

Gene Therapies: A Guide to Aseptic Single-Use Connectors

Transferable Lessons From the Bioprocessing Industry

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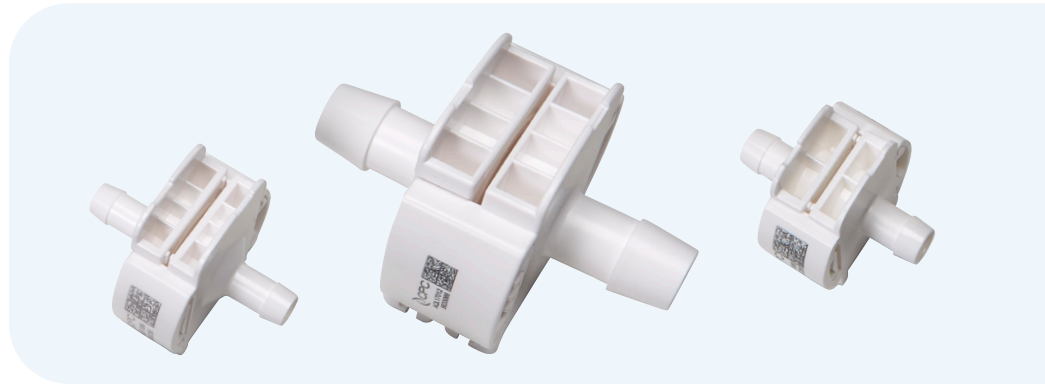
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The biopharmaceutical industry has seen much diversification, innovation and breakthroughs in recent years. For instance, gene therapies are in development that can both treat diseases in new, more effective ways and treat rare diseases that haven't had available options historically.

The Office of Tissues and Advanced Therapies (OTAT), a brand of the FDA, has 22 gene and cell therapies listed as approved with 956 gene therapy molecules active in the pipeline. While these numbers hold much promise, it is important to evaluate your manufacturing process and gauge if improvements can be made to your efficiencies, aseptic conditions and timelines. Even components such as connectors can have a big impact on your productivity and quality.

Just as we are learning from today's rapid COVID-19 vaccine development, there are also many lessons to learn from traditional biologics like vaccines and mAbs as they have been early adopters of aseptic connectors and single-use technologies (SUT) overall. Some of the main benefits that led to SUT adoption are:

- Cost – Reduced manufacturing



costs by elimination of cleaning and sterilization steps

- Speed – Time and labor savings during setup and between operational cycles
- Sterility – Elimination of cross-contamination between batches

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-sterilized single-use systems – ready to open and use. They are used to connect single-use fluid paths – these fall into two basic categories based on how the connection is achieved: those that connect by welding or fusing together two fluid paths and those that mechanically couple two components installed in the fluid pathway.

You might ask, how should you determine if you should use a tube welder or a connectors. Tube welders are 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 you begin to scale-up, tube welding becomes timely and inflexible – as it takes time to weld a connection and you are limited to only Thermoplastic elastomer (TPE) tubing. Most biopharma companies use silicone tubing because of its advantages in terms of cost, chemical stability, low-level of particulate generation, and low extractables profile.

Your other option is aseptic connector. Aseptic connector work by simultaneously removing two porous sterile barriers, usually membranes from the connector assembly to open a sterile fluid pathway once the two components have been combined; this process only takes seconds.

The reason an aseptic connector can produce a sterile connection is because the protective barrier (membrane) prevents bacteria and other contaminants from entering the fluid pathway while the barrier is in place.

Aseptic connectors are available in both gendered and genderless versions. Here is an overview of each:

GENDERED CONNECTORS

Gendered connectors are composed of two different connectors (typically a male and a female component) connected together to create the fluid pathway. Gendered aseptic connectors have the same limitations and potential pitfalls as gendered open connectors when designing a single-use system.

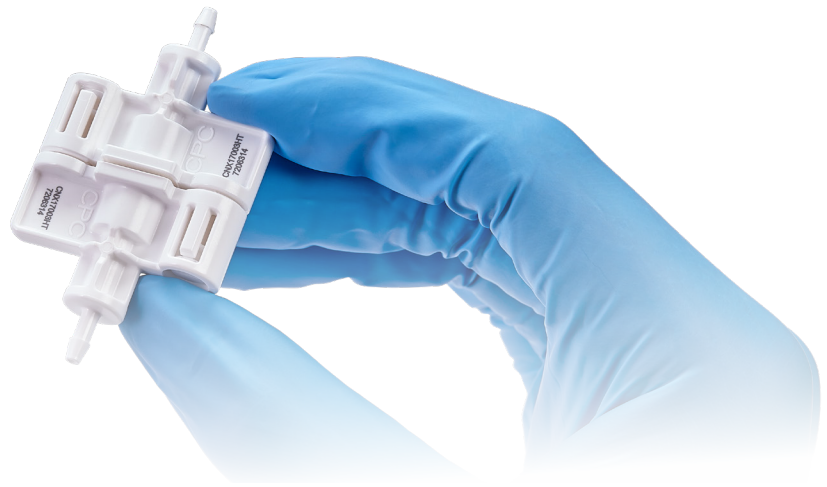
GENDERLESS CONNECTORS

In genderless connectors, the two components brought together to make the connection are identical, thereby eliminating all orientation, inventory planning, and design issues associated with gendered connectors and simplifying the design of a single-use system. Genderless connectors offer several significant advantages over gendered connectors leading to time savings, greater process security, simplified inventory requirements, and increased operational and design flexibility.

- 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 time frame. For example, an experienced operator making an aseptic connection using the push fit connector described earlier can make an aseptic connection in less than 10 seconds. This may not sound like a significant time savings when compared to a tube welder, which takes 3 to 7 minutes for the same connection. But, in a production environment where 100 connections are made per week, a tube welder will take 4 to 7 hours of operator time, depending on the tube welder. The same number of sterile connections can be made using the push fit connector described earlier in less than 17 minutes.
- Process Security - If two components are supplied with the same gendered connector but are required to be connected together, the end user is faced with quickly having to 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 at worst it can compromise and lead to the loss of an entire batch of product. Using genderless connectors eliminates the problem.

- Simplified Inventory - Use of gendered connectors requires the need to hold inventory of both the male and female components. If inventory of preassembled tubing sets is held, the number of components required to be held increases threefold as male-to-male, male-to-female, and female-to-female tube sets may be required. With the adoption of genderless connectors, only one component part or one tubing set has to be inventoried, as shown in Figure 8.
- Improved Operation and Design Flexibility - Genderless connectors typically offer a range of different hose barb sizes in the same connector family. Because all of 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 connects to a 1/4" genderless aseptic connector to form a sterile connection and also introduce a flow reducer at this step in the process.



Genderless aseptic connectors allow the connection of different size tubing on different size SUTs 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

In 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 prove to make a big impact to efficiency and speed as you scale-up.

References:

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