10 common pitfalls in cell and gene therapy facility design, and how to avoid them

Jason Rossi from AST reviews ten common mistakes in CGT facility design, from not being realistic about heat load, to not accounting for process bottlenecks

Cell and gene therapies (CGTs) continue to be an avenue for product development across the Life Sciences and illuminate new possibilities for patient outcomes. These products have led to a wholesale shift in how manufacturers approach and implement cGMP operations and to a reimagining of the production facility.

AST's Principal CQV Engineer Jason Rossi weighs in on 10 common errors and solutions when undertaking the design and build process.

1. Saving in initial capital expenditure, losing in long-term production

A critical aspect of CGT facility design is strategic resource allocation and how early capital investment assessments affect long-term design outcomes. There's a clear need for a fiscally responsible and advantageous plan at the foundation of a facility design. Too often, short-term cost containment results in the deferral or elimination of infrastructure that ultimately becomes essential. Front-end

savings rarely translate to better total cost of ownership. The realities of an operation over the long term (understanding the ins and outs of production processes, planning for day-to-day operations and logistics, and anticipating the scale-up of production) should all serve as fog lines for your initial resource planning.

2. Not going with the flow: bottlenecks and material transfer issues

Optimal cell and gene facility design is, at its core, all about the flow. Flow in and out of the facility is crucial to regulatory compliance and contamination control. And one of the more underappreciated and practical strategies of building a facility is designing around your personnel, material, and process ingress and egress.

Cross-traffic between clean and dirty pathways or commingling of waste and product streams introduces significant risk to contamination control and GMP operations. A strategic suite design with distinct paths and areas for product and waste not only reduces risk but also allows for other economical utility-based solutions to be implemented.

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3. Insufficient warehouse space

One of the first areas either underestimated or sacrificed during facility planning is warehouse capacity. A common rejoinder is that warehouse space does not generate revenue; production space does. However, no aspect of CGT production occurs in a vacuum. While there are common workarounds (e.g., renting warehouse space), numerous challenges can arise. What are the downtime risks of managing materials through an off-site facility? Can your batch afford a delay if a component is dropped or lost? Part of the holistic emphasis inherent in Quality by Design principles is to account for any and all factors that could affect your process.

4. Following drug substance principles instead of drug product principles

Much of the risk in misapplying traditional pharmaceutical standards to CGTs arises from adhering to drug substance standards rather than drug product standards. The latter is considered a non-sterile process in design and is subject to additional formulation and filtration. This isn't the case in cell and gene manufacturing, where, in many instances, the final drug product and drug substance are nearly identical. What does this error practically look like in the cleanroom? Misgraded operations, improper pressure cascade design, and skip-grade setups are aspects that can be easily improved by adopting a more principled aseptic processing approach.

5. Purpose-built but with no flexibility

Many facilities are necessarily built around product specifications, and rightfully so. However, a common misstep is not anticipating the flexibility necessary to navigate a sometimes unpredictable development process. Process optimisation, changing product pipelines, and scaled-up production can all lead to new demands on the facility. Having contingencies and projections in place is essential. The better you understand your process and associated outcomes, the more prepared your facility will be. A phrase we use often on my team is, "Flexibility is the antidote for uncertainty."

6. Underestimating utilities

In CGT manufacturing, the stakes are always high, especially for the patient. Downtime is never just downtime; it could mean a lost viability window and ultimately a lost

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treatment opportunity for a patient. A large part of successful cell and gene facility design is redundancy and contingency planning, and utilities are an essential part of that conversation. Do you have backup systems in place to cover all critical operations? Critical operations must be supported by appropriately classified backup systems. Are you prepared when, for example, equipment autoclaves go down for preventative maintenance? Designing in more utility capacity prevents downtime and saves on additional construction costs and re-validation.

7. Having nothing to "break in case of an emergency": when power loss becomes product loss

Imagine this: Crucial donor material is being processed from an immunocompromised patient who just underwent leukapheresis. The process has to be done sparingly to protect the patient, sometimes taking weeks between blood draws. The batch is midway through, and a worst-case scenario happens: the power to your facility goes out. What happens next? The question becomes whether adequate contingency power systems are in place to sustain critical operations. It's vital to understand the needs in your facility around an uninterrupted power source (UPS) versus delayed backup power, a distinction that can often be underconsidered in contingency planning.

8. Not considering realistic heat load and capacity needs

Whether it's exceeding the allotted personnel or adding equipment, once an operation's workflow demands are in real time, there's an understandable tendency to overuse a space. If you're using a room beyond initial capacity estimates, high heat loads likely don't reflect an HVAC issue; they reflect a planning issue. It can be challenging to accurately predict the exact capacity of air handling you'll need in a room. A practical solution here is to err on the side of caution and design rooms to a grade above what they'll be running at in practice. This accounts for possible expanded growth and provides manufacturers with an additional layer of flexibility.

9. Not accounting for the full equipment lifecycle during installation and integration

Every manufacturing operation, especially those producing CGT products, understands the value of reducing downtime. Three aspects of equipment integration should always be considered in this equation: initial installation and logistics, service needs, and the preventative maintenance program. A biosafety cabinet comes with fewer limitations than larger equipment like isolators or, larger still, bioreactors. Service access planning for installation, clearance, maintenance, and calibration should all be detailed in the facility design.

10. Not getting input from multiple stakeholders in the design phase

It seems intuitive, but it's common for stakeholder groups not to have open communication or be included during the initial stages of planning and design. Designing around the process and the GMP demands of an ATMP facility is essential, and engineering teams often don't have those inputs from SMEs on the ground level of a project. Getting a clear CQV perspective, along with feedback from your facility operations team and ultimately the operators who will be running the equipment, will save critical time and prevent costly scope adjustments down the line. If the goal is a robust, efficient cGMP cell and gene manufacturing facility, comprehensive expertise, resources, and best practices will set pharmaceutical manufacturers up for long-term success.

For more information

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