Disposables in Clinical Manufacturing

Single-Use Technology

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Introduction

The range of available disposable bioprocessing components expands continually. Current offerings include media and buffer bags, bioreactors, mixing systems, capsule filters (both defined pore and depth filters), cross-flow filters (including all wetted surfaces), chromatography modules, sterile connectors, valvesand sensors (pressure, conductivity, temperature, oxygen, CO2 and biomass).

The campaign-based multi-product biopharmaceutical production facility, with its relatively frequent new product introductions (NPIs), provides a specific set of characteristics to the analysis (including costeffectiveness) of whether to employ single-use technologies. These characteristics can include:

- Relatively short campaigns
- Facility requirements imposed on the process, rather than the reverse
- Emphasis on a modular validation program with re-useable elements
- Focus on clinical production (early phase products) creates additional characteristics:
- Even shorter campaigns, including some comprised of a single batch
- Lack of at-scale process knowledge at the start of most campaigns
- Greatly reduced need for or existence of process validation

Media and Buffer Bags

Perhaps the most frequently considered consumable is the media or buffer bag; this is compared with a portable stainless steel tank, as shown in Figure 1. Key to this analysis is the starting position of the facility, in particular, whether it already has stainless steel tanks. For any new product introduction (NPI), the lead-time to start-up of the process is a key factor. From a blank slate (no existing tanks), the time to design and manufacture tanks, typically 26 weeks after approval of drawings, will be compared with the time to produce a new custom bag, typically around two months. In a comparison of tanks vs. bags in an existing facility, there are three real variants: new stainless steel tanks, existing stainless steel tanks, and bags.

For bags over a few hundred liters in volume, the mechanical support and transportation device tends to be a piece of capital equipment (especially if the bag is to be moved while full). A common implementation of this support is an off-the shelf rigid cylindrical plastic container set on top of a stainless steel dolly.

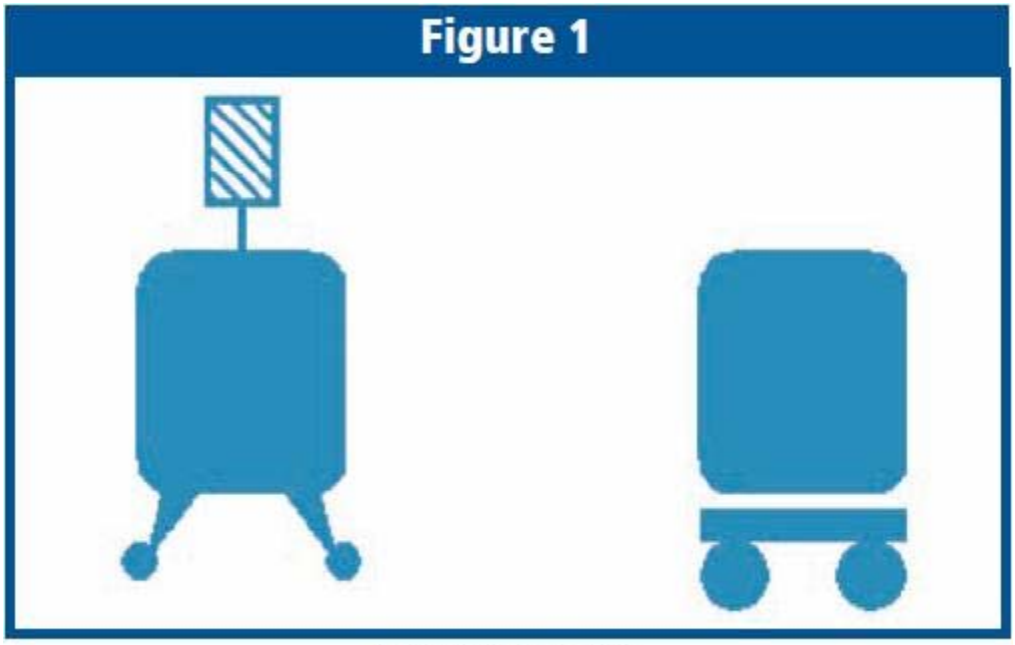

Figure 1. Tanks vs. Bags

Case Study #1 - 500L Process Model

In an existing facility equipped with 3000L and 6000L bioreactors, an evaluation was performed to determine whether it is more cost efficient to use stainless steel or disposable equipment to run a 500L cell culture process. Key cost elements included:

- Utility cost - Water for Injection, Purified Water, etc.
- Labor
- Materials
- Consumables - resins, filters, bags, etc.
- Waste disposal
- Capital

A process model was constructed including these elements and allowing selection, step-by-step of which unit operations to perform using single-use technologies.

The unit cost of pure water used in calculating savings can vary depending on whether the goal is to optimize an existing facility or decide on how to fit out a new facility. For the existing water purification and distribution system, the water cost used should be the marginal cost of producing the additional water. For new construction, the cost of the system itself (or at least the cost of increasing its size for a given scenario) might reasonably be included in the calculation. For our existing plant, we calculated a WFI cost of less than $0.02/L. This greatly reduced the utility cost savings for disposables, compared with other plants that based their calculations on higher water costs.

The conclusion of this evaluation was that the entire process train could be replaced with single-use technologies, with the exception of Protein A resin. The economics did not completely justify the choice of disposables, but together with the other cited advantages (below), it was determined that most disposables should be used wherever possible in the plant.

Key Limitations

While some processes have been implemented using entirely disposable wetted surfaces, the boundaries to the available single-use technologies are more limited than to the available reusable technologies.

Sensors - Lack of robust and redundant sensors for some measurement types remains a key limitation of disposables. For example, bioreactor bags, unlike their stainless steel counterparts, do not have dual pH probes or DO probes. Chromatography sensors, such as UV flow cells, are not available with disposable wetted surfaces.

Chromatography - In typical (non single-use) processing, chromatography is performed using expensive gel/resin packed into columns, with the number of available cycles identified and, for commercial processes, validated. Using these available cycles is key to the process economics. In the clinical production environment, where campaigns can be as short as one or two runs, this can challenge process development organizations. One disposable approach is to replace a column with a membrane adsorber cartridge (which can be considered a single-use form of chromatography, although still quite an expensive one). Taking advantage of the improved flow properties of the membrane configuration, one approach to single-use chromatography is to rapidly cycle a single, smaller adsorber cartridge (or set of cartridges) during processing of a single batch. This can allow use of some of the available cycles while still avoiding the sanitization and storage steps, retaining the regeneration steps.

Using chromatography gel/resin instead, an alternative approach still approaching processing maturity is rapid cycling of a small column.using the relatively complicated hardware required for simulated moving bed operation. The choices in this area include expensive permanent hardware and a nascent system with a completely disposable fluid path.

Protein A Chromatography - Protein A is a special case of chromatography. While some modes of chromatography are commercially available in the form of membrane adsorbers, thisgenerally has not been feasible for the even more expensive Protein A ligand, at least if one is attempting to provide the same binding capacity per purification cycle. Protein A chromatography resins are typically validated for cycles in the dozens, unlike their ion exchange counterparts, which often can run for hundreds of cycles. For process economics, it is even more critical to use the available Protein A cycles.

Flexible Tubing - Compared with the typical design of modern bioprocessing facilities, with its relatively robust, orbital-welded stainless steel tubing, single-use bags include less secure tubing between vessels, increasing the physical risk to batch success. While one would expect to address this in design of a purpose-built facility, an existing facility switching to single-use containers or even back and forth between single-use and stainless steel needs to address this change as part of that implementation.

Mixing - The available mixing equipment in stainless steel systems includes in-tank mixers, angled or in baffled tanks and high-shear in-line or in-tank mixing systems. A variety of singleuse alternatives has been developed, including magnetically-coupled impellers, perforated disks moving vertically through the prep, and a sheathed rod waving in a rotating motion through the prep. While the power of super magnets has increased significantly in recent years, the total mixing power available in disposable systems is still less than might be required to prepare some concentrated undefined media.

Volume - The largest available disposable tanks, currently around 2000L, cannot approach the volume available in fixed tanks. While the maximum bag size seems to be continuing to increase, the cost of individual bags (especially for bioreactors) in the larger sizes tends to run to the thousands of dollars. Additionally, the mechanical support needed to hold the bag and to get it into position without tearing it becomes a significantly more involved. It can have a capital cost comparable to its stainless steel counterpart and can have a lead-time similar to that of other large, custom equipment.

Unavailable Unit Operations - Most typical biopharmaceutical unit operations have single-use variants, however, a key limitation to single-use technologies is the lack of certain unit operations. One of these is high g-force centrifugation. Depending on the platform technology in use at a given facility, this may or may not be significant. In mammalian cell culture facilities, the harvest technologies of depth filtration, cross-flow filtration and centrifugation are not easily made interchangeable.

Key Advantages of Disposables

Cycle Time Reduction - is one of the most significant advantages of single-use. Applied to bottleneck processes, cycle-time reduction directly translates into greater production output. The main factor contributing to this cycle-time reduction is elimination of steps such as CIP of tanks and regeneration of chromatography columns. Elimination of preparation time, such as gathering and assembling the non-disposable equipment can also reduce cycle time.

Labor Savings - This reduction can be another key advantage, coming from eliminated steps and from reduced maintenance and validation. Achieving actual value from these savings in an existing facility depends on the organization's ability to aggregate the savings, in order to eliminate positions or re-deploy them to other areas. Failure to take these steps cancels the value of the improvement. Addressing actual job changes or reductions can be a challenge in some organizations; these organizations need to recognize that they need to focus their efforts on the benefits they can realize. A new facility, in contrast, can develop a staffing model that fits the streamlined operations.

Shorter NPI - Especially when off-the-shelf disposables are selected, the lead-time to implement new processes can be greatly reduced in campaign-based multi-product facilities. This advantage will tend to most benefit organizations that do not strictly adhere to a platform process, as described below.

Flexibility - The ability to change the detailed configuration of a process system sets single-use technology apart from stainless. For example, while the mechanical support apparatus and control system of a disposable bioreactor can be re-used for two different processes, the configuration of the bags installed in it can be changed significantly between those campaigns without any capital cost.

Overall Capacity - The time required to increase tank storage capacity for a process in existing stainless equipment can take as long as constructing the original equipment. By comparison, especially for smaller size bags and filters, more of the same disposables and their respective holders/totes/supports can be acquired using already approved specifications, in far less time.

Key Disadvantages of Disposables

Depending on the particulars of its implementation, single-use technology can have the following disadvantages:

Leachables - The need to characterize leachables and extractables has been established for all product contact elastomers. In disposable systems, the wetted surface for these materials can be as much as 100% of the total wetted surface area. This increases the criticality of any quantified leachables. More such tests and validations will be required for a given process because more process steps include a "significant" amount of wetted area comprised of plastics and elastomers.

Direct Cost - Disposable technologies are still very expensive. Except for a facility or process that will only need its equipment for a very few runs, in general the direct cost of the consumables over the life of what would have been (for example) a tank is much greater than the capital and operating cost of permanent equipment. A facility making the change from stainless to disposable will need to significantly revise its operating budget. The increased material cost of the consumables can be partly offset by reduction in other materials:

- Eliminated column regeneration steps correspond to eliminated buffers and their materials.
- Eliminated CIP steps reduce the use of CIP solution.
- Equilibration of membrane adsorbers can use fewer "column volumes" than gel-based chromatography, again reducing raw material consumption.

Vendor Audits - As a greater palette of consumable options is implemented in a facility, a greater number of vendors will be involved. For example a single bag might involve a vendor, a designer and one or more

component manufacturers. Various bags in a single facility might come from different vendors if, for example, a different bag geometry is needed in certain areas. Some pharmaceutical manufacturers consider the manufacturer of the wetted path to be a "critical" vendor, requiring an in-plant quality audit of the vendor. More key component material vendors to audit translates into more audits.

Increased Inventory - As increasing numbers of single-use items are defined and stocked, each with its own re-order point, the total amount of inventory will continually rise. Especially in cases where each campaign requires new assembly designs, a significant challenge is posed when the number of batches in short-run campaigns cannot be determined up-front, as is sometimes the case when there is no at-scale process experience.

Single Sourcing - Some of the single-use technologies are only available from single manufacturers. Drug manufacturers generally strive to avoid dependence on individual manufacturers, especially for key pharmaceutical products.

Supply Chain Complexity - A larger number of material vendors translates to more coordination needed for starting, stopping and increasing production, as well as more potential points of failure in the creation of final product.

Increased Component Scrap - When part configurations change rapidly in a plant, remaining inventory of obsolete configurations represents future scrap. In some cases, this is driven by newly availabletechnologies or changing personnel preferences. In other cases, NPI
activities can require new configurations.

Waste Disposal - Most of the single-use products are currently not recycled. Generally, they are comprised of multiple clear layers of film or other plastics that cannot economically be separated. The onlypractical option in most cases is to recover some the energy value of the items by incineration in a waste to energy plant.

Risk Impact of Disposables

Use of disposables can have significant influence on the risk analysis for a facility or process. This risk impact is summarized in Figure 2.

Assembly error is marked as a question to denote that whether this represents a risk reduction depends on the two organizations involved. In particular, the lower risk of assembly error depends on whether it is the drug manufacturer or the disposable manufacturer that has better change control and adherence to procedures in creation of assemblies.

For sterile operations, such as media feed containers to bioreactors, the reduced risk of sterility failure resulting from complete irradiation of the single-use components can be the most important factor driving use of the single-use components.

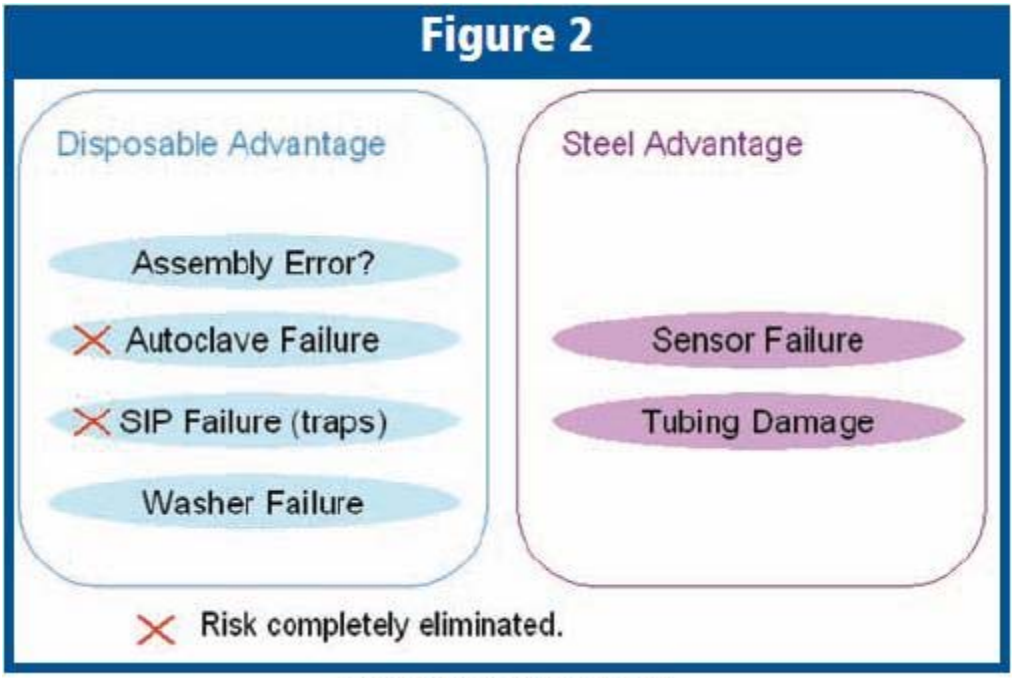

Figure 2. Areas of Risk Impact

Platform Technology

Increasingly, biopharmaceutical manufacturing organizations are adopting platform technologies. In broad terms, this tends to mean that a given facility or organization will use the same base cell line, cell culture media, purification steps, order of purification steps and even buffers, regardless of the specific active substance. Given the impact of the active substance on all aspects of the process, this approach can only work for an organization manufacturing a narrow range of molecules. For example, a series of different monoclonal antibodies can potentially be produced using a very similar process, provided that process media are the same.

The timeline for approval of disposable configurations can be mitigated in a multi-product facility by adherence to a platform technology. Running the same process allows use of existing, stocked single-use items.

For organizations that do not adhere to a platform technology, a disadvantage for single-use technology can be increased scrap as specifically configured components expire due to newer designs for current campaigns.

The contract manufacturing organization is a key exception to the consistent use of platform technology, as a significant fraction of processes may be developed outside the organization. In these cases, customer preference can drive the decision on whether to use disposables.

Impact on Process

Harvest operations tend to be standardized. Some facilities use high g-force centrifugation, while others use filtration or a mixture of the two, as depicted in Figure 3. As noted above, high g-force centrifugation does not have a single-use variant, so implementinga disposable process in a facility that uses it requires changing to another harvest process entirely. Depending on the stage of product development, this can impact regulatory filings.

Media filtration is a potential area for optimization of the single-use component mix. A single bag/filter combination is a common starting point, as illustrated by Scenario A in Figure 4. For a multi-productfacility, whether campaign-based, multi-suite or both, it is likely that the bag size is the constraint for one media while the filter capacity is the constraint for another media. In this scenario, filter capacity is wasted for the first and bag capacity is wasted for the second.

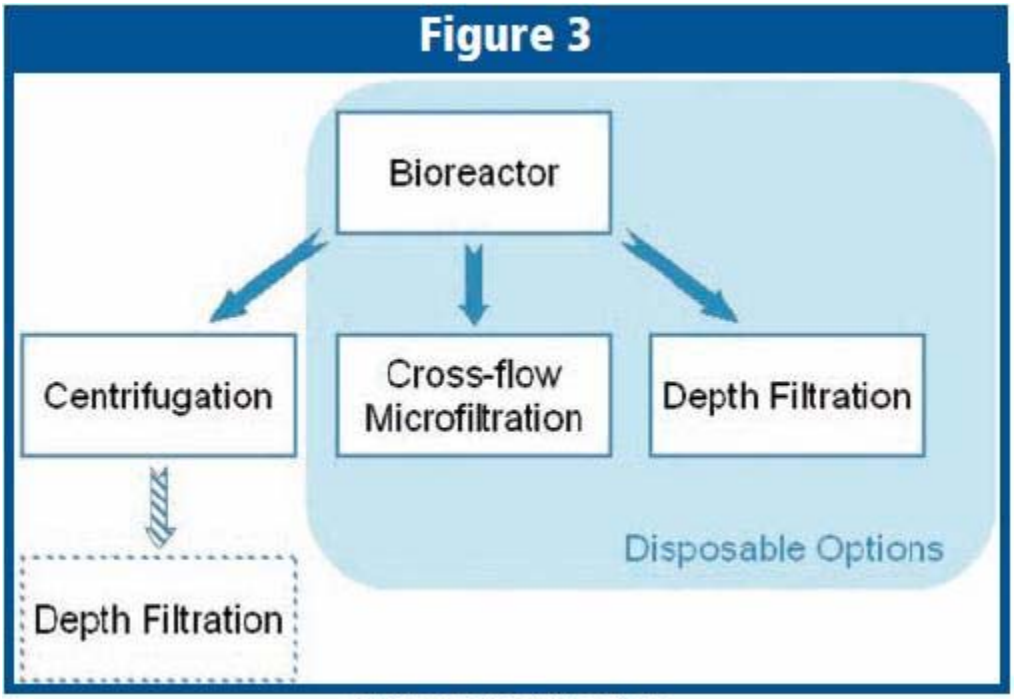

Figure 3. Harvest Operations

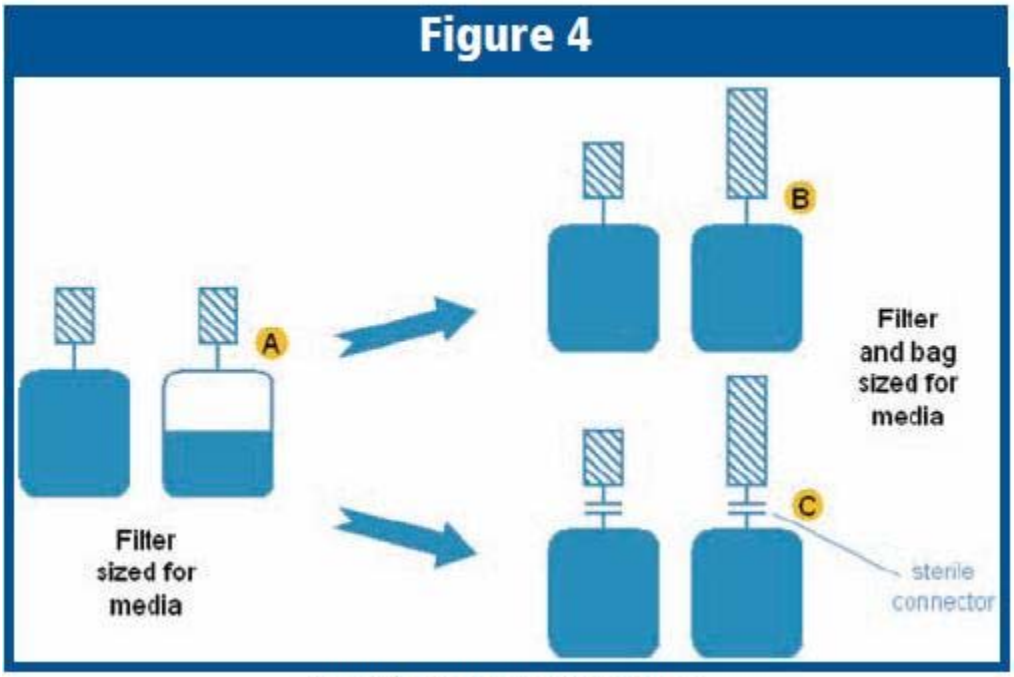

Figure 4.Media Filtration Flexibility

Splitting the bag and filter into two sterile assemblies allows developing the disposable models. for the procurement of two filter sizes to use with the same bag. More variations can optimize cost per consumable use and better accommodate operations, but can increase inventory and associated costs. Scenario B is optimal for part count and flexibility only as long
as we have only the two media types (with respect to filterability) and one volume of media. As soon as we introduce additional volumes or media types, Scenario C is optimal for part count and flexibility.

Scenario C adds the cost of the sterile connectors to every operation. It also increases the process complexity by requiring the operator to first select more components correctly and then to connect them.

A facility that does not adhere to a platform technology may be able to mitigate the impact on consumable inventory levels of its changing process by using modularization to achieve flexibility, as illustrated above. A platform-based facility, on the other hand, may be able to implement less flexible solutions at a lower overall cost and with less risk of failure; both advantages result from fewer sterile connectors per configuration.

Case Study #2 - Configuration Diversity

At Abbott's campaign-based biopharmaceutical production facility in Worcester, MA, the relative cost of various bag diversities was studied. Compared with the existing state of a single standard buffer bag size, an assortment of three sizes was found to reduce annual buffer bag cost by 7%. Note, however, that the cost reduction in switching from a 600L bag to a 200L bag for a single buffer batch, by itself, tends to be somewhat small; the vendors describe most of the cost as coming from the customization features, e.g., various fittings, filters and hoses.

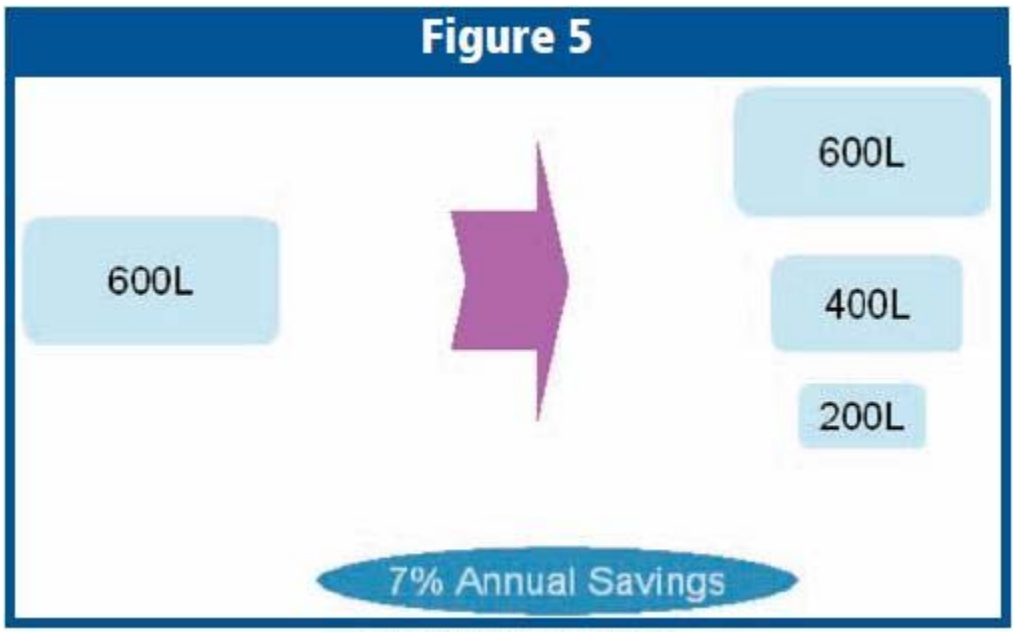

Figure 5. Buffer Bag Diversity

Conclusions

Single-use technologies increasingly find an appropriate place in biopharmaceutical production. Commonly held assumptions regarding their true advantages need to be tested for each facility to determine when disposables should actually be used. Non-economic advantages can be more important than economic factors in some cases.

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