital to ensure compliance with these guidelines in order for your innovative therapies to successfully reach those who need them.

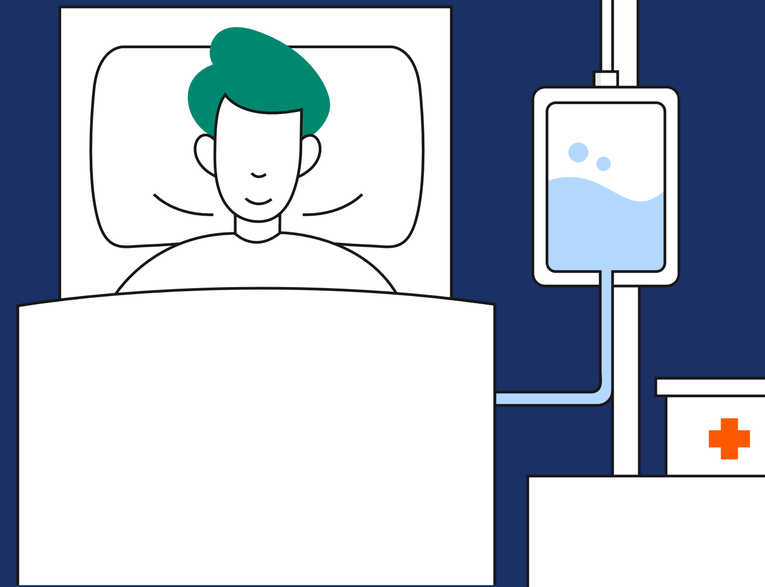
The image below illustrates the approval process for cell therapy products, outlining the steps manufacturers must complete to obtain approval. One key aspect to note: during the pre-IND phase, changes can still be made. However, once you reach Phase 1 of the IND phase, you're largely committed to the instruments, media, and reagents you've selected. So, it's crucial to choose products that are compliant and robust enough to carry you through to approval. Many trials don't progress beyond Phase 2, as demonstrating robustness can be challenging, and instrument limitations are often encountered. By making informed decisions early on, you can improve your chances of reaching the desired outcome and advancing to the next stages of development.

What are the regulatory requirements for CGT manufacturers in the US?



PD challenge	Solution
Rigorous regulatory requirements	Ensure your supplier will provide comprehensive support so you can confidently submit necessary documentation

It's vital to ensure compliance with these crucial guidelines, so your innovative therapies can successfully reach those who need them.



Key considerations

a) Timing, technology, and people

Process development optimization is essential for successful commercialization, and three considerations should be taken into account: timing, technology, and people.

Consider timing as you map out the four phases of therapeutic development into realistic schedules. Estimate the duration of each phase — such as an eight-to nine-month process for CAR T manufacturing — so you're well-prepared.

Choose the right technology that meets both immediate and long-term growth strategies. Select scalable, functionally closed, and adaptable systems to stay ahead of the curve.

And don't forget about your team. When partnering with a CDMO, ensure all necessary agreements are in place, such as Confidential Disclosure Agreements, Master Services Agreements, Quality Agreements, and Scope of Work documents. Look for a good cultural fit and an understanding of the science and manufacturing processes — this will enhance collaboration.

Through proper consideration of these three components, you can better ensure that your efforts are leading toward a successful commercialization journey.

b) Process optimization

When making decisions that best optimize the therapy you're developing, take the following into consideration.

Autologous or allogeneic

When it comes to process optimization for autologous and allogeneic therapy development, scaling plays a crucial role. For autologous treatments, the focus is on scaling out (i.e., using multiple small bioreactors for your process). For allogeneic therapies, on the other hand, the focus is on scaling up (i.e., starting with one smaller bioreactor and then moving that culture into a larger bioreactor to produce multiple batches in one. Any future scaling plans — whether scaling up or out — should be considered early on to best optimize your process.

Cell dose

Optimizing cell dose in cell therapy relies on understanding each patient's unique needs, the most challenging aspect of the therapeutic puzzle. Before selecting the right instruments, it's crucial to identify the specific indication you'll be treating, as this will determine the number of cells required per dose. With this knowledge, you can confidently choose the appropriate equipment that accommodates the required cell count range.

Considering the future of your program, always be forward-looking and adaptable. For instance, even if you initially focus on autologous CAR T therapies — which require a smaller scale — ensure your chosen equipment has the flexibility to scale up when needed. This way, you'll be well-prepared to pivot towards allogeneic applications, staying at the forefront of innovative therapeutic approaches.

Transduction versus transfection

When considering transduction versus transfection, key factors include cost, effectiveness, and scalability. Currently, many developers prefer lentiviral transduction. However, it can be expensive and time-consuming due to the growing demand. Some are exploring non-viral transfection as an alternative, but its scalability has yet to be fully realized, and its effectiveness may not meet expectations.

Media and reagents for cell growth

Key factors in choosing media and reagents for process optimization: With a wide variety of commercial options available (many of which are GMP grade), selecting the right media and reagents for your specific process can be quite challenging. It's common to perform media screening to identify the best-performing options for your particular process, optimizing factors such as cytokine concentrations and supplementation. The ongoing discussion around serum versus serum-free approaches is particularly significant. Many developers are aiming to transition away from serum-dependent media, although it's worth considering that serum can enhance cell expansion. Also, there's a growing preference for chemically defined, xeno-free, and animal origin-free media. However, these options may be limited and more costly.

Another crucial aspect to consider in cell culture is the cytokines, as the appropriate selection can significantly influence the desired phenotype. By understanding which cytokines will achieve the specific outcomes you're looking for, you can confidently move forward in the process optimization journey.

Equipment connectivity needs for each step

When it comes to equipment connectivity, consider both digital and physical aspects. In the digital realm, it's essential to have a service enabling you to manage, operate, and monitor your equipment seamlessly throughout your process. Prioritizing digital traceability ensures accurate record-keeping and efficient operations.

As for physical equipment connections, implementing closed systems is crucial. Utilizing closed connection devices, such as sterile welding, helps maintain the integrity and sterility of your process as you transition between instruments and consumables.

Assays for in-process analytics

Many teams rely on standard assays, and there's no shortage of commercial options designed to tackle these tasks. But have you considered the speed of your assays, the consistency of the readings, and the instrument's downtime for maintenance? These factors are essential as they help you meet the critical quality attributes (CQAs) of your product. So, if cell number and viability are among your CQAs, you'll likely use an automated cell counter.

c) Balancing in-house and outsourcing strategies

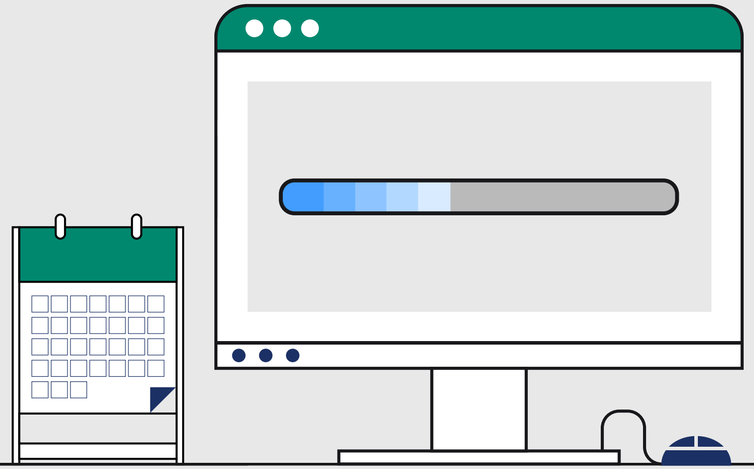
Deciding on the most effective approach for your process development projects, whether it's taking charge in-house or collaborating with a trusted external partner, is a crucial step in the journey.

When considering whether to outsource or keep processes in-house, reflect on these key factors:

- **Project management:** Is there a project management team in place to ensure the project stays on track?
- **Closed and automated systems:** Are you aware of the closed and automated systems required for approval, and if so, do you have a comprehensive understanding of their usage and capabilities?
- **Media development:** Do you plan on creating your own media and have the knowledge to do so?
- **Tech transfer:** Are you familiar with the process of tech transferring to a CDMO, or do you intend on handling manufacturing internally (which differs from in-house PD)?
- **Speed to market:** Lastly, do you recognize the challenges in reaching the market quickly and effectively?

It's important to acknowledge that, while it's possible to manage these tasks internally, it can be quite challenging. Fortunately, there are experienced industry professionals available to support and enhance your development efforts.

Need help with your cell therapy process development?
Visit cytiva.com/cgtmanufacturing to learn more



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