PALL Life Sciences

White Paper

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Expanding Adoption of Single-Use Systems Drives Need for Wider Range of Sterile Connector Technologies

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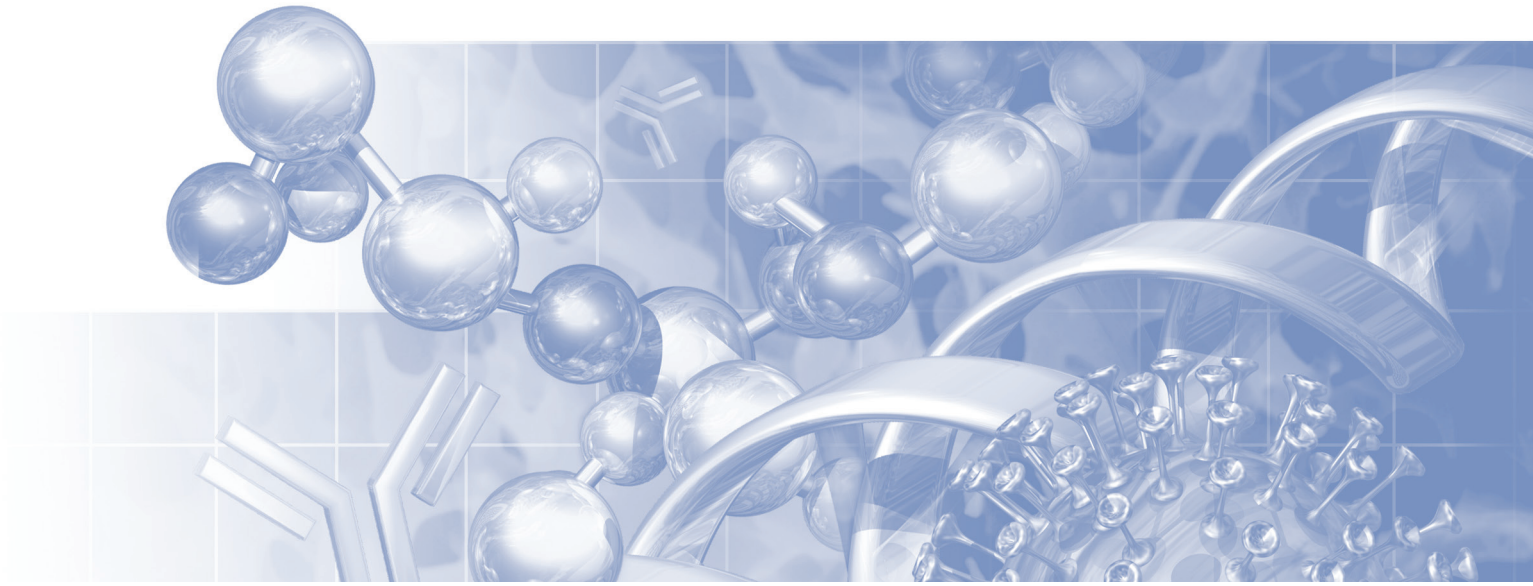


Since disposable technologies have demonstrated their numerous benefits and reliability at the development and clinical scales, biopharmaceutical manufacturers are slowly increasing the implementation of single-use systems for commercial-scale manufacturing in upstream, downstream and fill/finish operations. In response to changing customer needs, Pall Life Sciences has expanded its established and widely used portfolio of Kleenpak® sterile connectors to include new genderless Kleenpak Presto sterile connectors.

Expanding Applications for Single-Use Technologies

According to BioPlan Associates, the market for disposable technologies in biopharmaceutical manufacturing is expanding at a very healthy rate of 16-18%. In addition, Transparency Market Research estimates that currently only 25% of the market can be attributed to commercial cGMP manufacturing applications. With significant expected growth in this segment comes a great need for adaptable technologies.

The adoption of disposable bioprocessing equipment has already been widespread for small-scale applications at the development and clinical manufacturing stages. Now that the concerns about the reliability and robustness of single-use systems have been alleviated and the extent of their benefits have been clearly demonstrated, many biotech and contract manufacturing organizations are actively moving toward the implementation of disposable technologies for commercial manufacturing, particularly in newer multi-product production facilities.

In 2015, BioPlan Associates reported that more than 90% of facilities use single-use/disposable technologies and, when planning their manufacturing strategies, companies now typically consider both dispoable and stainless steel options before making equipment purchases. The same study also found that 69% of respondents attributed improvements in bio manufacturing performance to the adoption of disposable technologies.

Single-use systems are attractive because they eliminate the need for cleaning and cleaning validation, resulting in reduced capital expenditures and faster setup and turnaround times. They also eliminate the risk of cross-contamination and provide greater flexibility to meet changing market needs by facilitating system reconfiguration ease and, as such, are ideal for multi-product facilities that may need to be replicated in multiple locations. Furthermore, disposable technologies can enable Quality by Design approaches, the use of process analytical technology, and continuous processing—all of which are encouraged by the US Food and Drug Administation.

Connectors Hold the Key to Sterility

Single-use systems consist of multiple components such as biocontainers (bags, bioreactors, etc.), mixers, pumps and other devices joined to specially designed silicone or thermoplastic tubing via sterile connections. These sterile connections are crucial to the functionality and the sterility of a single-use assembly; without effective sterile connectors that can maintain clear fluid pathways, the sterility of a single-use system will be breached.

For all sterile connectors on the market their claim is to provide sterile transfer of fluid between 2 unit operations. Because of the capability of these devices, many customers also use them in non-sterile application to control bioburden and reduce the manual handling risk for these critical operations.

There are different types of connectors available on the market and thus selecting the most suitable connector technology for any given biopharmaceutical processing application is important to ensure that process quality, and sterility requirements can be met.

Gendered vs. Genderless Connectors

Sterile disposable connectors can be classified into two main categories. Gendered connectors are designed such that “male” connectors can only be joined to their “female” counterparts. Genderless connectors do not have any distinction so that any one connector can be used with another.

There are perceived advantages to both types of connectors depending on the end-use application. Genderless connectors provide greater flexibility when installing single-use systems and generally reduce complexity with respect to inventory management and part number maintainence. On the other hand, gendered connectors often present a lower risk of operator error because it is not possible to make incorrect connections[2].

In its 11th Annual Report and Survey of Biopharmaceutical Manufacturing Capacity and Production, BioPlan Associates investigated the preferences of 26 users for gendered and genderless connectors. While nearly three-quarters of the respondents indicated that, in general, they would like to use genderless connectors for clinical and larger-scale bioprocessing because of the reduced inventory requirements, when asked for more detail, they revealed that risk mitigation was their greatest concern with sterile connectors and therefore, in reality, they prefer gendered connectors[3].

Given customer interest in both gendered and genderless connectors, Pall Life Sciences has added the Kleenpak Presto sterile connector to its globally recognized portfolio of gendered Kleenpak sterile connectors to provide the widest possible range of single-use connector solutions.

Customer-Driven Development

Pall Life Sciences was the first supplier to introduce sterile connectors with the launch of the Kleenpak sterile connector over 16 years ago. Today, Kleenpak sterile connectors are widely used in the biopharmaceutical industry. When industry research indicated that the connector portfolio needed to expand to meet evolving customer demands, long-term relationships were drawn on to identify key features that should be incorporated into the new connector technology. End user feedback was sought throughout the entire development and commercialization process.

Figure 1
Kleenpak Presto Sterile Connector

Kleenpak Presto sterile connectors allow sterile connections to be made in unclassified environments in three simple steps using genderless technology. This capability eliminates the need for laminar airflow hoods and glove boxes to carry out sterile connections. In addition, because they are easy to use, Kleenpak Presto sterile connectors provide enhanced levels of sterility assurance, using error free features to ensure that the connection is made the correct way 100% of the time.

The genderless design allows for reduced part numbers and simplified single-use systems. Unlike other gender-less products on the market, Kleenpak Presto sterile connectors do not have separate part numbers based on the sterilization method (irradiation or autoclave) and therefore provide a higher level of inventory simplification.

The Kleenpak Presto seal technology provides leak-free, high-pressure operation—up to 3 barg for up to 90 days and 4 barg for 2 days. Across the pressure range they withstand operating temperatures from 2 to 60 °C and can be stored at temperatures as low as -80 °C. They are compatible with a wide range of solutions and solvents including acid and basic solutions from pH 2 to 12 respectively. Thus, Kleenpak Presto sterile connectors are designed with a level of robustness that enables a wide variety of applications, including single-use tangential flow filtration using a pulsated pressure of up to 4 barg.

These new connectors are safe for biopharmaceutical manufacturing applications and can be used with single-use systems intended for all bioprocess operations. Notably, Kleenpak Presto sterile connectors are the only sterile connectors currently on the market that have individual device traceability, which gives even greater levels of sterility assurance. Extractables testing has been conducted in line with the recommendations of the BioPhorum Operations Group (BPOG) specifically to meet end user requirements. Furthermore, each and every connector is inspected using a proprietary automated Vision system, providing 100% inspection for integrity of the peel strip and of the weld.

Finally, Kleenpak Presto sterile connectors come in a wide range of sizes (¼ in., 3/8 in., ½ in., and 5/8 in. hose barb and ½ in. mini sanitary connectors) to enable the handling of different volumes. More importantly, the universal face allows for step up and step down connections and each size has a different colored protective cap, providing a clear visual indication for the end user. The caps are also tamper-evident for enhanced end-user confidence between point of manufacture to the point of use of the single-use systems.

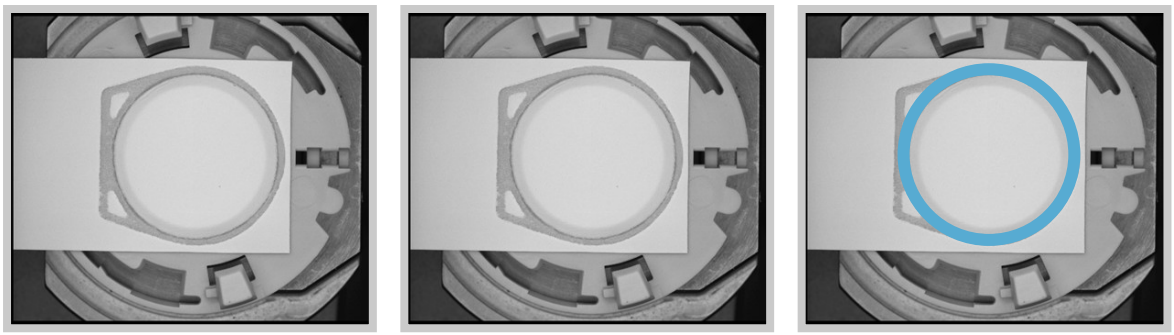
Key features incorporated into the new Kleenpak Presto sterile genderless connectors in response to end user input include:

- *Intuitive 3 step operation to eliminate variability in connection and make procedures easier to follow*
- *Usability in a wide range of applications, including upstream and downstream processing and fill/finish operations*
- *Same part number for connector regardless of whether it is sterilized by autoclave or gamma irradiation*
- *Compliance with all mandated regulations*
- *Traceability/security of supply to provide greater assurance for commercial-scale manufacturing operations*

Highest Level of Traceability

Kleenpak Presto sterile connectors are manufactured at Pall's Ilfracombe Devon, UK plant, in a Class 10,000 room (ISO Class 7). An on-line Vision system is incorporated into the automated assembly line and used to test 100% of the connectors for
absence of peel strip defects, weld defects, and seal integrity (see Figure 2) in a non-destructive manner. The images from the Vision system are stored and linked to the batch and serial number of each device for full traceability. This system therefore provides the highest level of traceability for sterile connectors in the industry.

Figure 2
Visual Inspection System Detects Peel Strip and Weld Defects



Kleenpak Presto sterile connectors are constructed in compliance with all applicable USP requirements (see Table 1). The PES that is used for manufacturing is also certified to be BPA-free.

Table 1
Compliance of Kleenpak Presto Sterile Connectors with USP Standards

	Standard No.	Title
Construction materials	USP <87>	Biological reactivity *in vitro*
Construction materials	USP <88>	Biological reactivity *in vivo*
Construction materials	USP <661>	Containers, physicochemical tests, plastics
Release testing	USP <788>	Particulates
Release testing	USP <85>	Endotoxins

Extensive validation of Kleenpak Presto sterile connectors has also been performed (see Table 2).

Table 2
Validation Testing Summary of Kleenpak Presto Sterile Connectors

Test Type	Test Function	Test Type	Test Function
Mechanical tests	Burst test Leak test	Biological safety, cleanliness and physicochemical tests	Compliance to USP <87> Compliance to USP <88> Compliance to USP <661>
Functional tests	Water flow Extended operation Bacterial challenge Fluid compatibility	Release testing	Compliance to USP <85> Compliance to USP <788>
Extractables test	Determination of extractable compounds in line with BPOG matrix	Shelf life studies	Confirmation of claimed shelf life

Many Applications

One of the key performance expectations of customers looking for state-of-the-art single-use sterile connectors is applicability in a wide range of biopharmaceutical processing operations. Kleenpak Presto sterile connectors were therefore designed to be sufficiently robust and compatible for use in various activities related to cell culture, cell removal, downstream, and formulation and filling operations (see Table 3).

Table 3
Applications for Kleenpak Presto Sterile Connectors

Upstream	Harvesting/Downstream	Fill/Finish
Media preparation and transfer	Bioreactor harvest	Buffer preparation and transfer
Cell cultures additives preparation and transfer	Tangential flow filtration	Bulk handling of sterile materials
Transfer of inoculum to bioreactor	Buffer preparation and transfer	Sterile filtration manifolds
Sampling during fermentation / cell culture	Sampling	Connection of bulk sterile material to filing machine
Sterile / bioburden controlled transfer between unit operations	Sterile / bioburden controlled transfer between unit operations	Connection of bulk sterile material to mixer
Probe insertion	Sterile filtration manifolds Collection of bulk sterile material Sterile waste removal from process streams Probe insertion	Probe insertion

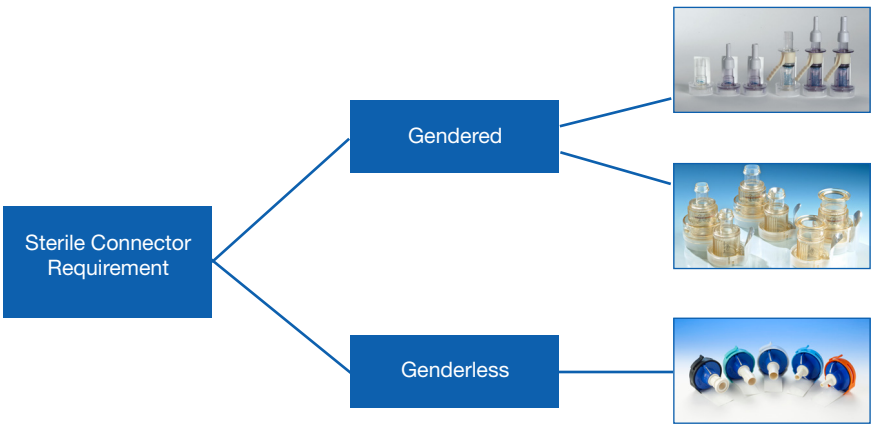
Expanded Portfolio Designed to Meet Customer Needs

Sterility assurance is a crucial issue for the biopharmaceutical industry and sterile single-use connectors, while small components in disposable assemblies, play a direct highly critical role in ensuring that sterility is achieved. The new Kleenpak Presto sterile connectors developed by Pall are available in addition to the existing portfolio of Kleenpak sterile connectors, which have been specified, validated and installed in many customers applications in upstream downstream and formulation and filling.

Figure 3
Expanded Kleenpak Portfolio

The most appropriate connector should be selected on a case-by-case basis depending on the given customer application and process needs and based on risk assessment. Figure 4 presents a decision tree for guidance with connector selection.

Figure 4
Kleenpak Sterile Connector Selection Guide



Kleenpak gendered connectors are available for both large- and small-volume applications. When genderless connectors offer the best solution, Kleenpak Presto sterile connectors would be the best choice. With their high level of traceability, Kleenpak Presto sterile connectors are also ideal for assemblies in which there is no isenpreference for gendered or genderless connectors.

Whether or not there is a preference for gendered or genderless connectors, Pall's portfolio includes effective solutions for any bioprocess application.

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