Cell and Gene Therapy Manufacturing

Best Practices

It is vital to establish a robust contamination control program for your cell and gene therapy (CGT) manufacturing process to protect your products and increase speed to market. This document introduces common challenges experienced in CGT manufacturing and best practices for addressing them.

Implement a Contamination Control Program

Success for any CGT operation begins with a robust contamination control program. Designing a contamination control program involves three essential steps:

1. Identify the contamination risks for your operation (material transfer, personnel, etc.) and the control measures (procedures, control methods, etc.) you will take to minimize contamination.
2. Validate and document the measures from step 1 to provide evidence of an effective and compliant contamination control program.
3. Confirm these measures provide the necessary state of control through periodic environmental monitoring and data trending.
4. Adjust procedures (frequency of cleaning, material transfer procedures) according to what the data tells you to maintain the desired state of control.

A robust contamination control program reduces downtime and the expense of investigating environmental excursions. Most importantly, it reduces the risk of product rejection.

Minimize Risk

CGT manufacturing presents many risks, and success hinges on controlling contamination to avoid setbacks.

Your contamination control program should be based on the use of validated, science-based products and processes aligned with industry regulations and best practices. This will ensure your operation remains efficient and compliant at every step of your manufacturing process.

Maintain Regulatory Compliance

While regulatory guidelines for CGT manufacturing are currently less defined than in other areas of pharmaceutical manufacturing, you can apply several related guidelines.

The following industry regulations and guidance documents are relevant to CGT manufacturing:

- USP 43 <1072> Disinfectants and Antiseptics
- EU GMP Annex 1 – Sections 4.33-4.36
- PIC/S Annex 2A – Manufacture of Advanced Therapy Medicinal Products for Human Use
- EudraLex – Volume 4 – Good Manufacturing Practice (GMP) Guidelines
- ISO-14644-5: Cleanrooms and Associated Controlled Environments

Applying the procedures outlined in these regulations and guidance documents will ensure your operation remains compliant.

Optimize Material Transfer

The transfer of materials into aseptic areas is one of the primary sources of contamination[1]. To maintain microbiological control, it is necessary to implement procedures for decontaminating materials transferred into an aseptic environment. You must identify the most appropriate method for each material as part of these procedures.

For heat-tolerant materials, such as stainless-steel components, steam sterilization is ideal. The use of sterility maintenance products, such as Purefit™ Sterilization Bags and Covers, can help maintain the sterility of the item during transfer and storage and enable aseptic presentation during use.

For temperature-sensitive items, Vaporized Hydrogen Peroxide (VHP™) biodecontamination before entry is an automated and validated method for minimizing bioburden.

If neither steam nor VHP is available for on-site sterilization, or if the sterile items must be transferred through the facility to the aseptic area, wrapped or double-bagged materials may be wiped or sprayed with a sporicide prior to introduction into the aseptic field.

Likewise, if disposable, pre-sterilized items are to be used, they should be sprayed or wiped down with a sporicide prior to introduction to the aseptic area. Additionally, any cart that is used to transport these items should be treated with a sporicide, paying particular attention to wheels.

Establish a Thorough Cleaning and Disinfection Process

The following items are key for any cleaning and disinfection process:

- A one-step cleaner and disinfectant
- A sporicide based on an assessment of your environmental monitoring data
- A rinsing agent

Bacterial and fungal spores are a significant contamination risk for CGT manufacturers because of their inherent resistance to sterilization products and processes, and their ubiquitous presence in the environment. Therefore, a robust contamination control program must include the rotation of a disinfectant and a sporicide.[2]

The selection of a sporicide must take into consideration the specific demands of each operation, including schedule, infrastructure, staffing, etc. Liquid sporicides, such as Spor-Klenz™, and gaseous sporicides, such as VHP, have merits and special requirements.

You should validate the cleaners, sporicides and disinfectants used in your operation through a robust Disinfectant Qualification (DQ) process. This process begins with Disinfectant Efficacy Testing (DET), which offers in vitro evidence of performance against environmental isolates. DQ also includes in situ assessments and routine environmental monitoring, which demonstrates that your operation is in a state of control while using these products and processes.

DQ includes three components:

- **In vitro efficacy testing** to evaluate if the chosen biocides are effective against your environmental isolates on surfaces that represent your aseptic manufacturing areas.
- **In situ testing** to demonstrate the ability of disinfectants to control microorganisms by conducting environmental monitoring in your facility before and after application of the disinfectant, under worst-case conditions of expected microbial levels. Examples include start up after shut-down for preventative maintenance events.
- **Routine environmental monitoring** to support continual assessment of your contamination control program and ensure your operation remains in a state of control.

Without the requisite experience, DQ can be challenging. However, leveraging the expertise of a trusted contract service such as STERIS's DET services can enable you to meet your disinfectant validation and compliance goals more easily.

Questions?

The STERIS Life Sciences team is here to help you optimize your CGT manufacturing operation. If you have any questions, please contact a member of our team today.

References

1. European Commission. (2022, August 22). "The Rules Governing Medicinal Products in the European Union Volume 4 EU Guidelines for Good Manufacturing Practice for Medicinal Products for Human and Veterinary Use."
2. Lee, Y., Parikh, S., Polarine, J., Ramsey, S. (2023, February 1). "A Risk Assessment Approach to Address Fungal Spore Contamination in a Cell and Gene Therapy Cleanroom and Modern Methods for Control." *American Pharmaceutical Review*.