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A Next Step in Implementing Disposables: Transfer Lines

Single-use transfer lines are emerging as cost-saving alternatives to stainless steel equipment.

John Boehm

Abstract

The implementation of single-use systems—which can deliver significant value through added flexibility, improved production yields, and cost savings—is gaining momentum in the biopharmaceutical manufacturing industry. The initial single-use systems that gained market acceptance consisted of tubing, bags, filters, and connectors. Today, additional types of disposable technologies are being used throughout the production cycle. This article discusses how single-use transfer lines can be incorporated into seed train and final fill applications as well as suite-to-suite transfer operations.

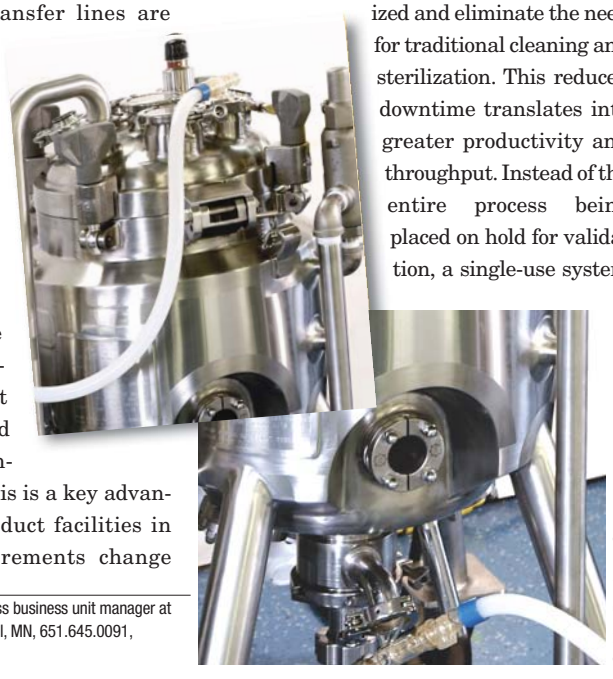
Manufacturers across industries rely on innovative technology to meet two critical production requirements, speed and cost-efficiency. With the increasing pressure to reduce time to market and costs, biopharmaceutical manufacturers are exploring new technologies to meet these challenges.

With the costs to manufacture a single drug approaching $1 billion and time-to-market ranging from eight to 12 years, biopharmaceutical manufacturers are under tremendous pressure to commercialize new drugs faster at a lower cost.

To meet these intense market demands, manufacturers are being forced to continuously boost manufacturing speed and efficiency by relying on innovative technology that can be easily integrated into their existing production processes. One solution that continues to gain momentum is single-use systems, which can deliver significant value through added flexibility, improved production yields, and significant cost savings.

The initial single-use systems that gained market acceptance consisted of tubing, bags, filters, and connectors. These systems were used in bioprocessing facilities for process storage applications and sterile cell culture media. Single-use bioreactors then entered the market in research and development laboratories and rapidly moved into pilot plants and larger-scale production facilities as integral systems for seed train scale-up and production.

Now, single-use transfer lines are emerging as yet another option for manufacturers to save time and cost. Unlike hard piping, the flexible tubing incorporated into single-use transfer lines allows manufacturers to quickly change process steps or convert to a new product without costly and time-consuming cleaning and validation. This is a key advantage for multiple-product facilities in which process requirements change depending on the drug being produced. Innovative manufacturers now incorporate single-use transfer lines in seed train and final fill applications as well as suite-to-suite transfer operations.



Colder Products Company

John Boehm is the bioprocess business unit manager at Colder Products Company, St. Paul, MN, 651.645.0091, john.boehm@colder.com.

The Benefits

The key benefit of single-use transfer lines is the ability to boost productivity and accelerate the time to market by reducing the downtime associated with equipment cleaning and validation. Between each production batch, fixed tubing and re-usable valves must be cleaned to maintain desired sterility. Single-use systems are presterilized and eliminate the need for traditional cleaning and sterilization. This reduced downtime translates into greater productivity and throughput. Instead of the entire process being placed on hold for validation, a single-use system

Figure 1. A traditional stainless steel process for seed train scale-up.

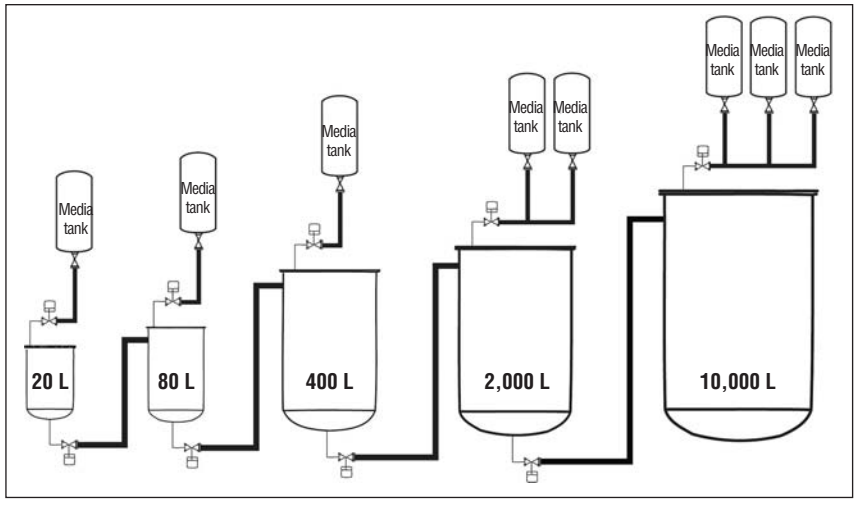
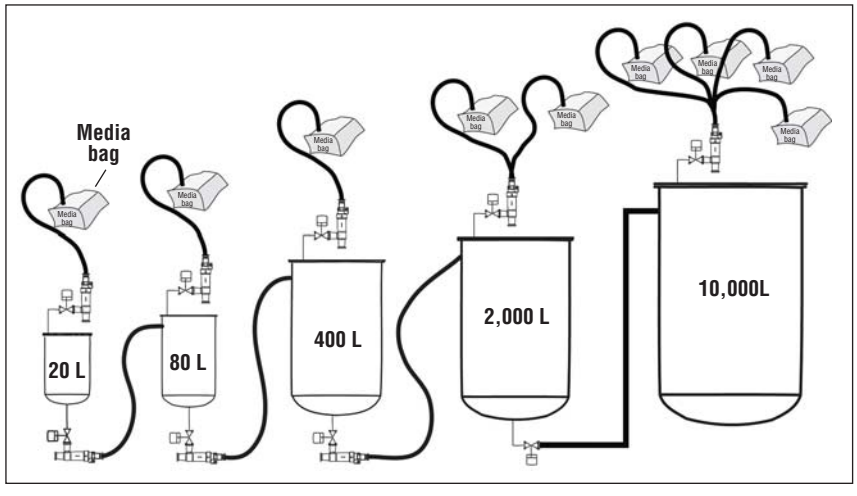


Figure 2. A seed train set up using stainless steel bioreactors and single-use media bags and transfer lines.



can allow the process to be up and running sooner, thereby increasing output and accelerating the time to market.

Additional cost savings result from reduced labor, chemical, water, and energy demands associated with cleaning and validation. Not only do single-use systems reduce costs, they also improve the safety of drug development and delivery. Presterilized, single-use assemblies reduce the risk of cross contamination that may lead to product loss or reduced yields. This benefit is further magnified for companies that produce multiple products within single facilities.

Seed Trains

Modern bioprocessing facilities feature production bioreactors with capacities of 5,000, 10,000 and even 25,000 liters. Scaling up inoculum from a few million cells in several milliliters of culture to these production volumes is a challenge that requires aseptic transfer at each point along the seed train. Traditional bioprocessing facilities accomplish scale-up using a dedicated series of stainless steel bioreactors linked together with valves and rigid tubing (Figure 1).

To prevent contamination between production runs, a clean-in-place (CIP) system is designed into each bioreactor, vessel, and piping line to remove any residual materials. Sterility assurance at the start of each culture is provided by a steam-in-place (SIP) system consisting of steam pipes, temperature sensors, and condensate collection piping. These CIP and SIP systems require extensive validation testing and the valves and piping contained in these systems can create additional validation challenges. In addition, CIP and SIP systems must be revalidated following significant maintenance or changes to the connecting piping and valves network.

Recent advances in single-use system technology allow bioprocess engineers to replace most storage vessels and fixed piping networks with single-use storage systems and transfer lines. Single-use systems reduce maintenance and capital expense by eliminating expensive vessels, valves, and sanitary piping assemblies.

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Figure 2 depicts a 10,000-L production suite, which relies on stainless steel bioreactors, but integrates single-use technology for cell culture media storage and key transfer lines.

Single-use media storage systems are routinely manufactured for volumes ranging from 20 to 2,500 liters. Media storage systems arrive at the bioprocess facility sterilized by gamma irradiation and often are fitted with integrated filters, sampling systems, and connectors. Using an SIP connector allows operators to make sterile connections between these presterilized single-use systems and stainless steel bioreactors for aseptic transfer of media.

Similarly, single-use transfer lines may be used to transfer inoculum between bioreactors using either a peristaltic pump or head-space pressure for flow rates up to 30 liters per minute. Such transfer lines can reduce the number of reusable valves required for transfer, and eliminate problem areas for CIP and SIP validation. Terminating each presterilized transfer line with a single-use SIP connector provides sterility assurance equal to that of traditional fixed piping at lower capital costs.

With the acceptance of single-use bioreactors, some bioprocess engineers are using these systems for both seed trains and small-scale production. Single-use bioreactors range in volume from 1 to 1,000 liters

and use two modes of mixing: rocking platform and impeller. Rocking platform bioreactors consist of pillow-style bags that are secured to a tray mounted on pneumatic lifters. Impeller-based single-use bioreactors are based on three-dimensional drum bags fitted with a single-use impeller before sterilization. These systems are connected to a cell culture media storage bag (either by aseptic welding or aseptic connectors) using flexible tubing.

Similarly, flexible tubing with aseptic connections are used as transfer lines from one reactor to the next. For production volumes over 1,000 L, a single-use bioreactor must ultimately seed one or more stainless steel bioreactors. SIP connectors incorporated into the single-use bioreactor design can link the single-use and stainless section of a seed train. Figure 3 shows a model facility that incorporates single-use media storage and bioreactors, using stainless steel bioreactors for the two largest vessels of 2,000 L and 10,000 L.

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Suite-To-Suite Transfer

After upstream production, the medium containing protein must be aseptically transferred to a different location in the production facility for the final filling operation. This suite could be in a room next door or much farther away. Traditional bioprocessing facilities accomplish this transfer by using stainless steel with piping or reusable hoses as transfer lines. This equipment requires validated CIP and washing procedures before use and sterilization before each media transfer.

Process engineers are now incorporating single-use transfer lines between the bioreactor in the process suite and the transfer vessel to simplify this process. By using presterilized connectors and tubing, the medium can be moved from the production suite to the preparation suite without the need to sterilize stainless steel piping or equipment.

In addition to faster production, these single-use systems also give the manufacturer greater flexibility to determine which process to run in production suites. The enhanced mobility eliminates many of the restrictions that hard-plumbed piping can place on the manufacturing facility.

The risk of cross-contamination in the suite-to-suite transfer process is high, especially in multiproduct facilities. Presterilized, single-use assemblies reduce these risks and improve the speed and safety of drug development and delivery. Such assemblies are used in processes requiring a flow rate of less than 30 liters per minute, but more recently, suppliers have increased the diameter of single-use tubing and SIP connectors to enable bioprocessing facilities to incorporate single-use transfer lines into larger and larger production processes.

Figure 3. A model facility that incorporates single-use media storage and bioreactors using stainless-steel bioreactors for the two largest vessels of 2,000 L and 10,000 L.

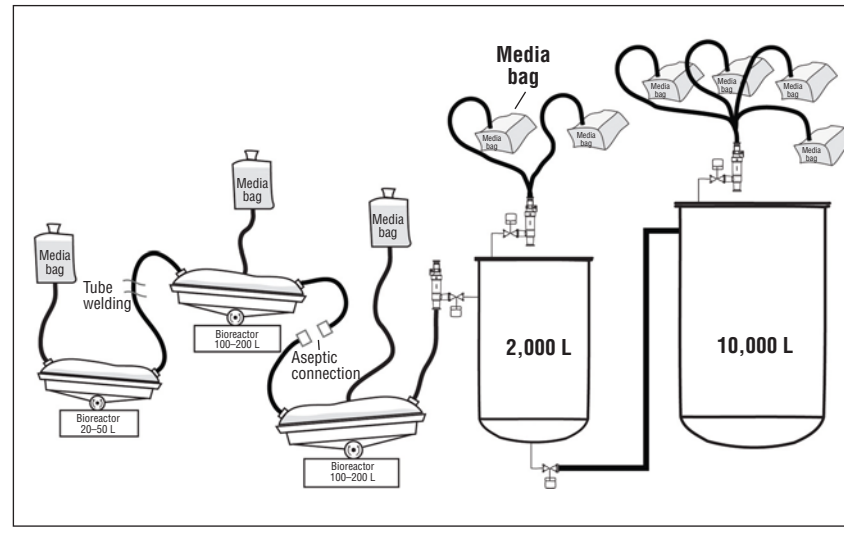
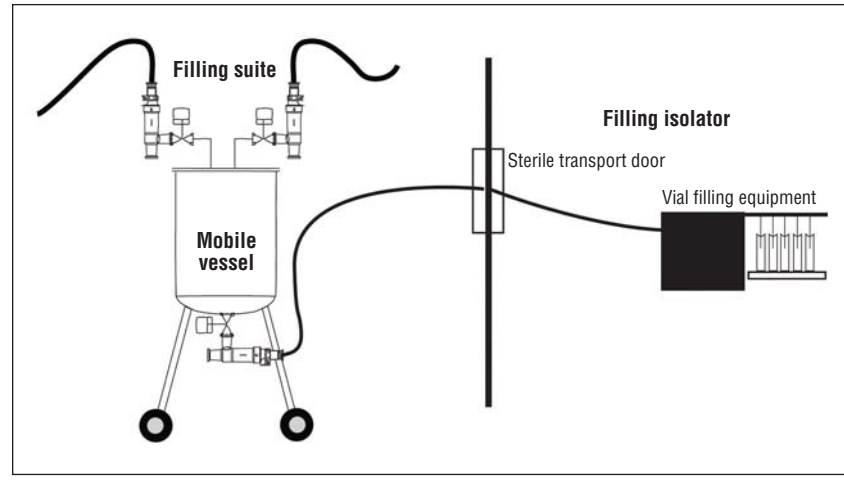


Figure 4. A final fill application using a mobile transfer vessel with multiple single-use lines and a complete outlet line system.



Final Fill Operation

The final step in the production process is transferring the product from the transfer vessel or bags into smaller vials, bottles, or containers for distribution. In the past, the final fill operation consisted of stainless steel equipment connected by reusable valves, rigid tubing, and steel pipes. This equipment also requires validation and must be subjected to a CIP cycle after each filling cycle is completed. Today, many process engineers are designing this operation with single-use transfer lines to reduce sterilization time and cost.

One example of integrating single-use

systems in a final fill operation is to simplify mobile stainless steel transfer tanks. Final fill tanks are designed to transfer formulated product from formulation suites to storage areas and ultimately to filling suites. To allow sterile connection to and from these vessels, designers add three-way valve assemblies to fill and drain ports to facilitate SIP operations. The design of these three-way valves makes it difficult to validate cleaning procedures. In addition, these valves require regular maintenance and may add significant weight to mobile vessels, especially in tanks with multiple inlet and outlet ports. Replacing these three-way valve assemblies with single-use transfer lines eliminates cleaning validation and maintenance steps while reducing mobile vessel weight by tens of kilograms.

Single-use transfer lines can be attached before vessel SIP sterilization with SIP connectors (used as either steam access or condensate drainage sites), or steamed separately, just before fluid transfer. For vessel outlet, combining a number of single-use components into the transfer line can create a very robust system to ensure product safety. For example, outlet transfer lines could incorporate a single-use SIP connector to attach to the sterile holding tank. Then, a through-the-wall fluid transfer system is used to bring a portion of the transfer line into an isolator where filling occurs. Next, a quick-connect fitting or aseptic connector is used to attach the transfer line to the filling machine.

The integration of single-use systems with traditional stainless steel equipment will continue to grow.

Figure 4 depicts a mobile transfer vessel with multiple single-use inlet lines and a complete outlet line system.

Conclusion

As more manufacturers take advantage of the benefits of single-use systems, their integration with traditional stainless equipment will continue to grow. All biopharmaceutical manufacturers are able to benefit greatly from single-use systems, but biotech start-ups can gain additional operational advantages by saving time and expense in the design, building, and validation of new facilities. Manufacturers also benefit by retrofitting existing facilities with single-use transfer lines to increase scheduling flexibility, production capacity, and improve production yields with minimal expenses.

Single-use transfer lines are not limited to upstream or downstream processes and the benefits can be seen in all operations (large or small), or new and existing facilities. Whether it's connecting within a process or across different processes, this is a technology with bottom line advantages throughout the manufacturing operation. **BP**

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