Disposable Assemblies in Biopharmaceutical Production

Design, Implementation, and Troubleshooting

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Confidence in process stability and the promise of lower operations costs are driving biopharmaceutical process managers to implement disposable assemblies in production. These goals are achievable with a thorough understanding of the technology underlying disposable assemblies and careful implementation of these systems.

A Legacy in Disposables

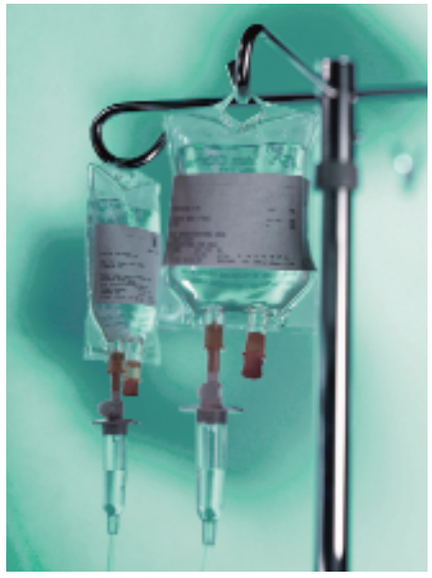
Presterilized disposable assemblies in biotechnology have their roots in the technology of sterile intravenous (IV) applications. The well-known intravenous bags, tubing, filters, and sampling sets have clear analogies in the fermentation process. Both require the controlled transfer of sterile nutritional fluids to living organisms. The use of sterile disposable assemblies was therefore a natural extension of this existing technology.

The Bayer Healthcare production site in Berkeley, CA, used this technology foundation to implement disposable assemblies in production. When owned and operated by the former Cutter Medical Company, the same site earlier produced blood bags and IV sets. Bayer recognized early that disposable assemblies enabled innovation in process development by allowing rapid bench-and pilot-scale modeling. Engineers designed full production implementation and capacity scale-ups using lower cost production-scale prototypes. Bayer is well into its second decade of successfully using innovative disposable assemblies for production of its parenteral rFVIII protein, used to treat hemophilia.

Capital and Efficiency

Capacity requirements and process complexities determine the impact of disposables technology on controlling costs.

A paper by Sinclair and Monge describes a business model for disposables (1), describing the advantages of disposables in production for a typical monoclonal antibody process. The authors show that designing and building a plant with disposables is more cost effective than retrofitting existing facilities and that presterilized assemblies present a tremendous business advantage to a biotech enterprise. With disposable assemblies, bins are not exposed to media, buffers, culture harvest, and other fluids. Cleaning is necessary only during routine preventive maintenance. The bins themselves cost much less to purchase, install, and validate than sterile steel process tanks. One byproduct of less frequent cleaning is a reduced use of cleaning agents and water for injection (WFI). Less WFI is used for cleaning, reducing capital costs. The advantages of disposable technology in developing a multiproduct facility are described by Hodge (2). While noting the lower capital costs, Hodge also points to less obvious cost savings, such as eliminating maintenance, calibration, QA review of equipment-related documentation, and utilities and support systems activities.



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Design, Customization, and Efficiency

Although the concept of a sterile, single-use, disposable bag is the same for blood and bioprocess bags, there are significant differences. Because bioprocess bags are larger than blood bags, they are designed to contain a greater weight of fluid. The bioprocess bag sits inside an open steel vessel commonly referred to as a bin. The bin provides support by limiting stress and

deformation of the bag film. The bin need not be water- nor airtight because fluids are contained in the bag. For smaller volumes (750 L or less), a rigid plastic drum or a smaller steel bin provides support and portability. For very small volumes (less than 20 L), hanging bags can fill and drain in a manner similar to their blood bag ancestors.

Suppliers of disposables work in partnership with biopharmaceutical manufacturers to develop custom assemblies. In large-scale operations, the bin layout will dictate the manifold design. A prudent choice of bin layout can reduce long-term costs of the assemblies by optimizing tubing lengths, filter positions, and connections. An unwise choice can lead to wasteful assembly designs or, in a worst case, having to inventory special low-use assemblies.

Custom bag assemblies are ideally designed so that an operator will have to make a minimum number of sterile connections. Although individual bags may provide greater flexibility, connecting them with a sterile tubing manifold can increase the risk of contamination during sterile connections. Emerging technologies such as sterile tubing welders and sterile tubing connectors may reduce contamination risks.

The better assembly designs account for human factors and ergonomics. Details such as correct tubing lengths and proper hoisting systems for bags not only reduce ergonomic problems (such as injuries), but also can significantly improve efficiency. Assemblies based on design input from production operators and supervisors are often easier to implement and less problematic than those designed without their input.

In-House Requirements

Personnel and Laboratory Facilities: Bayer recognized early that facilities designed to use plastic disposable assemblies required a technology base that included polymer science as well as mechanical and biochemical engineering.

Building on the technology legacy from Cutter, Bayer continues to develop technical expertise in the fields of plastics and polymer engineering as it applies to bioprocessing. The plastics process development engineer performs multiple functions. In addition to collaborating with suppliers to design assemblies and select materials, the engineer tests and validates to ensure that the assembly is appropriate for the bioprocess. During the design phase, the engineer applies fundamental polymer joining principles to assembly engagements, connectors, and components to ensure the integrity of the assembly. Troubleshooting takes many forms, including training operators on the proper handling of plastic materials and working with suppliers when redesign is necessary.

Laboratory facilities for building and testing prototypes speed the development of assemblies. They further allow laboratory-scale research experiments to support process development. The laboratory is ideally staffed with individuals trained in plastics testing and assembly construction.

The Bayer research organization has a plastics biomaterials group that is responsible for design, testing, and technical investigations into assembly failures. The group has experts in plastics assembly design, which is based on fundamental knowledge of polymer science and engineering. Working closely with suppliers, the group develops test methods and protocols to ensure proper function during design and prototyping to minimize the occurrence of production upsets.

Design and Materials Selection: Component selection requires an evaluation of application design needs including biocompatibility, use temperature, and mechanical properties. Plastics that contact final products should, at a minimum, meet USP class VI standards for leachables. The surfaces must be inert to the materials contained. In most cases, oxygen transmission is undesirable because it can reduce product potency and stability. The assemblies must be easily sterilized, preferably by gamma irradiation.

The plastic assembly provides a sterility barrier with the surrounding environment. Leaks are potential entry points for microbial contamination; hence, the method of joining or engaging components to ensure leak resistance is factored into the selection of materials. During production, a leak usually necessitates replacement of an entire assembly because of the potential for contamination.

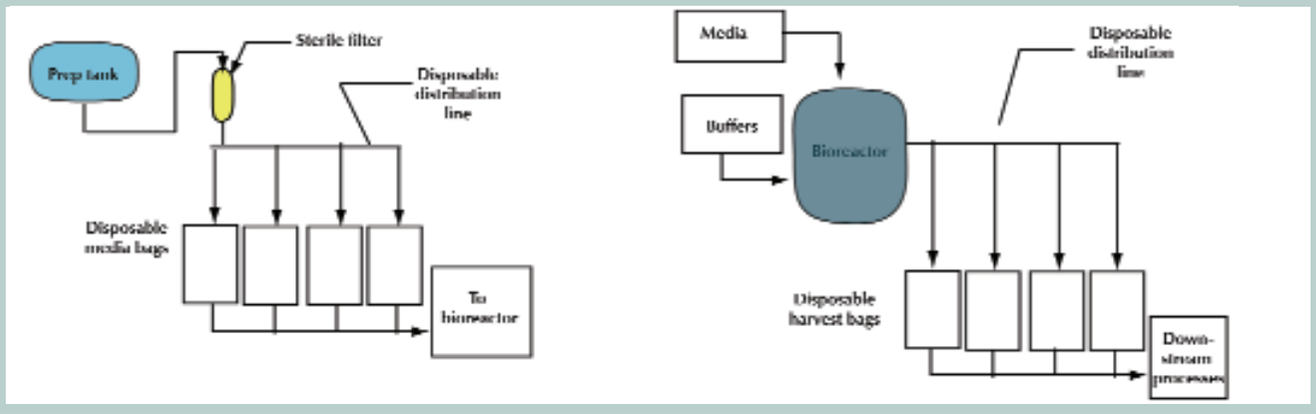
To assemble the components, a number of joining methods are used, which may include radio frequency (RF) sealing, solvent bonding, and heat sealing. In some cases simple cable ties connect tubing to barbed connectors. Combinations of joining techniques provide additional margins of safety against leaks.

Prototype assemblies are designed and assembled to test fit and function. Prototypes can be designed, built, and tested in-house during the concept phase. Sample assemblies from suppliers are required before finalizing design and purchase specifications. Minor design modifications such as part substitutions, tubing lengths, and part joining criteria are agreed upon with the supplier at this time.

When a design agreement is reached with a supplier, a raw

Figure 1: Damage to bag film from mishandling

Figure 2: Disposable assemblies used in a continuous perfusion fermentation process.



material purchase specification is issued with a detailed assembly drawing, parts list, and materials clearance references. Sterility requirements and any special assembly techniques are also described.

Regulatory/GMP/Quality: Qualification is important to determine a disposable assembly's acceptability for use. Prototypes must be rigorously tested for fit and function. Prototype testing should include leak resistance and assembly integrity to ensure internal sterility. Individual assembly components must be tested for compatibility with the fluids they contact, with traceability to the resin grade and lot. Holman reported on validation strategies for disposables in a recent article (**3**).

Troubleshooting

Unfortunately, discrepancies can occur during the use of disposable assemblies. Discrepancies typically manifest themselves as leaks. Because of the potential risk of sterility breaches, those leaks usually require disposal of entire contents, with financially significant consequences.

When a leak occurs, the biomaterials group conducts a forensic-style investigation on the assemblies. The lab determines the mode of failure, the likely cause, and whether the leak is associated with mishandling in-house or a defect in manufacturing from a supplier. Figure 1 shows two examples of leaks due to mishandling of a small bag used for postpurification product. To reduce the risk of such damage, steps are taken to educate users on the fragility of some plastic systems, and engineered systems are being developed to act as shock absorbers to protect the bags. Designs are corrected in close collaboration between the biomaterials group and the supplier so that quality improvements are carefully documented.

A Fermentation Example

In spite of the reality of leaks, the quality and business benefits of a disposable assembly outweigh the disadvantages. A rapid turnaround on the cleaning process and the associated reduction in QA tracking and documentation is particularly valuable in a continuous perfusion fermentation process. With campaigns as long as six to eight months, such a process requires a steady flow of media into a bioreactor. The disposable bag assembly allows for a steady continuous feed with less wasted space. As media storage bags empty, operators refill or replace them rapidly, and the process stream continues without interruption. Without disposable assemblies, large steel tanks must be cleaned, inspected, and validated regularly; this process is labor intensive. Figure 2 shows a typical continuous perfusion process.

A series of bins containing disposable assemblies is maintained to supply media to the bioreactor as it is needed for the continuous perfusion process. The contents of each bin are sampled using small sampling bags that are built onto the manifold. A separate manifold assembly supplies the bioreactor. As bags are emptied and discarded, the manifold allows for attachment of new bags using quick connects. Downstream of the reactor, culture harvest is collected using similar manifolds and bags.

Unmatched Efficiency

The emergence of custom disposable assemblies for biotechnology production is a result of the strategic business and quality advantages that those systems make possible. With an understanding of the plastics technology underlying a disposable assembly, a process scientist has tools available for faster development and new product innovation. The same understanding leads to an effective implementation of corrective actions when a technical issue arises. Despite the occasional technical issue, disposable assemblies afford significant efficiency advantages that are unmatched by hard-piped systems.

References

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2 Hodge G. Integrating Emerging Technologies to Create a New Multiproduct Facility Design. *BioProcess International* 2(5) 2004: 74–80.

3 Holman NBT, Phelan M. Defining an Application-based Validation Strategy for Implementing Disposable Technologies. *Pharm. Processing* 14 April 2004.

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