Single-Use Technology in Cell and Gene Therapies: Transferable Lessons from the Bioprocessing Industry

The biopharmaceutical industry has experienced significant diversification, innovation and breakthroughs in recent years. For instance, gene and cell therapies in development can both treat diseases in new, more effective ways and address rare diseases for which treatment options have not previously been available. The Office of Tissues and Advanced Therapies (OTAT), a branch of the U.S. Food and Drug Administration, has more than 20 gene and cell therapies listed as approved, with nearly 1,000 gene therapy molecules active in the pipeline.

While these numbers hold much promise, it is important to evaluate manufacturing processes and gauge potential improvements to efficiencies, aseptic conditions and timelines. Even components such as connectors can have a big impact on productivity and quality.

Although gene and cell therapies have distinct needs, a great deal of knowledge can be transferred from the bioprocessing industry. As early adopters of single-use technologies and aseptic connectors, manufacturers of traditional biologics like vaccines and mAbs offer useful lessons. Some of the main benefits that led to the adoption of SUT in the bioprocessing industry include:

- **Cost –** Reduced manufacturing costs by elimination of cleaning and sterilisation steps
- **Speed –** Time and labour savings during set-up and between operational cycles
- **Sterility –** Reduction of cross-contamination risks between batches.

To explore all SUT products available on the market today would be outside of the scope of this article, therefore we will focus on one of the most important but often overlooked decisions when developing a single-use-based process – the correct connection technology. Without connection technology the various elements required to create a single-use process could not come together. Importantly, the right connection technology can also allow the aseptic connection of single-use to non-single-use steps in the process while maintaining a fully closed system. Get it wrong, and the implications in terms of scalability, reproducibility and security of the process could be serious.

Where fluid connection technologies are concerned there are two basic categories, each based on how the connection is to be achieved. The first is a connection made by tube welding or fusing together two fluid paths. The second is achieved by mechanically coupling two components installed in the fluid pathway.

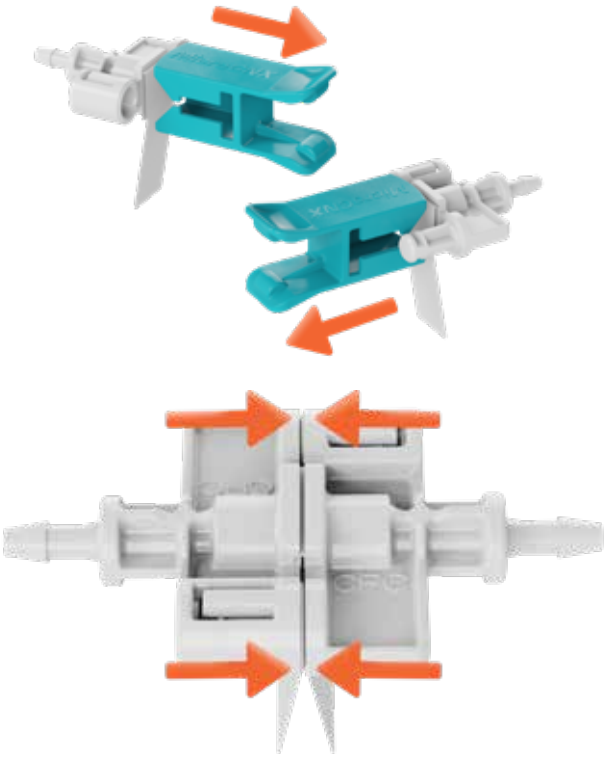
To select the appropriate technology for an application, it is essential to understand the critical technical differences both between the main technology types and between the subgroups within each technology group, plus the operational impacts those differences would have on the process and the benefits of each technology.

Tube Welding or Aseptic Connection? What You Need to Know

Given these connection options, which should be used for gene and cell therapy processing? Tube welding equipment is commonly used in the laboratory and even the clinical environment where a small number of connections per day are required and where only one size and type of tubing is used. As your operations begin to scale up, tube welding becomes more time intensive and inflexible. Multiple welds require time to create. Perhaps more importantly, tube welding can only accommodate thermoplastic elastomer (TPE) tubing. Most biopharma companies use silicone tubing because of its advantages in terms of cost, chemical stability and low levels of particulates extractables.

In contrast, aseptic connectors work by simultaneously removing two porous sterile barriers, usually membranes, from the connector assembly, to open a sterile fluid pathway once the two components are connected. This process generally takes only seconds. The aseptic connector's protective barrier (membrane) prevents bacteria and other contaminants from entering the fluid pathway while the barrier is in place, thus creating a sterile connection.

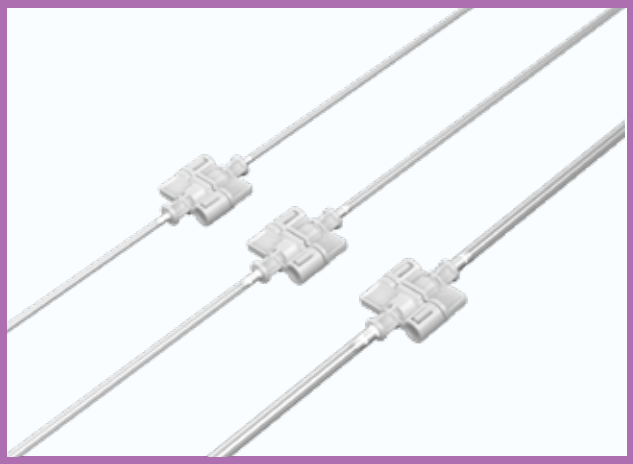
There is a wide range of processing technologies for connectors. They can be supplied as either discrete components or more often as pre-validated, pre-sterilised single-use



systems – ready to open and use. They are used to connect single-use fluid paths, which can either be welded together or mechanically coupled by components installed in the fluid pathway. Generally, a connector that is simple to use has few operational steps and works with a wide range of different tubing types and sizes, offering greater operational flexibility to the user.

MicroCNX™ Series Connectors from CPC are specifically developed for small-volume bioprocessing (under 10L). The MicroCNX connector is the first in a new category of ultra-compact, aseptic micro-connectors for small-volume, closed system processing that eliminate the need for cumbersome multi-step tube welding. The genderless MicroCNX connector represents the first and only alternative to tube welding for creating sterile closed systems using small tubing sizes.

Delivering a consistent flow path with every connection using a simple three-step Pinch-Click-Pull connection, MicroCNX connectors are lightweight and help avoid tubing kinks that can affect flow rates. Their size, weight and geometry also fits well with the trend toward compact automated equipment for use in processes like cell expansion.

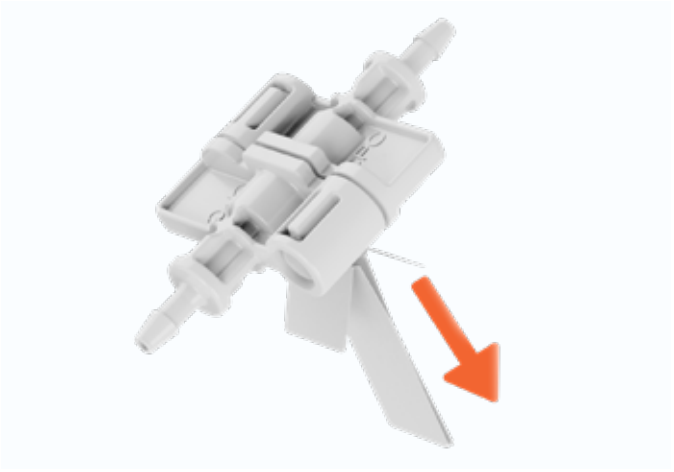


Genderless vs. Gendered Aseptic Connectors

Aseptic connectors are available in both gendered and genderless versions. Gendered connectors are composed of two different connectors (typically a male and a female component) connected together to create the fluid pathway. With genderless connectors, the two connecting components are identical. This design can help simplify single-use system design and eliminate any orientation, inventory planning and design issues associated with gendered connectors.

Genderless connectors offer time savings, greater process security, simplified inventory requirements and increased operational and design flexibility, as outlined below:

- **Time savings.** Genderless connectors can be activated with few steps and are intuitive and easy to use, creating a sterile connection in a very short timeframe. For example, an experienced operator can make a connection with push-fit aseptic connectors in less than 10 seconds. Operators using a tube welder, on the other hand, can take up to seven minutes to create a connection.



- **Process security.** If two components are supplied with the same gendered connector but need to be connected together, the end user must quickly make a bridging connector to link these two components. This type of issue is usually discovered only at the point of use when time is short and a solution is required immediately. The inability to make the connection when required can lead to delayed production, but in the worst cases can compromise an entire batch of product, leading to its loss. Genderless connectors eliminate the problem of having to create an adapter to connect parts that otherwise would not fit together.

- **Simplified inventory.** Use of gendered connectors requires inventory of male and female components. To ensure availability of components that fit, manufacturers would need three types of preassembled tubing sets in their inventories: male-to male, male-to-female and female-to-female. With the connection flexibility of genderless connectors, only one type of component part or tubing set has to be inventoried.

- **Improved operation and design flexibility.** Genderless connectors typically offer a range of different hose barb sizes in the same connector family. Because all the connectors in the same family of products can be connected together, genderless connectors can also replace flow reducers or enlargers in a fluid stream. For example, a 3/4" genderless aseptic connector can connect to a 1/4" genderless aseptic connector to form a sterile connection while simultaneously serving as a flow reducer at this step in the process.

Genderless aseptic connectors allow the connection of different size tubing on different size single-use components into a seamless system. Flexibility is added in a number of ways. Issues of not being able to connect are eliminated. Design of the assemblies is simplified and the more-flexible production platform can easily be changed or adapted to a new cell therapy process by simply replacing any of the bag components with either different size bags or a different processing step using the same connection technology.

Conclusion

It is important to evaluate your processes while you are in a smaller scale. The improvements you make today, even to aseptic connections, can make a big impact to efficiency and speed as you scale up. For CGT companies, the adoption of single-use connection technology within an operation drives a standardised approach to future components and platform designs. Two important benefits of this are: 1) reduced system complexity and production costs and, 2) the biopharmaceutical market overwhelmingly sees standardising connector compatibility as an important issue.

As the gene and cell therapy industries continue to develop and grow, bringing more cutting-edge technologies to the market, the opportunity to take advantage of the benefits SUTs have already demonstrated in protein, mAb, and vaccine manufacturing will only increase.

Given the product requirements and the personalised nature of autologous cell therapies, there is really no alternative to SUTs. Tremendous knowledge of SUT applications and capabilities exists within biopharma manufacturers, SUT manufacturers, as well as in industry organisations such as PDA, ISPE, BPOG, and BPSA, and many lessons can be learned from the application of SUTs in these markets. In addition, the unique requirements of the cell and gene therapy markets will have a significant impact on the future development of SUTs, including connection technologies. As gene and cell therapy producers gain more knowledge and better understand the requirements and variability of their processes, SUT manufacturers will have an improved ability to address their specific needs.

Amber Sherrick

Amber Sherrick joined CPC as a Market Manager for Biopharma in April 2021. Amber has twenty years of experience in various marketing communications and market development roles. The last decade of her career has been dedicated to market development for single-use, cell culture, purification and pharma analytical product lines. An active member of the BioPhorum Operations Group (BPOG) and a member of the Risk & Business Continuity Management Workstream, Amber has a passion for the single-use segment of the industry. She believes it has a place in creating efficiencies, and mitigating risk in all bioprocessing applications, including cell and gene therapy.