CELL & GENE THERAPIES: A GUIDE TO SINGLE-USE CONNECTIONS - 10 Transferable Lessons From The Bioprocessing Industry

By
Derek Pendlebury, PhD

OEM Channel Manager, Bioprocessing
CPC - Colder Products Company
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The pharmaceutical industry has proven it can successfully develop cell and gene therapies (CGTs). Eight CGTs are FDA approved: Gencidine, Oncorine, Rexin-G, Glybera, Neovasculgen, Imlygic, Strimvelis, and Zalmoxis.[1] Over 400 therapies[2] are in preclinical to Phase 3 development, and approximately 1,700 clinical studies are underway globally. Recent FDA approval of therapies based on chimeric antigen receptor - T-cells (CAR-T) has heightened interest and investment in CGTs. Notably, autologous cell therapies grew 65 percent from 2016 to 2017. Now it's time to tackle the challenges of sustainable and cost-effective commercial manufacturing of these emerging therapies.

While there is much learning to do, some of it can be transferred from the bioprocessing industry. CGTs have many of the same manufacturing needs as biopharmaceuticals. Because of that, industry experts expect the single-use technologies (SUTs) used in biopharmaceutical clinical trials and commercial production to play a large role in the future development and production of CGTs.

SUTs are already used in the development of CGTs today. However, many of those SUTs cannot be transferred from laboratory scale into commercial manufacturing for a variety of reasons, including extractables, leachables, supply chain security, reproducibility, and scalability. These issues will need to be overcome, and solutions developed in the near future, to meet the pace of CGT development.

As CGT manufacturing processes evolve to meet regulatory, economic, and patient safety needs, some learning will come from bioprocessing, while other learning will have to emerge that is specific to CGTs.

This article captures high-level learning about the use of SUTs in biopharmaceutical manufacturing that can be applied to CGTs, with a special focus on connection technologies.

1. HOW ARE BIOPROCESSING AND CGT PROCESSES SIMILAR AND DIFFERENT?

To manufacture biologic products using genetically modified organisms, cells are modified to produce the biologically active molecules. This makes the cells the process and the active molecule the product. To produce CGTs, the cells are the raw material, the process, and the product. Therefore, the production tools and techniques used to make these different therapies have some similarities and some differences.

SUTs are widely used in the biotechnology industry for the development and production of both large and small molecule drug products. A wide range of processing technologies exists, supplied as either discrete components or more often as pre-validated, pre-sterilized single-use systems

ready to use once opened. SUT adoption provides many well-documented benefits for commercial operation,[4,5,6] including:

- 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.

SUTs are used at all stages in the development and manufacture of biopharmaceutical drug products from bench-scale research through all phases of clinical testing and into commercial manufacturing.

SUTs are also widely used and accepted for the development and production of cell therapies and personalized medicines. The reasons for their use are strikingly similar to those for bioprocessing — cost, speed, and sterility.

One noticeable difference, however, is the scale. Bioprocessing scales are larger than those used in the development and production of autologous cell therapy products.

A second difference is the types of SUTs used. In the biopharmaceutical market, SUTs include filters, cell culture systems, mixing systems, storage vessels, tubing, sensors, valves, sampling systems, and connectors.

For cell therapies, traditional uses of single-use systems include clinical and R&D uses for such devices as pipettes, blood collection bags, and T-flasks. The use of these products will continue but is being supplemented with the expansion of SUTs to include collection sets, fluid transfer sets, small-volume cell culture systems, and specifically with the widespread utilization of single-use bags and bag assemblies for media, washing, rinsing, cell harvest, waste collection, and even cryopreservation.

2. ARE TODAY'S CELL THERAPY MANUFACTURING PROCESSES ADEQUATE FOR COMMERCIALIZATION?

Currently, the cell therapy industry is composed of a wide range of disciplines, experiences, technologies, and applications. Different groups working on the research and development of therapies bring different levels of knowledge and perceived requirements to the discussions on SUTs and systems.

Many of the technologies and equipment currently used for CGT were originally designed for other purposes and have been adapted for use in cell therapy manufacturing. Therefore, it is unlikely that all the technologies and systems used initially will have either the appropriate technology or the required documentation to support the manufacturing requirements for late-stage clinical phases and commercial production.

In order for a manufacturing process to move from development into commercial manufacturing, the following issues have to be addressed:

- extractable and leachable data
- limited chemical, heat, or gamma stability
- limited or no supply chain security
- lack of manufacturing reproducibility
- limited or no product scalability
- non-validated manufacturing operations
- lack of reproducible performance.

THE CGT MANUFACTURING PROCESS

Cell therapies are developed using a variety of processes today. The process is dependent on many factors, including cell source, processing requirements, methods of cell harvesting, cell selection, cell washing, cell expansion, gene modification, and gene transfer. The process steps for CAR-T development are shown in Figure 1 in the outer circle. Examples of technologies that can be used for each process step are also shown below in the inner circle. Some of the technologies listed are very similar to those used in large-scale bioprocess manufacturing applications. As more cell therapy products enter both the clinical trial pipeline and commercial production, it is important to identify the benefits SUTs can offer for cell therapy developers and manufacturers and to implement SUT where appropriate. Equally important, the industry needs to define the knowledge gaps, the potential pitfalls of SUTs, and the path forward for obtaining the information to make decisions.

The consequences of not planning ahead are significant. Imagine reaching a late-stage clinical trial only to learn a change to a single-use manufacturing component has to be made. This could result from product discontinuation, lack of scalability, supply chain issues, or validation issues. The impact of having to make a process change could be significant delays in time to market, increased costs for revalidation, and potentially additional regulatory investigation of the other technologies used in the manufacturing process.

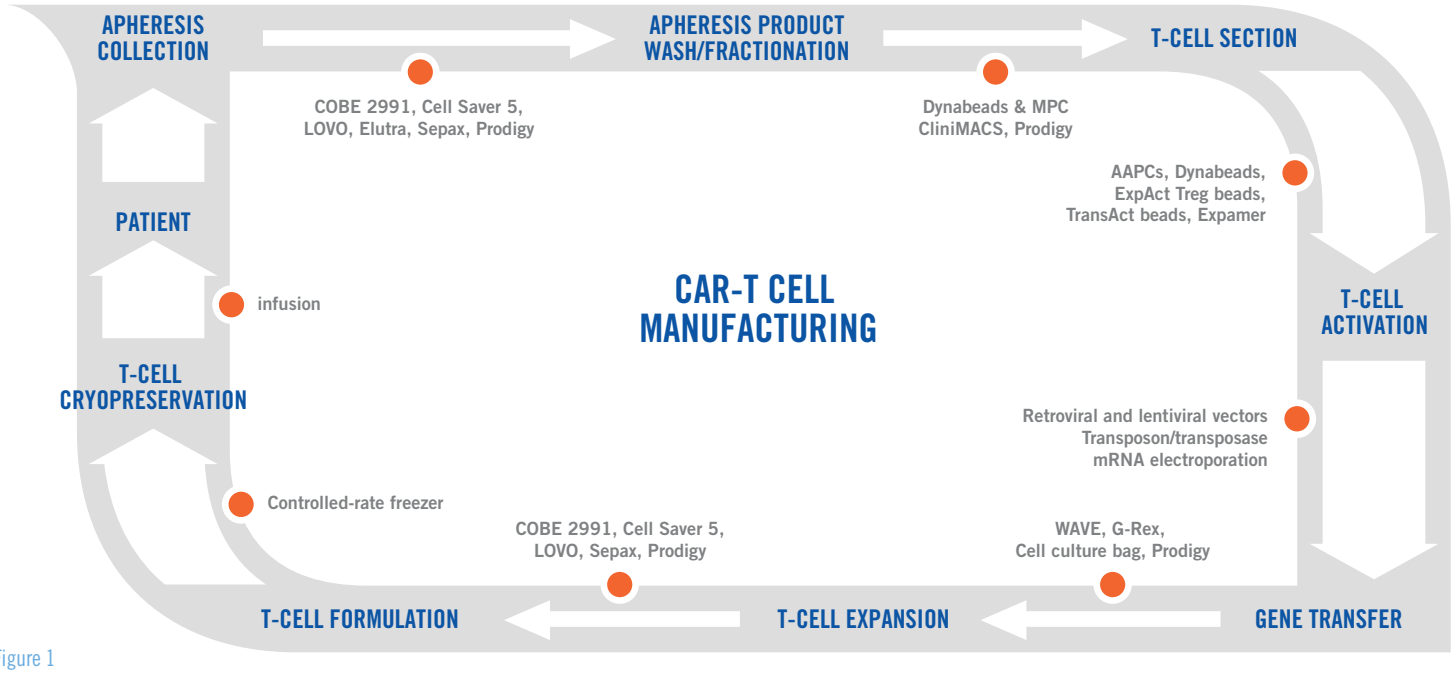


Figure 1
CAR-T Process

IS THE CURRENT CGT MANUFACTURING PROCESS COST-EFFECTIVE ?

In a recent presentation,[3] the cost of manufacturing a single therapy using current labor-intensive processes was provided based on the following scenario:

- CAR-T therapy to treat acute myeloid lymphoma
- 20,000 patients per year
- 14-day process per patient
- 55 new patient processes initiated and completed per day
- 770 patients treated in parallel
- Current processes, techniques, and equipment

Estimated operating cost is $400 million annually, including:

- a dedicated 70,000-square-foot facility
- a workforce of approximately 3,700 trained technicians and scientists

However, because of the manual processes, the risk of process failure would be high, thereby significantly reducing the number of patients who could be treated and substantially increasing the cost of each effective therapeutic treatment. This is clearly not a long-term, sustainable, cost-effective option.

SUT EQUIPMENT AVAILABLE TODAY

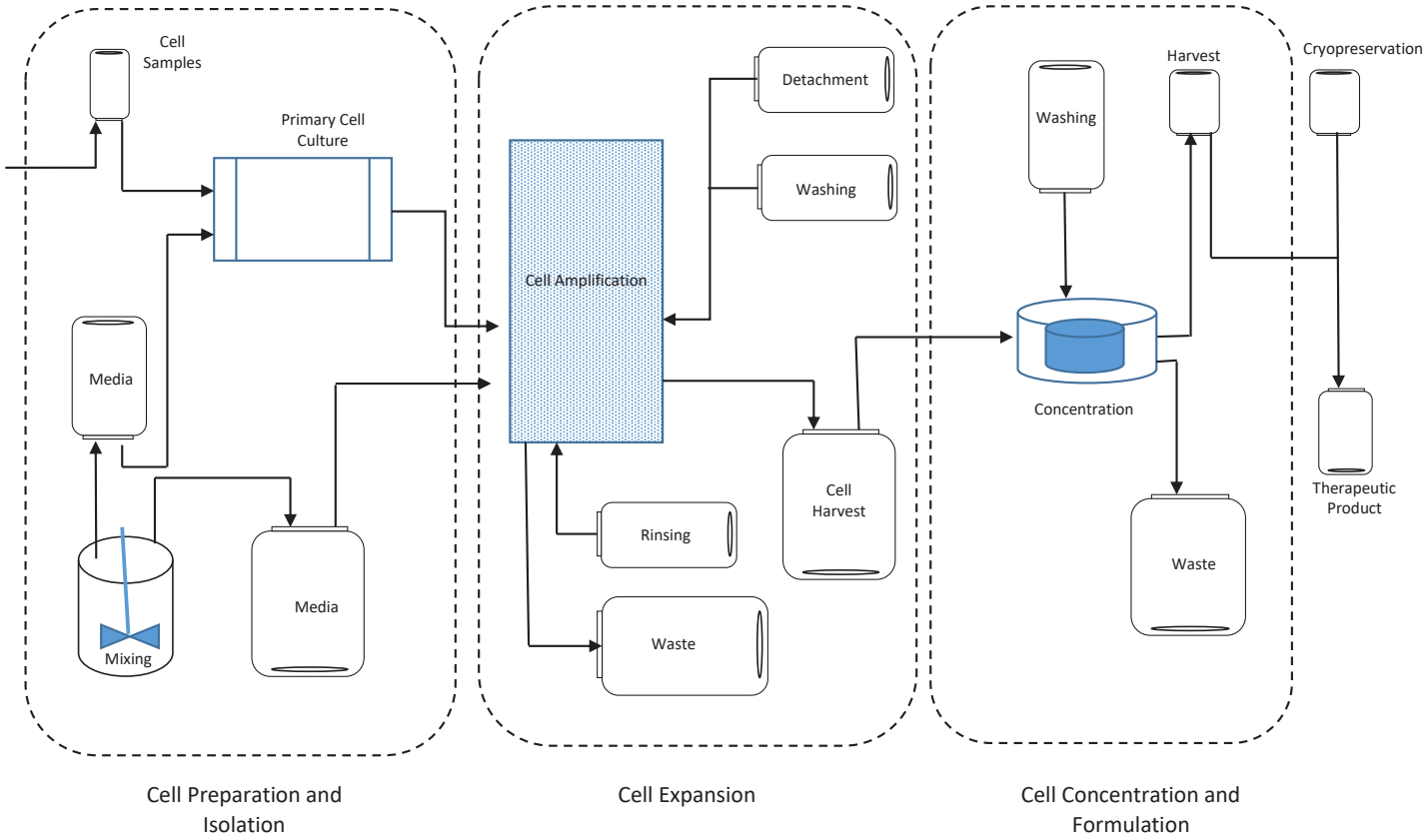
Cell therapy manufacturers should be aware of the wide range of SUTs available. The sheer number of SUTs, even within a component type (e.g., storage bags, connectors, or cell culture systems) can be daunting. New users should anticipate a steep learning curve. Fortunately, a tremendous amount of application, technical, and processing information about SUTs exists in the public domain and from single-use manufacturers and industry organizations.

The scope of this paper does not permit exploration of all SUT products, but instead focuses on one of the most important but often overlooked decisions when developing a single-use-based process — the right connection technology. Connection technology is what brings all the pieces of the single-use jigsaw together. The right connection technology can allow the aseptic connection of single-use to non-single-use steps in the process while maintaining a fully closed system. Selection of the wrong connection technology can have serious implications on the scalability, reproducibility, and security of the process.

3. WHAT ARE THE WAYS TO CONNECT SINGLE-USE FLUID PATHS?

Fluid connection technologies 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.

Figure 2
CAR-T Process in SUT



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.

How many connections will be required within a cell therapy process? While the answer is totally dependent on process, product use, and scalability, Figure 2 shows an example of a cell therapy process based closely on the CAR-T process from Figure 1. It is composed of flexible film-based SUTs. In this proposed system, each bag in the process could be 50 mL to 5 L in size depending on the application and volume of liquids handled at each step. Figure 2 illustrates the number and location of connections required as part of this process.

4. HOW DOES THE PROCESS SETTING INFLUENCE THE TYPE OF CONNECTION TECHNOLOGY USED?

An important factor in determining the appropriate connection technology is design of the processing system. Will it be open or closed? Typically, the location of the process development stage has a significant impact on the design of a processing system and the components used (Table 1).

In a clinical or academic laboratory, product development looks very different than in a biopharmaceutical company. Not only are the technologies different, but the longer-term objectives are different as well. The biopharma company typically takes a longer-term view of developing a product and process with the ultimate objective of commercializing the therapy.

SUTs, such as easy-to-use aseptic connectors, can address the requirement of greater process robustness and reliability.[9] While SUTs are being increasingly adopted in recombinant manufacturing processes, their adoption in cell therapy bioprocessing is essential due to sterility concerns.[10] In contrast to the well-established automated processes used in recombinant therapy production, the poor automation, labor-intensive, and open nature of cell therapy manufacturing make it more prone to operator variability and contamination risks.[11]

In its Technology Roadmap to 2025[12], the National Cell Manufacturing Consortium clearly identified in the section

Table 1

Differences in cell therapy processing are influenced by the product development setting.[8]

SETTING	COMPONENTS	PROCESS STEPS	PROCESS	SYSTEM
LABORATORY	Tissue culture dish, plates, flasks, vials	Transfer by pipette	Manual	Open components and processing
CLINICAL	Syringes, processing and storage bags, transfer sets	Luer connectors, sterile docking, tube welders	Manual with some automation	Closed connectors and processing
BIOPHARMACEUTICAL COMPANY	Rocker bags, culture bags, roller bottles, bioreactors	MPC/MPX connectors, asepctic connectors, tube welders	Manual with high level of automation	Fully closed system

on Standardization and Regulatory Support that establishing standards with the appropriate regulatory authorities is required for both open and closed systems. The type of system required and the environment in which each process step and connections for each step will be undertaken determine the type of connection technology that should be used.

5. WHAT DO I NEED TO KNOW BEFORE CHOOSING BETWEEN TUBE WELDERS AND CONNECTORS?

Tube welders are widely used in both the laboratory and in clinical environments to form sterile tubing connections and are also used in the commercial production of some biopharmaceutical drugs. Typically, these are applications where a small number of connections per day are required, where only one size and type of tubing is used, or where a small number of production batches are required.

HOW DO TUBE WELDERS WORK?

Tube welders work by heat-welding tubes together using an end-to-end weld, also called a butt weld. Most tube welders join two tubes together to form a single weld joint; however, some can make two welds simultaneously. The critical component in the welding process is the blade used to both cut and heat the tubing. During the process, the blade is heated to the correct temperature, then moved to cut the tubing. The open ends of the tubes to be joined are positioned opposite each other while the blade is still in position. Once the blade is retracted, the two ends of the tubes are brought together and a weld is formed. The temperature of the blade during the heating process, approximately 500 degrees Fahrenheit (260 degrees Celsius), is high enough to both weld the tubes and maintain sterility of the cut ends during the process to produce a sterile connection.

WHAT TO CONSIDER WHEN EVALUATING THE USE OF TUBE WELDERS

1. Tube welding, irrespective of the choice of welder, requires the use of thermoplastic tubing, also referred to as TPE (thermoplastic elastomers). Some types of tubing, including silicone, cannot be welded simply because they are not thermoplastic. However, silicone tubing is widely used in the biopharma industry because of its cost, chemical stability, low level of particulate generation, and low extractables profile. Biopharma companies, CMOs, and regulatory authorities are very familiar with the use of silicone tubing in commercial manufacturing operations.
2. Different types of thermoplastics cannot be welded together. For example, C-Flex cannot be welded to Advantaflex, PVC cannot be welded to EVA, and Advantaflex cannot be welded to PVC.
3. Tube welder manufacturers recommend using a new blade for each weld. Depending on the manufacturer and the model of welder, the cost of a blade can be as high as $15 each.
4. Tube welders require electricity to operate, which may require the use of extension cords.

5. Tube welders cannot join tubing of different physical sizes together. For example, they cannot weld ¼" tubing to 3/8" tubing.
6. Tube welders cannot weld tubing of the same diameter but different wall thicknesses together.
7. Tube welders require approximately 12 to 18 inches of free tubing on each of the tubes being welded to allow them to work efficiently without putting excess strain on the weld once it is formed. This additional tubing has to be taken into consideration when calculating the relative costs of each connection method.
8. Tube welders take 3 to 7 minutes to complete a weld (depending on the manufacturer and model used). If multiple welds are required, the time to complete these has to be factored into the production planning and costing process.
9. If several different size tubes (ID and OD) are used in the same system, different tube holders will be required for each size, which means added capital costs.
10. Some welders will only weld one size of tubing, which means different welders will have to be purchased for each tubing size used.
11. If the tube welder fails, the facility will be without the capability to make sterile connections while the welder is repaired or replaced. The alternative is to have a second welder as a backup system.
12. The welding process can generate particulates which cannot be allowed to enter into the closed fluid stream of a cell therapy process.

ADVANTAGES OF CONNECTORS VS. TUBE WELDING

Connectors can offer several advantages over tube welders when designing a system. These include

- flexibility to work with any type of tubing and allow any type of tubing to be connected to any other
- no electricity required
- little, if any, training needed
- no maintenance required
- no particulates generated
- faster speed of connection.

6. WHAT ARE THE KEY CONSIDERATIONS WHEN CHOOSING A CONNECTION TECHNOLOGY?

EASE OF USE

How simple and intuitive is it to make the connection? With more complexity and steps required to make a connection, the risk of operator error increases. Currently, aseptic connectors require three to 10 steps by an operator to make a connection. Simpler is better.

ROBUSTNESS

Connectors need to withstand intended use, as well as unintended abuse. One of the most common issues with connectors is their inability to withstand side loading. Side loading can occur after a connection is made if the connector is subject to external forces that distort the connector and may compromise the security of the connection. An example of this is if a connection is made between two lengths of tubing that are not supported during fluid transfer. The combined weight of the tubing plus the fluid within can result in excess force on the connector, causing distortion and potentially breaching the security of the connection. Side loading is unavoidable when working with tube and bag assemblies. So the ability of a connector to handle high side loading forces in less-than perfect conditions benefits the security of the process.

SECONDARY EQUIPMENT

Ideally, connectors should not require additional equipment such as tri-clover clamps, fixtures, or assembly aids to make the connection. If additional equipment is required, this may indicate the connector is not as robust as the process requires. Additionally, the requirement to install secondary equipment is another potential source of operator error. Usage errors could make the connector nonfunctional and compromise the entire single-use assembly.

SEAL DESIGN

The seal design is the last line of defense against leakage or microbial ingress into the connector and the system. Therefore, understanding what is providing the final seal is very important. When evaluating connector options, bear in mind that a well-designed seal ensures the seal stays in place throughout the actuation steps and that the connector will withstand side loading, flexing, and tensile forces without compromising the integrity of the seal. Larger, more robust seals in both halves of the connector are preferred over smaller, less robust seals, which are sometimes located in only one half of the connector.

7. WHAT ARE THE TYPES OF CONNECTORS AND THEIR ADVANTAGES AND DISADVANTAGES?

The two categories of connectors are open and aseptic. Open connectors require a controlled environment in which to make an aseptic connection. Aseptic connectors can make an aseptic connection in any environment,

Figure 3.
Showing male (left) and female components of an open MPC connector

even one with a high bioburden. Aseptic connectors are provided in two forms: gendered and genderless.

OPEN CONNECTORS

"Open connector" refers to any connector technology that requires a sterile or aseptic environment in which to make a sterile connection. The most common examples include luer fittings and MPC-type connectors. These connectors are installed on a single-use system and plugged or capped to seal the connector and maintain sterility until use, followed by bagging the complete assembly and gamma irradiating it for sterilization. They are typically used in a laminar flow hood that provides a sterile environment when the connection is being made.

Open connectors have two parts which are not the same, as shown in Figure 3. This type of connection is typically referred to as a gendered connector, as they are comprised of a male and female connector. To make the connection, the two parts are brought together and locked. This means during the design stages of a single-use system, the orientation of each connector on each tube and its relation to the component it is connecting to have to be planned to ensure the whole assembly will connect together when in use. When mistakes are made at the design stage of a single-use system, the end result can look like Figure 4.

If open connectors are used to connect a system in an uncontrolled environment (e.g., an open laboratory bench), once the caps or plugs are removed from the connector, the connector fluid path is no longer sterile. The sterility of the entire system being connected is compromised. Yet these types of connectors can be used to make an aseptic connection, for example, when used under a laminar flow hood. Once a connection is made, the connectors are reasonably secure. The operator has to physically depress a latch or turn the connector to disconnect them. However, this does not totally prevent accidental disconnection.

Some advantages of open connectors:

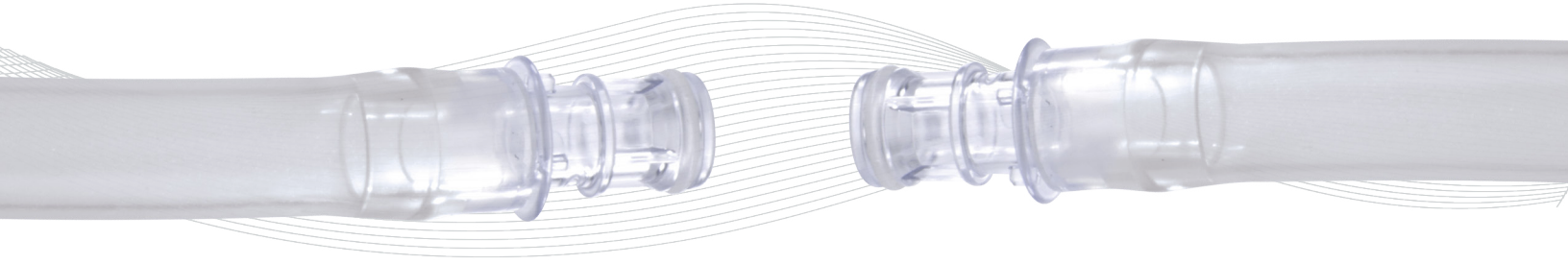
- Their intuitive use and inexpensive cost helps keep the cost of a single-use system low.
- The wide variety of sizes available is a critical consideration for an industry operating with very small volumes of highly valuable material.
- A broad number of sourcing options is available due to the technology no longer being protected by patent or intellectual property. Connectors from different suppliers typically connect together without issue.

ASEPTIC CONNECTORS

Aseptic connectors were first introduced in the early 2000s. They allow the end user to make a sterile or aseptic connection in an uncontrolled environment as well as in a controlled environment, a significant advance in the science of connection technology.

Currently, all aseptic connectors work by simultaneously removing two porous sterile barriers, usually membranes,

Figure 4.
Result of an incorrectly designed system



from the connector assembly to open a sterile fluid pathway once the two components of the connector have been brought together. The mechanisms by which the different connectors are assembled, connected, and operated vary widely. Some are very simple to use with three steps, and others are more complex, with up to 10 steps to complete before an aseptic connection is made. Connectors also vary widely in the diameters of tubing that they can work with. This wide variability in operational capability of the available connectors must be taken into account when developing a single-use process for the cell therapy market. Generally, a connector that is simple to use, has few operational steps, and works with a wide range of different tubing types and sizes offers greater operational flexibility to the user.

8. HOW DOES AN ASEPTIC CONNECTOR PRODUCE A STERILE CONNECTION IN A NON-STERILE ENVIRONMENT?

Each connector half is supplied with a protective barrier, usually a membrane, welded across the fluid flow path. Once the connector is assembled into a system and sterilized, the protective barrier prevents bacteria and contaminants from entering the fluid pathway while the barrier is in place.

HOW ASEPTIC CONNECTORS WORK

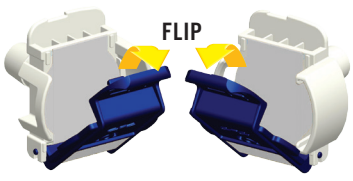
In the example below, the dust covers are flipped down to expose the membrane (Figure 5). The two halves of the connector are pushed together until an audible click is heard from both sides, indicating the secure connection has been made (Figure 6). The membrane barriers are clicked together and then pulled from the assembled connector to open the sterile fluid pathway, as shown in Figure 7. Most aseptic connectors require a final twist of the assembly to securely lock the two halves together after the membrane has been removed. This represents a potential for operator error if the final twist is not completed and can result in a non-sterile connection being made. However, the connector shown in Figures 5, 6, and 7 only requires a push fit to make a secure connection, and the removal of the membranes is the last step in the process.

HOW DO MANUFACTURERS OF ASEPTIC CONNECTORS ENSURE RELIABILITY & STERILITY?

Manufacturers of aseptic connectors have implemented several procedures to ensure the connectors do not compromise the drug product or substance being processed. These include:

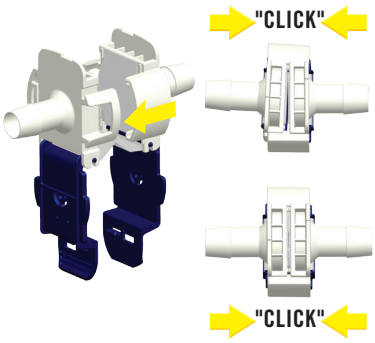
- certification to a minimum of ISO9001; some manufacturers are also certified medical device manufacturers to ISO 13485
- strict and controlled raw material supplier evaluation and selection criteria
- robust and rigorous supply chain management and continuous evaluation
- well-documented manufacturing SOPs in controlled environments with trained operators
- rigorous testing of their designs and finished product to validate the connectors work as promised, do not allow a sterility breach of the process, and do not extract unwanted materials into the solutions passing through them.
- The tests fall into four primary categories:
  - Testing and validation of the raw materials and component parts to show compliance with accepted industry standards such as USP Class VI Plastics test, USP<87>, USP<88>, and USP<661>

FLIP-CLICK-PULL Assembly Procedure



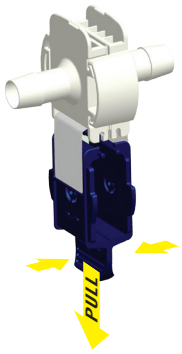
1 Unsnap and flip down the protective pull tab covers on each connector half.

Figure 5.



2 Align the connector halves with the pull tabs hanging down. Slide the two halves together. Independently squeeze each side of the connector until you hear an audible “CPC Click."

Figure 6.



3 To complete the connection, simply snap the pull tabs together by pushing on the CPC logos and pull the membranes from the connector.

Figure 7.

- Testing of the mechanical strength of the assembled connector. These tests can include side load testing, tensile strength testing, creep rupture testing, burst testing, helium leak testing, flow rate testing, and freeze-thaw testing to low temperatures (minus 80 degrees Celsius)
- Extractables testing against a panel of identified solvents, under controlled conditions, over predetermined time periods to determine the potential for unwanted substances to extract from the materials of construction
- Bacterial ingress testing of the finished assembled connectors. The purpose of bacterial ingress testing is to demonstrate the ability of an aseptic connector to make and maintain a sterile connection during use under extreme conditions. To meet these requirements the example of bacterial ingress testing shown in Figure 8 uses both liquid and aerosolized bacterial solutions to challenge the connection during testing. The solution of Brevundimonas diminuta (ATCC 19146) used is the same organism, but in a more concentrated solution than those used to challenge 0.2µm sterilizing grade filters using standard sterile grade filter test methodologies. [13,14,15,16,17]

TUBING SIZES THAT CAN WORK WITH ASEPTIC CONNECTORS

Aseptic connectors are designed to work with a range of tubing sizes. However, because the technology was initially developed to support the biopharmaceutical processing market, the development focus of most suppliers has been on systems to handle larger flow rates, not on smallvolume fluid handling. Therefore, it is imperative to consider the complete range of available tubing sizes that can be used with a connector family when selecting a connector. Most suppliers have connectors with 1/4", 3/8", 1/2", and either 5/8" or 3/4" options. Only one supplier, CPC - Colder Products Company, has a family of aseptic connectors that goes below 1/4" to 1/8".

9. WHAT ARE THE TYPES OF ASEPTIC CONNECTORS AND THEIR ADVANTAGES OR DISADVANTAGES?

As mentioned previously, aseptic connectors are available in both gendered and genderless versions.

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.

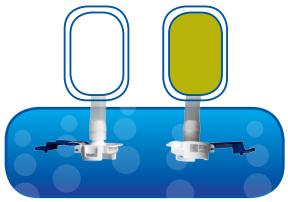
- *Time savings* - Genderless connectors can be activated with few steps and are intuitive and easy to use, creating a sterile connection in a very short time frame. For example, an experienced operator making an aseptic connection using the push fit connector described earlier can make an aseptic connection 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

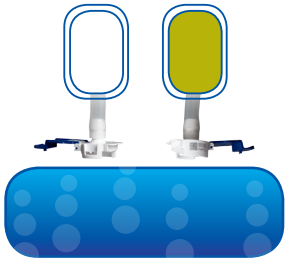
Figure 8.

BACTERIAL INGRESS TESTING METHODS

Presterilized prior to testing

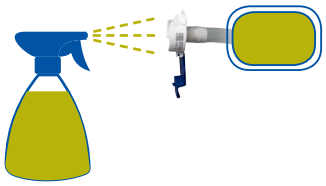


Each half is submerged
Agitated for 30 seconds

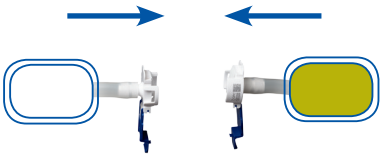


Each half removed from bath
and allowed to dry

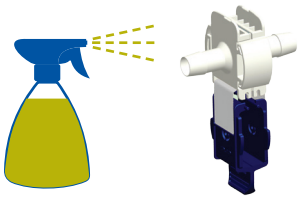
Presterilized prior to testing
Each half sprayed with Brevundimonas
diminuta, >1 x 108 CFU/ml



First stage connection



Spray again as membranes are
removed



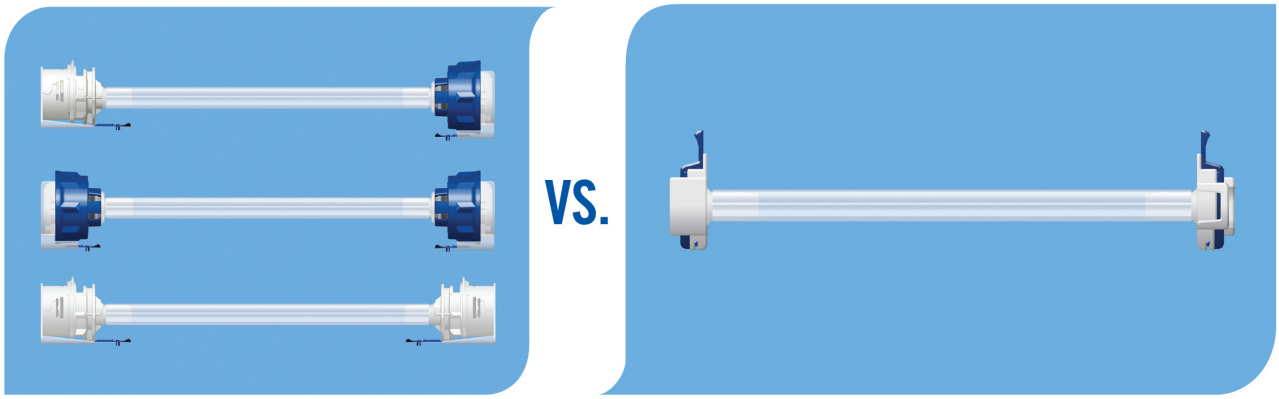
Go to
SUBMERSION TEST

Submerge previously dipped and
sprayed in microbial bath

Transfer growth media through
flow path

Incubate at 30 to 35° C for 7 days
Inspect for growth

Figure 9.
A 3X reduction in tube set designs achieved by implementing a genderless 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, in Figure 9, a 3/4" genderless aseptic connector (left) connects to a 1/4" genderless aseptic connector (right) 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. Referring back to the process example depicted in Figure 2, the use of the same family of genderless connectors on all bags in the process will allow any bag to be connected to any other bag.

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.

10. WHAT IS THE PATH FORWARD FOR CGT?

The adoption of a single-use connection technology within an operation drives a standardized approach to future components and platform designs. Two important benefits are reduced system complexity and production costs.

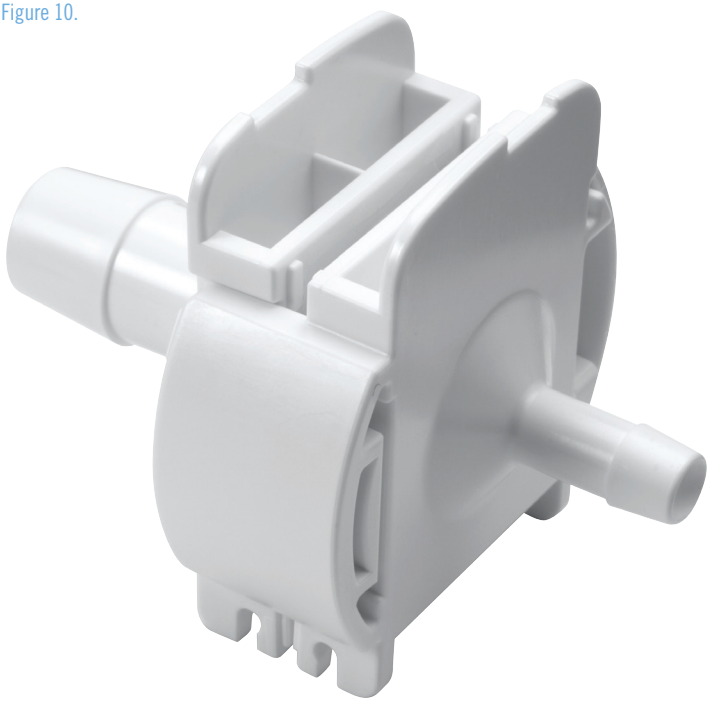
The biopharmaceutical market overwhelmingly sees standardizing connector compatibility as an important issue. According to BioPlan Associates research:[18]

- 88 percent of respondents in the biopharmaceutical market viewed standardizing connector compatibility as an important issue for the industry. Two years later, this number increased to 90 percent.[19]
- 73 percent of respondents from the same study[18] showed a preference for genderless connectors as an answer for both standardizing single-use systems and eliminating many of the issues experienced in using SUTs.

As the cell therapy industry continues 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 personalized nature of autologous cell therapies, there is really no alternative to SUTs. Tremendous knowledge of SUT applications and

Figure 10.



capabilities exists within the biopharma manufacturers, within the SUT manufacturers, as well as in industry organizations such as PDA, ISPE, BPOG, and BPSA. Many lessons can be learned from the application of SUTs in these markets.

The unique requirements of the cell therapy market will have a significant impact on the future development of SUTs, including connection technologies. As 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 the specific needs of the cell therapy producers.

There are many unanswered questions in the CGT industry. Many are unique to the industry, but some have already been addressed by the biologics market, providing areas where cross-industry experience and learning can be transferred to offer a solid knowledge base from which to build.

Questions that remain include:

- How will the processes for allogeneic products differ from more traditional biologic products?
- What is the right level of system or component validation in autologous manufacturing?
- How should assembled single-use systems be tested to provide relevant extractable and leachable data?
- Should CGT single-use systems be integrity-tested pre- and post-use, and, if so, how?
- Where and how can standardization of manufacturing processes or procedures be used to help drive down cost of goods?
- Can adoption of standardized processes help overcome the issues involved in technology transfer of CGT therapies from preclinical trials to clinical investigation and commercial manufacturing stages?
- What are the standardized processes and how can the adoption of SUTs benefit the industry?

At the January 2018 Phacilitate Cell and Gene Therapy World Conference in Miami, there were significant panel discussions about the potential benefits standardized methodologies could bring to the industry. These discussions focused on all processes in areas of cell collection, assays and quality testing, diagnostic methods, and automation of processes. The inherent variability of the critical raw material (i.e., the patient's own cells) makes full standardization of a manufacturing process an almost impossible task. However, there are common manufacturing components, such as connectors, tubing, bag materials, and vent and gas filters, where standardization of designs and material of construction could help reduce the costs associated with validation of a system or its components.

SOURCES OF ADDITIONAL INFORMATION

1. For more information on the use, applications, benefits, and validation of SUTs, please visit the following websites:
- Bio-Process Systems Alliance (BPSA)
- BioPhorum Operations Group (BPOG)
- Parenteral Drug Association (PDA)
- International Society for Pharmaceutical Engineering (ISPE)

2. For more information about connectors, including product specifications, dimensional drawings, extractable information and product validation guides, please visit cpcworldwide.com/bio.

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ADDITIONAL RESOURCES

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About The Author

Derek Pendlebury has worked for over 32 years in the development and supply of SUTs for the biopharmaceutical industry. His experiences include sales, product management and development, sales management, corporate marketing, and corporate management in senior positions with Sartorius, Pall Corporation, Agilent Technologies, 3M, ATMI, and Charter Medical. Dr. Pendlebury has authored numerous papers and book chapters and has presented on SUTs at over 20 conferences. He is an active member with the BPSA, PDA, and ISPE. He holds a bachelor of science in biology from Coventry University, U.K.; a masters in marine biology from the University of Leeds, U.K., and a doctorate in marine biology from the University of Manchester, U.K.