WHITE PAPER

Gene therapy manufacturing: Custom and GMP-grade reagents to accelerate your scale-up plan

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Gene therapy manufacturing: Custom and GMP-grade reagents to accelerate your scale-up plan

Finding the right platform, the right system, and the right expertise to advance therapeutic commercialization

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Executive Summary

Gene therapies are in for an extraordinary ride over the next few years: What's a $10B market in 2024 could grow to five times that by 2033[1] with increased commercialization of these novel treatments.

Driving that growth are legions of therapeutic developers poised to take their drugs to market for the first time, with 38 gene therapies already approved by the FDA and an estimate that up to 20 new cell and gene therapies will be approved per year by 2025. [2, 3]

Despite that promising pipeline growth, however, producing those therapies is an ongoing challenge.

In fact, market intelligence suggests clinical manufacturing is among the biggest hurdles holding back new funding for cell and gene therapies (CGTs).[4] Among other manufacturing challenges, CGTs require smaller, more customized batches of reagents and buffers, making them a significantly different beast than small molecules or even traditional monoclonal antibodies made at larger scales utilizing standardized reagents.

"The CGT production playbook hasn't been written, forcing innovators to operate in an unserved white space as they seek to 'crack the code' of advanced therapy manufacturing," says Stephen Gunstream, President and CEO of reagent producer Teknova.

"The existing manufacturing infrastructure was not designed to produce these new drugs," he adds. "To solve for this challenge, the industry needs clinical-grade reagent formulations that are easily customizable, scalable, and efficiently manufactured."

If you're facing these challenges, this white paper is for you. Sharing insights from Gunstream along with other Teknova experts, we'll discuss the critical requirements that gene therapy manufacturers should consider when evaluating their unique reagent needs during tech transfer from process development into clinical manufacturing.

You'll learn:

- The importance of having a **manufacturing platform** that offers speed, flexibility, and customization to enable scalable reagent production
- What a comprehensive **quality management system** should look like for custom and GMP-grade reagent manufacturing, from training and documentation to validation and continuous operation
- Opportunities to **save time, resources, and costs** during tech transfer from process development to clinical manufacturing to help get your new therapy into the clinic faster

What to look for: Flexibility, customization, and speed

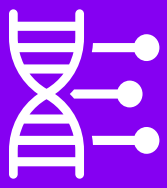
"Gene therapies are highly complex products subject to intense regulatory scrutiny due to their novel nature. As such, it's important to look for solutions that support the **agile, flexible production of research- and clinical-grade reagents** as they move from RUO to GMP," says Gunstream.

"You need to ensure your reagent partner has the ability and capacity to manufacture many different products that can be customizable by format, batch and container size, formulation, etc.," he notes. "Ultimately, to best support the need for iteration and scalability that gene therapy developers demand, it's critical to have a manufacturing platform that can easily flex its infrastructure to support their changing requirements."

In turn, that flexibility to mix and match across manufacturing lines supports **speed-to-production** when reagent producers can plug and play systems to meet the needs of custom runs. When facilities are designed not only to process multiple simultaneous work orders, but also to change and reorient equipment in real-time, it saves time and costs compared to more fixed and limited building capabilities.

As another platform must-have for custom reagents, look for **redundancy in the facility's design**. Gunstream explains:

"A facility's design needs to balance redundancy and failure protection," he says. "The manufacturing facility should be completely redundant, including duplicate clean rooms, HVAC systems, and equipment. You'll have more confidence in your investment and the



Gene therapies require a new approach at virtually every stage of the clinical manufacturing process—especially when it comes to custom and GMP-grade reagent formulations.

outcome if you can switch from one area to the other if there's a problem."

Consider also any opportunities to incorporate **automated and manual dispensing** across multiple production processes. "Gene therapies, with their diversity in batch sizes and formats, are highly idiosyncratic—which drives the need for both automated and manual processes, depending on the need," suggests Nicky Young, Senior Director of Sterility Assurance at Teknova.

"Smaller batches require less automation and are easily dispensed manually, creating the ability to manufacture faster," Young says. "Larger batches use automated systems to produce large volumes of material with consistent critical quality attributes."

Additionally, mind the format requirements: Most gene therapy innovators prefer **single-use systems** using bags and liners for sterility assurance as they transition from process development into clinical manufacturing. Alternatively, if a reusable container is required, look for contamination control measures including a clean-in-place (CIP) and sterilization-in-place (SIP) process and equipment.

Lastly, consider opportunities to seamlessly **bridge the transition from RUO to GMP**—something Teknova has offered through a new manufacturing grade called RUO+. This model "greases the skids" for commercialization by manufacturing a custom reagent utilizing the same production environment as GMP, without the rigorous documentation and expense required of GMP.

"With a solution like RUO+, you can follow the exact same process using the same equipment in the same facility that you'll eventually need for GMP-grade manufacturing, but you can do it under RUO quality conditions. That helps streamline the transition by making it more affordable and faster," Gunstream explains. "It's a huge opportunity for gene therapy developers, because this point during scale-up often requires significant rework and having the right grade at the right time can help save time and money."

What to look for: Quality management systems

A quality management system (QMS) spans multiple manufacturing functions, from training and documentation to equipment qualification, validation, and certification. While the QMS is a standard part of any GMP-grade reagent manufacturing process,

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> Teknova

the specialized needs of CGTs in particular call for an additional element: partners should not just comply with the requirements of ISO 13485:2016, but they should also demonstrate **compliance while maintaining flexibility** in manufacturing.

“Because gene therapies are so dependent on flexible manufacturing, the question is really how do you make flexible manufacturing compliant?” comments Gunstream. “You need a quality management system in place that has validated how to control multiple manufacturing processes.”

Bracketed validation is an approach Teknova has taken to enable that flexibility without compromising quality and compliance. With this model, producers can collectively validate a range (or “bracket”) of products, equipment, containers, fill volumes, processes, and personnel that can be assessed over the course of a specific timeframe in the cleanroom.

“By completing and validating a facility using a bracketed validation approach, the reagent partner can receive and manufacture a wider range of custom orders, instead of needing to validate the facility for every new order or anomaly that comes in with inbound custom orders,” he adds. “Along the way, partners should always be looking to improve by measuring and assessing output efficiency, reassessing capabilities based on recent orders or customer requests, and staying on top of industry developments.”

What to look for: Supplier expertise

Aside from the manufacturing facility and QMS, gene therapy manufacturers should evaluate the expertise of their custom reagent partners. Given the nuanced needs and sensitivities of gene therapies, Gunstream recommends careful scrutiny around **sterility assurance and compliance**.

“Bringing onboard quality leadership that has **pharmaceutical manufacturing experience is critical,**” he notes. “Many diagnostics and other products don’t have the same amount of rigor around contamination control and sterility. Onboarding experts who have been on the other side in quality and manufacturing in the biotech or pharmaceutical space is absolutely essential.”

At the same time, it’s not just about having experience with large biotechs or pharmaceutical companies. One trap manufacturers can get caught in is relying on the experts who primarily worked with widely prescribed drug products requiring large-scale production runs of a single type of therapy.

"You can't operate that way in gene therapy, because these are not the types of products where mass-production, single-run experience is helpful," he explains. "This modality requires smaller volumes of custom reagents, even during commercialization. The combination of varied, smaller volumes with a high degree of customization necessitates the hiring of industry experts with inherent problem-solving skills who love the challenge that a constantly evolving manufacturing environment presents."

Additionally, look for **specialized consultation and resources** the reagent producer might offer, such as the opportunity to meet with a manufacturing science and technology group at the outset. "Such experts can guide decisions from raw material and vendor selection, to container and labeling options, and even provide stability studies or expedited production services—everything a gene therapy manufacturer might need to help get them the exact high-quality reagent they need, quickly," adds Gunstream.

8 ways to optimize custom reagent development

1. Ensure reagent partners have a **manufacturing platform** that supports agility, speed, and a seamless transition from RUO to GMP.
2. Look for **redundancy in building design**—with redundant layouts, HVAC systems, generators, and other design elements.
3. Ask about the possibility of **automated and manual dispensing** to accommodate a variety of batch sizes, formats, and needs.
4. Ensure **single-use systems** are an option—or otherwise that **strict sterilize-in-place** and **clean-in-place standards** exist for reusable vessels.
5. Evaluate a partner's ability to be **compliant while maintaining flexibility** in manufacturing.
6. Look for **bracketed validation** methods that collectively validate a range of production factors at once.
7. Assess the credentials of partners and ensure they have **relevant pharmaceutical experience**.
8. Ask whether the partner offers **specialized consultation resources** to support any knowledge gaps on the therapeutic manufacturer's side, such as packaging, labelling, or supply chain strategy.

Should you rethink your custom reagent strategy?

Working with smaller batches and multiple production runs, gene therapy manufacturers need a flexible, customized, and compliant strategy for their reagents and buffer solutions. By ensuring reagent manufacturing partners have an agile manufacturing platform, compliant yet flexible processes, and unparalleled supplier experience, you're well on your way to overcoming one of the industry's most challenging of manufacturing barriers.

Is it time to start developing and scaling your required custom reagents and buffers? If you'd like to work with a manufacturing partner that ticks every box discussed in this white paper (and then some), learn more at XX[preferred link]XX.

1. https://www.novaoneadvisor.com/report/gene-therapy-market
2. https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products/approved-cellular-and-gene-therapy-products
3. https://www.biospace.com/gene-therapy-market-size-poised-to-surge-usd-52-40-billion-by-2033
4. https://www.nature.com/articles/s41587-024-02357-2

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Teknova makes solutions possible. Since 1996, Teknova has been innovating the manufacture of critical reagents for the life sciences industry to accelerate the discovery and development of novel therapies that will help people live longer, healthier lives. They offer fully customizable solutions for every stage of the workflow, supporting industry leaders in cell and gene therapy, molecular diagnostics, and synthetic biology. Their fast turnaround of high-quality agar plates, microbial culture media, buffers and reagents, and water helps their customers scale seamlessly from RUO to GMP. Headquartered in Hollister, California, with over 200,000 square feet of state-of-the-art facilities, Teknova's modular manufacturing platform was designed by their team of scientists, engineers, and quality control experts to efficiently produce the foundational ingredients for the discovery and commercialization of novel therapies.