

Effectively Securing Cell And Gene Therapies With Closed Systems

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The cell and gene therapy (CGT) industry is growing rapidly, due to their potential to target chronic and rare diseases that previously had limited treatment options. Yet, there are many challenges to developing these innovative new therapies that cannot be addressed using traditional manufacturing models and processes. Historically, these therapies are produced for small patient populations in clinical trials using laboratory scale equipment and utilizing manual, open processes completed under laminar hoods. An increased focus on efficiency and flexibility from the biopharmaceutical industry has accelerated the adoption of novel technologies and solutions to manufacture cell and gene therapies. Among these advancements is the implementation of a closed system design utilizing single-use technology (SUT).

Lab equipment originating from medical processes are quick and open to the environment and must be performed under laminar hoods to prevent contamination while closed systems are self-contained in order to prevent exposure from and to the environment. Thus, a closed system in cell and gene therapy manufacturing provides the protection of a cleanroom against outside contaminants without the costs associated with maintaining it. Although closed systems are already in use in SUT facilities

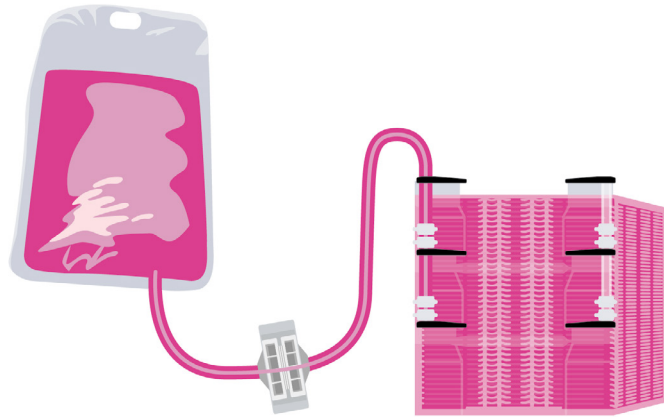


Figure 1

AseptiQuik[®] Connectors enable sterile media transfer between tube sets and bag assemblies, even in non-sterile environments

for monoclonal antibodies, recombinant protein, and vaccine production, there is still a lag in the adoption of closed systems at lab scale for smaller batches, for CGT manufacturing.

As the demand for CGT grows, the need for scale up to larger volumes has led to the utilization of SUT with open connections as well as other methods such as tube welding, multi-purpose connectors, quick connects, luers, and luer locks. These approaches are cumbersome and inefficient, though, leading to a greater need for closed manufacturing in CGT to protect and provide effective therapies.

THE CHALLENGE OF CLOSED SYSTEMS IN CELL AND GENE THERAPY

Reducing the risk of contamination is essential in cell and gene therapy manufacturing, where biologic drugs are inherently complex and sensitive. It is especially critical in CGT manufacturing,

where the patient's own cells are used for the treatment of an inherited or acquired disease. Losing that dose to contamination or mishandling it could mean not only the loss of the therapy itself but, for the patients using these innovative treatments as a last resort, it could also mean the loss of a life. Using a closed system offers the risk mitigation necessary to protect these personalized therapies. It also presents opportunities to efficiently provide effective therapies, which is another goal for the CGT market, not to mention the benefit of protecting employees who must handle the toxicity of cells.

Specifically, transitioning from lab scale to the commercial production of individual patient cells means identifying a process for economically scaling out, i.e., reducing the cost of manufacturing per dose, versus scaling up, i.e., reducing the cost per batch of multiple doses. Closed systems reduce the need for expensive HVAC and filtration systems as well as the labor-intensive and costly tasks associated with preventing contamination. Considerations

on how to move from connecting processes in biosafety cabinets to closed system connectivity should begin in the early stages of development. The final process must be able to scale up from lab equipment to larger scale bioreactors with ease. Oftentimes, this is done through the use of tube welding/sealing or aseptic connectors to connect one process step to another.

Tube welding, considered by the FDA to be a sterile connection, requires the use of pressure and heat to connect two pieces of tubing together. The tubing does not contain product at the time of welding; however, once the tubes are welded and product begins to flow through the tubes, any foreign particulates left behind could get into the product. If the weld is not done properly, there is also risk of occlusion, which is when the flow path in tubing is partially blocked during the sealing process. When this happens, any extrinsic particulates are now in the flow path. In addition, depending on the material the tube is made from, i.e., PVC, heat, and pressure during welding can also create extractables that can affect healthy cell population. And since tube welding is done in GMP processes, there is no pre-validating testing done to ensure

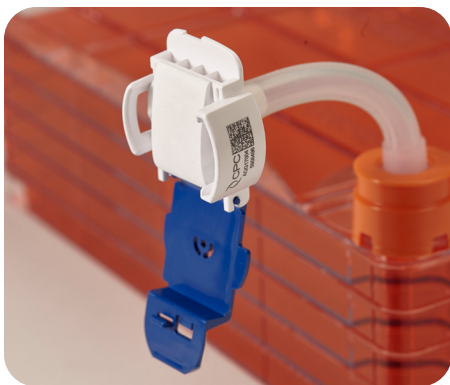


Figure 2

AseptiQuik® Connectors are available on the Corning® CellSTACK® custom closed systems and the Thermo Scientific™ Nunc™ Cell Factory™ Systems. The CellSTACK pictured here is courtesy of Corning.⁴

contamination did not occur. Furthermore tube welding requires longer tubing meaning product are held up in long tube sets instead of being part of the final product.

Filtration steps used in biopharma manufacturing cannot be utilized in most cell therapy as the cells that are required for the therapy will be filtered out. With the industry facing issues with low yields, there is an increased need for a safe alternative that allows for a closed system design for every process of CGT from upstream to final fill without creating new challenges for an already complex area of the market.

SINGLE-USE CONNECTORS: STERILITY, INTEGRITY, AND FLEXIBILITY

Single-use connectors offer an easy-to-use method for maintaining flow path sterility and integrity while enabling the protection needed to avoid costly failures from contamination. SUT's plug-and-play assembly eliminates the convoluted process for connecting tubes via tube welding, where a cart must be brought into the production suite and, along with all the necessary components, moved to the biosafety cabinet to be put together. With single-use connectors, manufacturers no longer experience the costs and delays associated with the extra time needed for open manual processes. This is critical with CAR-T and other autologous therapies where time is sensitive and patient immune systems are low. The faster the patient gets the therapy, the better. The approval of FDA of two CAR-T therapies by Novartis and Kite Gilead has created a demand for these therapies that the industry is currently not able to meet. Any delays in making these therapies only compounds the growing problem. And in an industry where labor costs are already high, the time to train operators

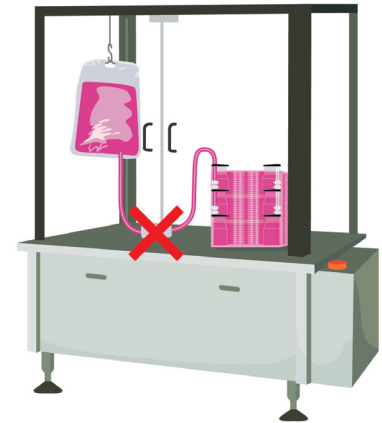


Figure 3

Eliminate the need for moving your production over to the bio-safety cabinet to ensure an aseptic connection.

to consistent welds contributes to the final price tag for manufacturing CGTs. Assembly also reduces operator error, which can pose additional costly risks.

The standardized approach of CPC's AseptiQuik® family of single-use connectors utilizes a "flip-click-pull" method, which is a three-step connection process that does not require the use of clamps, fixtures, or welders. This repeatable and reliable performance is the same regardless of what size connectors are being used. The "click" is an audible confirmation of assembly that reduces the risks of operator error by facilitating assembly without any additional hardware or the need to move equipment to a sterile area, i.e., media bag, connectors, and bioreactor. Integrated pull tab covers act as a protective shield during construction. Once CPC's single-use connectors are attached and the tabs are pulled, the membrane that was separating the connectors is also pulled, creating the sterile connection. CPC AseptiQuik connectors can be sterilized prior to use via gamma irradiation or autoclaving. For drug therapies with cold temperature storage requirements, the connectors can be frozen down to -80 degrees Celsius.

In addition, CPC single-use connectors are genderless, which means they connect regardless if the equipment they are attaching to has a “male” or “female” connection. This is especially useful in situations where the various pieces of equipment are coming from different vendors, allowing manufacturers the freedom to explore the entire field of equipment providers for the most economical solutions. And unlike tube welding, extensive extractables studies have been completed on SUT, so CGT manufacturers gain peace of mind that the equipment they are using will not impact the safety and quality of their product. The threat of extractables has become such a concern with the rise of SUT that regulators have increased scrutiny about testing for the presence of these materials. While specific testing requirements have not been provided by the FDA, a white paper written by the BioPhorum Operations Group (BPOG) has become an industry guideline for extractables testing by single-use suppliers.¹ CPC recognizes the critical need for extractables testing and has adopted and executed the BPOG protocol on its single-use connectors.²

Conclusion:

The market is growing rapidly, with an anticipated value of over \$35 billion by 2026.³ While this opens up exciting new opportunities for patient care, it also drives a greater need to develop processes that can deliver these life-saving therapies efficiently and economically. The industry and regulators are dedicated to exploring ways to do this, but it is difficult with CGT manufacturing still in its early stages of development. Partnering with suppliers who understand the needs of this market and can provide guidance in critical areas, such as best practices in closed system design, offers an advantage that may ultimately be the necessary key to success.

References:

1. Ding, Weibing, et. al. (2014). Standardized Extractables Testing Protocol for Single-Use Systems in Biomanufacturing. Pharmaceutical Engineering. Vol. 34;6 https://www.biophorum.com/wp-content/uploads/2016/10/17_file.pdf

2. Andrews, Todd. (2019). Extractables Testing On Single-Use Connectors. Retrieved from <https://content.cpcworldwide.com/Portals/0/Library/Resources/Literature/WhitePapers/Documents/CPC-Extractables-Testing-On-Single-Use%20Connectors.pdf>

3. Coherent Market Insights. (2019). Global Cell and Gene Therapy Market to Surpass US\$ Billion 35.4 by 2026. Retrieved from <https://www.globenewswire.com/news-release/2019/02/05/1710761/0/en/Global-Cell-and-Gene-Therapy-Market-to-Surpass-US-35-4-Billion-by-2026.html>

4. “Corning” and “CellSTACK” are registered trademarks of Corning, Inc. “Thermo Scientific”, “Nunc”, and “Cell Factory” are trademarks of Thermo Fisher Scientific, Inc.

About CPC

CPC (Colder Products Company), the leader in single-use connection technology, offers a wide variety of bioprocessing connection solutions. Our innovative designs offer flexibility to easily combine multiple components and systems including process containers, tubing manifolds, transfer lines, bioreactors and other bioprocess equipment. AseptiQuik® Connectors provide quick and easy sterile connections even in non-sterile environments—a critical capability for biopharmaceutical and bioprocessing manufacturers. Featuring a wide range of options including 1/8- to 1-1/2-inch sizes and genderless and gendered connections, AseptiQuik connection technology delivers sterile, high-quality single-use connections and easy media transfer with less error risk. For additional information visit cpcworldwide.com or call +1-800-444-2474.



Figure 4

Simply “flip-click-pull” for repeatable and reliable performance every time.

We Inspire Confidence at Every Point of Connection

