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The Use of Disposable Systems in the Manufacture of Biopharmaceuticals

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Biopharmaceutical manufacturers are constantly seeking new ways to lower production costs, while simultaneously increasing cost effectiveness without sacrificing quality. The U.S. biotech industry has grown from $8 billion in 1992 to $30 billion in 2002.[1] As productivity in biopharmaceutical manufacturing has increased, pressures to contain costs have mounted in the healthcare industry, coupled with increased demands by investors, which results in increased cost containment pressures on the industry as a whole.

Some biotechnology products need to be produced in large quantities (hundreds of kilograms per year) to meet both current and expected demand. This requires significant manufacturing capacity, and makes the types of incremental process improvements commonly sought in chemical pharmaceutical processing an attractive proposition for biopharmaceutical manufacturing.

However, the majority of biopharmaceuticals are produced in significantly smaller quantities, and for these products, improvements in manufacturing performance and profitability will come as a result of continuous process improvements, process optimization, and the implementation of new technologies. Taken together, these improvements have increased biopharmaceutical volumetric production by 150–300 percent in recent years.[2] Nevertheless, manufacturing costs typically represent over half of a pharmaceutical company's expenses, making them a prime target for additional cost reduction measures.[3]

Disposable Systems

Manufacturing operations constitute approximately 18–20 percent of a pharmaceutical company's operating costs. The most significant costs involved in manufacturing are facility time, which can represent up to 55 percent of the total manufacturing costs of a plant, and validation, which can account for between 10–20 percent of a plant's cost.[4] Industry has evaluated many options for reducing these fixed costs such as increasing product yield, increasing facility throughput in terms of the number of campaigns run per year, and installing equipment that allows plants to operate as both multipurpose and multiproduct production facilities.

One option that is increasingly adopted by biopharmaceutical manufacturers in an effort to reduce costs is the move to disposable manufacturing. "Use once, throw away" technology is being used by many manufacturers based on both improving throughputs by reducing the amount of downtime between campaigns, and also allowing the development of a multipurpose plant design because of the inherent flexibility of disposable systems. Many of the components in a biotechnology production suite can be supplied either in hard piped or disposable options. The key process components that are affected include containers, filtration, connectors, clamps, bioreactors, and tubing. Some elements of current manufacturing processes, for example centrifugation, large-scale chromatography, and large-scale tangential flow filtration (TFF) systems are not currently available as disposable options. A typical recombinant manufacturing process is shown in Figure 1 (in pale blue), illustrating opportunities for the use of disposable technologies.

Many of the components of disposable manufacturing systems have been available for some time. For more than 20 years, many vendors have offered single-use disposable capsule filters to replace single and multi-element cartridges in stainless steel housings. Disposable bioprocessing containers (BPCs) or bags and tank liners supported in plastic, aluminum, or steel totes (Figure 2) can be used to replace stainless steel tanks. Disposable bioreactors can replace bioreactors with working volumes of up to 500 L. Single-use membrane chromatography capsules can be used to replace traditional chromatography columns and resins for the removal of residual DNA, endotoxins, host cell proteins, and viruses. Platinum-cured silicone tubing replaces stainless steel pipe work, and disposable plastic valves and pressure gauges can replace their stainless steel equivalents in many instances, thus allowing a fully disposable processing system to be supplied presterilized and "out of the box."

The design of a disposable system is primarily dictated by the application. However, there are several key factors that need to be taken into account during the design phase. These include: the volume to be processed, chemical compatibility with the product, the number of production runs per year, processing conditions (*e.g.*, pressure, temperature,

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flow rates, mixing times), stability to extractables, and IQ/OP/PQ support from the vendors. These requirements represent only part of the process specifications that disposable components must be able to meet if they are to be considered as an alternative to more traditional methods. Other aspects that must be considered before a final decision is made include the scalability of the proposed system design, a cost/benefit analysis, quality and compliance issues, purchasing, inventory and procurement chains, risk-benefit analysis, and validation considerations.

No two manufacturing systems are identical. Therefore, when evaluating a disposable option, ensure not only that disposables can be scaled to meet forecast production requirements, but also that the selected suppliers can offer and manufacture customized products to meet the specific demands of the process. Disposable manufacturing, as with any process, has both advantages and disadvantages associated with its use.

The Potential Advantages of Disposable Systems

Design and Engineering

To facilitate functionality, the design of many system components will include the engineering that is required to allow that component to operate. For example, filter capsules perform the same function as filter cartridges located in stainless steel housings, but do not need to be assembled, cleaned, or sterilized prior to use. Additionally, no housing exists to require cleaning and validation after use. Disposable membrane chromatography capsules eliminate column packing and packing validation. Therefore, columns and associated packing and monitoring equipment are not required. Cleaning and cleaning validation of resins between batches is also eliminated. Cleaning validation represents a significant expense, especially when the application is chromatography for virus removal or virus purification. Disposable BPCs and disposable filter capsules that are pre-assembled and sterilized offer many advantages over traditional stainless systems requiring assembly, cleaning, and sterilization (Figure 3).

Quality and Regulatory Compliance

The use of pre-assembled, sterile, closed, disposable systems aid in quality and compliance in several ways.

a. Some of the most commonly cited good manufacturing practice (GMP) deficiencies are inadequate validation, and incomplete batch records and documentation. The use of disposables decreases the requirements for clean-in-place and steam-in-place (CIP/SIP) validation as well as the corresponding in-process documentation such as the batch records that document CIP/SIP.

b. For each disposable component that is used, there is one less cGMP record to keep, and therefore one less engineering drawing and batch record to track.

c. Using disposables eliminates the possibility that residual material from a previous batch will be carried over to the next batch.

Sterilization

Either the individual components, or more typically, whole systems, are supplied pre-assembled and pre-sterilized, usually by gamma irradiation. Not only does this approach make the engineering design and operational use of a system simpler, it also reduces the demands

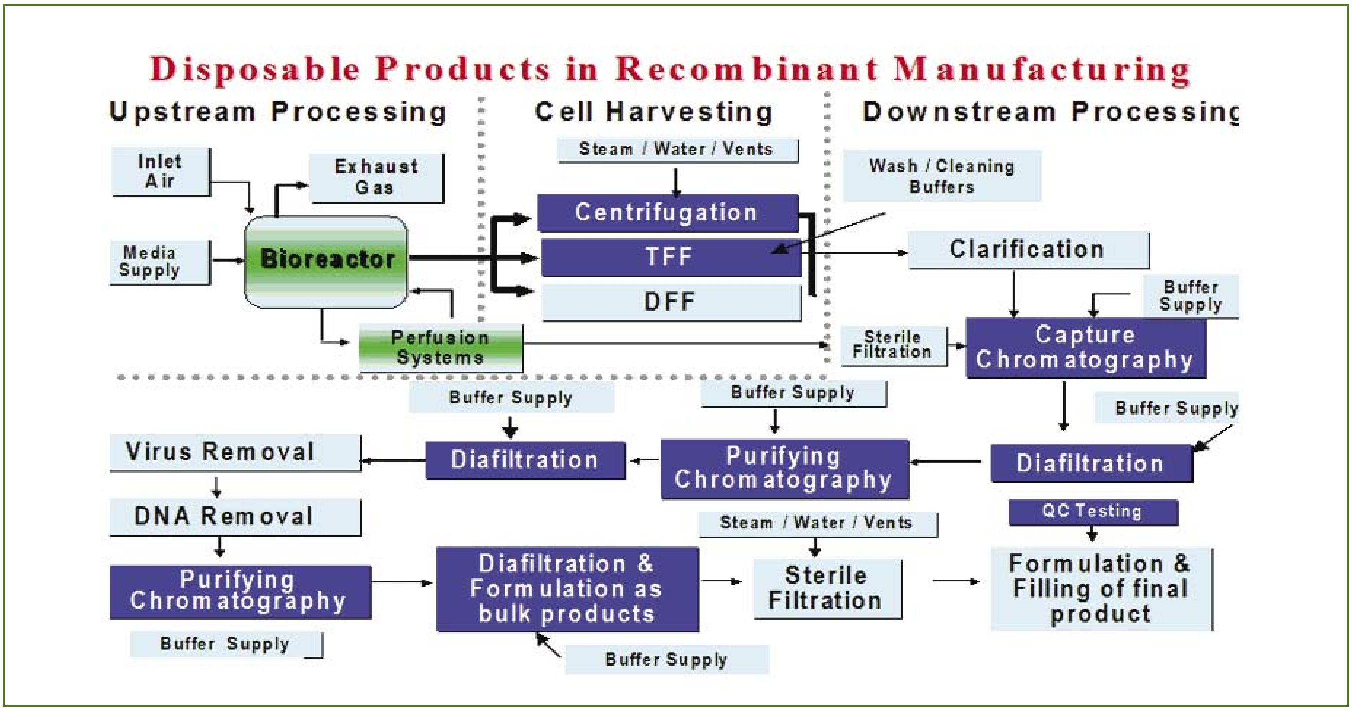

Figure 1.

and costs for utilities to support the manufacturing system.

Cleaning

One of the biggest advantages in using disposable manufacturing is that not only are systems supplied clean, sterile, and ready to use, but because they are designed not to be reused, cleaning is not required. This eliminates the cleaning operations and the utilities that are required to support them, thereby simplifying not only the initial design work in developing a system, but producing a simpler production system that is inherently more robust. Also, subsequent system validation is greatly simplified and much of the ancillary costs are eliminated.

Installation

Adopting disposable systems can eliminate long lead times in the initial manufacturing of stainless steel equipment. The elimination of both cleaning and sterilizing support equipment, which also involve long lead times, can greatly reduce delivery time, the time to install, the equipment required, and also reduce the requirements for completing IQ/OQ/PQ for each of the individual steps in a manufacturing process.

Operational Flexibility

With an increase in the number of different processes within a manufacturing facility, the demand to improve facility throughput and efficiency also increases. The advantages of using a modular disposable process become more apparent and appealing. The time required to assemble a disposable system by simply connecting all the pre-sterile components is significantly shorter than the time required to assemble a similar-sized stainless steel system along with the additional time required to sterilize the system. This time difference may be as much as a working shift. The time saving in down time between operations and the greater flexibility in manufacturing operations it confers, is one of the critical advantages that disposable systems bring to a manufacturer.[5]

Utilities

Disposable systems do not require cleaning or sterilization. Therefore, the requirements for supporting utilities such as water for injection (WFI), purified water, CIP skids, steam generators, cleaning solutions, and storage, are all significantly reduced. The greatest cost savings in this area is obtained when a large number of production operations use disposable components, thus allowing significant reductions across the whole operation. For example, it has been reported that every liter of WFI used in a process requires 5–10 times that volume in downstream operations.[6] These large-volume requirements can present a significant bottleneck during manufacturing operations.[7]

Validation

Eliminating or significantly reducing the cleaning and sterilization requirements of a system will also reduce the validation requirements of the system, and will usually result in a significant reduction in engineering complexity. In many cases, validation of sterilization and cleaning processes can be completely eliminated. The adoption of disposables also means that there are correspondingly fewer reusable components that must be tracked during installation qualification.

Space

Efficient use of available space is a goal for all manufacturing facilities. The use of disposable systems may lead to more efficient use of space. Using disposable bioprocessing containers with collapsible totes can significantly reduce the amount of storage space required for buffers used in chromatography, TFF, and other applications.

For example, a 750 L tank that is 8' x 4' x 4' in size continuously occupies 128^3 feet of space, whether it is being used or not. By comparison, 2 x 750 L disposable bioprocessing containers, with attached filters, occupy a folded space of 6^3 feet when not in use (data from Charter Medical Ltd.). Therefore, when not used, 42 disposable 750 L bags can be stored in the same space as a single 750 L tank. Because finished manufacturing space is the most expensive per square foot, its more efficient use will reduce costs.

Figure 2. Showing a 500 L stainless steel BioTrans Bioprocessing Container.

Labor

Disposable systems can demonstrate significant savings at all stages of drug development and manufacturing. Because validation support of equipment and facilities is still required during drug development, using disposables may allow the resources used in this area to be more productively used elsewhere.

During manufacturing operations, the use of clean, sterile, disposable components effectively outsources the time and costs of their cleaning and sterilization. If components are also supplied pre-assembled, significant reductions will be made in assembly time and, therefore, in cost. Equipment support, routine inspections, and scheduled maintenance are also eliminated or decreased as part of manufacturing overhead costs when using disposable systems.

The Potential Disadvantages of Disposable Systems

Vendor Dependence

The use of disposable components dramatically increases a manufacturer's dependence on its suppliers, therefore increasing the risk that a critical component of manufacturing may not be available when it's needed. For this reason, it is imperative that manufacturers who do not want to be totally dependant on a single vendor implement a primary, secondary, or tertiary vendor strategy so that at least two companies are validated to supply each individual component. This not only ensures continual product supply for the manufacturer, but also enhances the manufacturer's bargaining position when negotiating costs. It is also essential that full vendor audits are undertaken on a regular basis by the manufacturer to ensure that all protocols are followed and that all vendors are in compliance with both the manufacturer's requirements and the requirements imposed by regulatory agencies.

Both of the above strategies place additional burdens on the manufacturer when initially establishing a disposable system, as well as maintaining that system.

Environmental Impact

After use, disposable components become waste and have to be disposed of following the correct procedures.

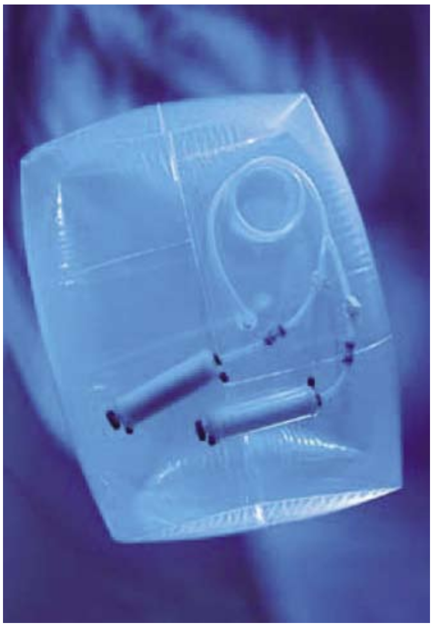

Figure 3. A 750 L disposable bioprocessing container and 0.1 µm filter assembly. This type of pre-assembled system allows BPC/filter capsule combinations to handle liquid volumes of between 1 L and 2,500 L, thus increasing both the flexibility of the manufacturing system, reducing set up and cleaning time, eliminating sterilization and associated costs, and therefore improving plant efficiency.

When treated as biohazard waste (for example, following contact with product), disposal is usually contracted out to specialized firms for removal and incineration, thus creating additional costs and a potential environmental impact. Disposables used for storing buffers, mixing buffers, and storing tissue culture media, however, may not require handling as biohazard waste, with corresponding reductions in handling and disposal costs.

In many cases, the additional costs are largely or completely offset by cost savings elsewhere. Published work comparing fixed vessel and disposable vessel models suggested that the increased use and disposal of disposable plastic components was offset by the large reductions in water and savings on the chemicals used in CIP operations for the fixed vessel model.[8]

Validating Extractables

As with fixed processing systems, disposable systems require validation before use, specifically regarding extractables. Extractables associated with a disposable system may be inherently present in the material, or derived as a result of their processing, use, or the sterilization process.

Extractables may occur as a result of chemicals leaching from the product contact surface, as a reaction between the product with the polymeric materials of the disposable, or as a result of adsorption of the product by the disposable. The extractable characteristics of the disposable may be altered by the process of sterilization, therefore, it is always essential to undertake extractables testing on sterilized products.

Manufacturers of disposable systems undertake time-based extractable testing using model solvents as part of their own validation protocols. However, system users must generate their own data to demonstrate that extractables do not adversely affect the product being stored or processed within or by the disposable.

Testing

The most commonly used test method is that of controlled extraction using a model solvent that simulates a worst-case exposure. The conditions are based on known characteristics of the product and the model solvent. Because the surface area to volume ratio of small bags is larger than for large bags, small bags represent a worst case total potential extractables load. Therefore, testing for worst-case conditions should be performed particularly on small bags. However, testing should cover the entire disposable assembly of the bag, tubing, filter, valves, connectors, and so on.

Costs

Disposables are, by definition, used once and thrown away. New components are purchased for each production run or operational step, which results in higher costs per batch. However, savings in validation and CIP/SIP costs, as well as decreased setup and dismantling time, usually offset the increased cost of individual disposables when compared with the cost per run over the life cycle of a non-disposable component.

Is a Fully Disposable System Possible?

The current manufacturing capabilities of companies supplying disposable components limit the capacity of a fully disposable process to between 5 and 500 L, depending on the processes involved. Current applications in patient-specific cell-based therapies, production of viral vectors, and personalized medicines all provide proof for the concept of fully disposable manufacturing on a small scale.

However, as discussed earlier, some routinely used processes in larger scale biotechnology manufacturing, for example centrifugation, capture, and purification chromatography along with large-scale cassette-based tangential flow filtration (TFF) systems, are not currently available as disposable options. Therefore, when evaluating the requirement for a fully disposable process, all processing steps at all scales have to be taken into consideration.

Disposable bioprocessing bags are routinely supplied in the 1 to 2,500 L scale using the same materials of construction. Filter capsules are available with between 20^2 cm and $20{,}000^2$ cm surface area per unit, and can be connected in series or in parallel to create high-volume multi-stepped processing systems. Membrane chromatography capsules are available with dynamic binding capacities from the picogram to the gram scale. Disposable hollow fiber TFF systems are available in sizes to process tens to thousands of liters of product. Tubing and connectors are available in a wide range of materials and sizes, and disposable valves and gauges are now available for incorporation into fully disposable systems.

Many studies have shown that adopting a disposables route can be effective in reducing operational costs.[9–11]

Summary

The use of disposable components in biopharmaceutical manufacturing can significantly impact manufacturing efficiency by potentially reducing capital costs, reducing plant complexity, improving operational flexibility, eliminating several aspects of validation, freeing up manufacturing space, eliminating the potential for cross contamination, reducing labor costs, and reducing some quality control and regulatory needs.

The applications for disposable components in biopharmaceutical manufacturing are expanding. As other disposable processing systems are developed, they will be incorporated into the matrix of tools that are available to the end user.

The short-term future (two to five years) for disposables will almost certainly bring further adoption and market expansion in the applications for which they are currently used. New developments, for example, in non-invasive mixing and non-invasive monitoring of cell culture systems, will expand the current market.

However, the development of a fully disposable manufacturing system remains in the future, and is dependent on new product developments, specifically in chromatography and TFF systems, as well as on improvements in film strength, film puncture resistance, and weld strength from bag manufacturers.

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