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DISPOSABLES: EQUIPMENT

Cost Advantages of Single-Use Technologies

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Single-use technologies are rapidly penetrating the biopharmaceutical and vaccine industries because they can help simplify equipment and facility design, thus bringing cost advantages. But, from an engineering viewpoint, how are these cost advantages realized and what criteria can be used to assess their impact?

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The biopharmaceutical and vaccine industries are embracing single-use technologies more and more as alternatives to fixed stainless-steel equipment. Although the technologies still have limitations of mass and heat transfer, the generally mild process conditions in biopharmaceutical operations are conducive to using a disposable plastic film surface as the product-contact layer. Disposable components also eliminate the need for surface cleaning to avoid contamination and cross-contamination.

Several factors enable the disposable plastic bags used for solution preparation, storage, and product-generation steps to promise potential cost advantages. Because single-use systems can provide sufficient volume (i.e., currently 2000–3000 L, depending on the application) to accommodate the capacity requirements of most commercially produced vaccine and biopharmaceutical products (including those whose quantities have been raised by yield increases from new cell lines), the use of disposables is posed to grow in the next decade.

As any biopharmaceutical-industry professional will probably testify, no two projects are alike. It can therefore be difficult to make general estimates about potential cost advantages. However, when making early estimates regarding technology concepts, it is practical and acceptable to put some rough criteria to use.

NNE Pharmaplan (Gentofte, Denmark) uses a modular approach to designing and engineering processes and production facilities. The company breaks down the project's scope into modules for structured engineering activities. Process modules are typically combinations of process equipment (e.g., one bioreactor with three associated feed tanks) so that they can be seen as the main building blocks of the production process.

This modular approach allows an overview of the factors that affect a project, and process modules also can be the basis for the cal-

culations that obtain cost-related criteria for the application of single-use technologies. Although experience has shown that these quick estimates can be remarkably accurate, this approach is clearly rough and should only be seen as an estimate.

Investment costs

Investment costs are probably the biggest and most obvious source of the cost advantages of single-use components over fixed, steel systems. The difference arises mainly because single-use systems require less instrumentation and fewer utilities. Because sterilization and cleaning processes are eliminated, installation and support systems are reduced.

This advantage clearly allows a manufacturer to purchase more capacity for a limited startup budget, but also has an effect on the variable costs because a much lower investment sum has to be amortized, compared with that of fixed steel systems. In fact, it is the low up-front investment cost, which lowers variables costs, that typically tips the scales in favor of single-use systems.

As seen in Figure 1, NNE Pharmaplan calculated the projected investment cost savings that single-use process modules would provide, compared with 100% stainless steel equipment, for an upstream biopharmaceutical operation (1). Figure 1 shows that investment cost savings of about 30% can be expected with single-use technologies, depending on the extent of their use, compared with a full stainless steel setup. The 30% point is actually an overestimation because microbial fermentation and centrifugation were included in these considerations, although single-use technologies are not readily available for these applications. Recent developments such as single-use microbial fermentors from Xcellerex and single-use centrifuges from CARRCentritech are starting to push these boundaries, however.

Area impact

Single-use systems have fewer utility requirements, and they also can be stacked or moved in certain volume ranges. These systems thus occupy a small footprint because of their improved designs and mobility, as well as their decreased demand for piping, valves, instrumentation, and the related maintenance space required. To be sure, single-use systems do require room for manipulation, transport, and waste removal, but even with these space requirements, they occupy less space than do fixed systems. To manipulate or maintain the equipment—which already occupies less space—it is possible to push the equipment aside to allow access. In this way, the process modules can share each other's footprints to a certain degree.

NNE Pharmaplan calculated the reduction in equipment footprint that could be achieved if single-use systems were installed as process modules instead of 100% stainless steel for the same upstream area (1). Figure 2 shows that it is possible to save about 25% of the space that a similar stainless steel installation takes, based on the extent to which single-use technology is employed. These reductions can come from flexibility for future applications or investment-cost savings that result from smaller building costs. Typical cleanroom cost ratios range from $3000 to $5000 per square meter. Therefore, single-use equipment also can lower buildings' fixed costs when used in cleanroom areas.

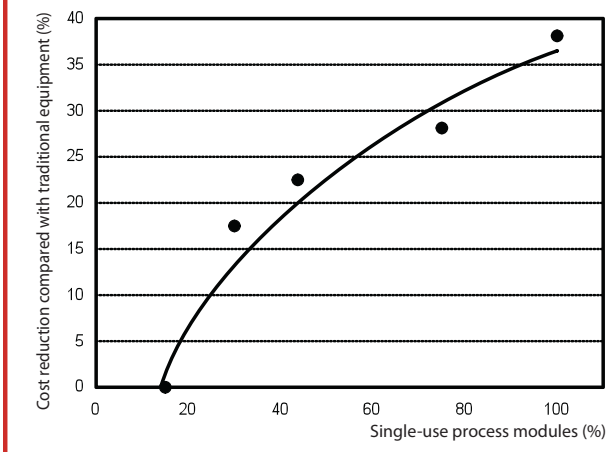

Figure 1: Reductions in investment costs associated with various degrees of single-use component installation in an upstream biopharmaceutical process. Simple single-use technology generally represents a smaller cost than does traditional equipment (1).

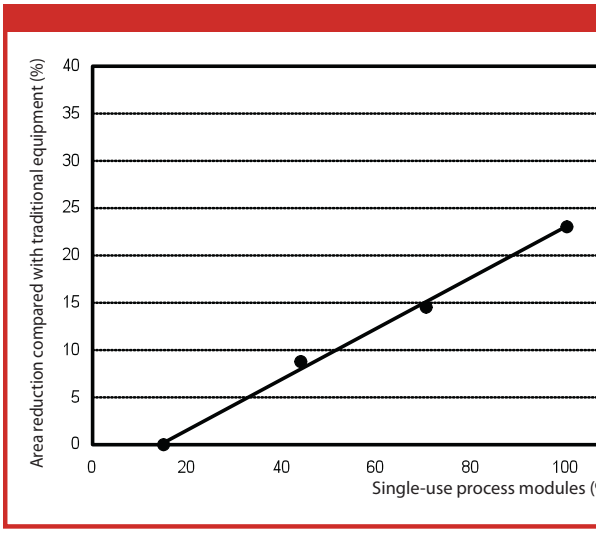

Figure 2: Reductions in process-room area associated with various degrees of single-use equipment installation in an upstream biopharmaceutical process (1).

Automation complexity

Another important feature of single-use systems is that their installation is simplified because the need for cleaning and

sterilization are reduced. This reduction again translates into reduced requirements for clean steam, clean-in-place, and waste collection and treatment. Although any reduction is important, it is really this elimination of entire systems that accounts for large cost savings because it is no longer necessary to install distribution systems.

The traditional stainless-steel system needs to be cleaned and sterilized, so instrumentation is necessary to allow the timely and safe execution of all the associated controls and monitoring efforts. It is therefore important to focus on system complexity when evaluating cost advantages. Seen from an engineering perspective, an efficient way of evaluating complexity is to estimate the number of in–out (IO) points (i.e., communications points in the automation system for valve control or temperature monitoring, for example). A high number of IOs signifies a complex system with high installation and qualification costs.

Each check (e.g., valve positions, temperatures, pressure, and timers) requires several IOs. A stainless-steel system needs significantly more IOs than do single-use systems that arrive precleaned and presterilized. Single-use systems only require IOs necessary for running the process in question.

NNE Pharmaplan compared the number of IOs for various stainless-steel and single-use bioreactors for simple and complex designs, which differ in their degree of automation because some manual operations are definitely possible in stainless steel systems (1). As demonstrated in Figure 3, single-use systems show a potential for dramatic reductions—at least 50%—in the number of IOs. At an average price of approximately $3000 per IO, these reductions can translate to significant savings in installation costs.

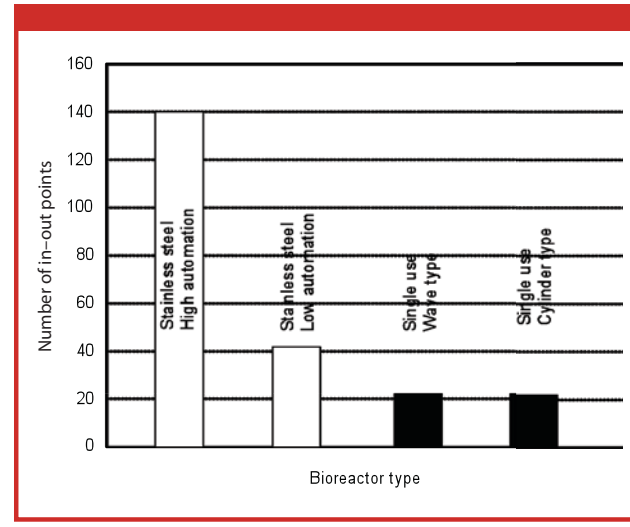

Figure 3: Comparison of the number of in–out points in various bioreactor systems (1).

Operation costs

In many cases—not including high batch-frequency operations—single-use technology compares favorably to stainless-steel equipment in terms of cost. This favorability obtains with respect to investment cost, but also with respect to variable costs when we include the cost of the capital required to operate a comparable stainless steel system. Amortization and interest over time must be added to variable costs, and many case studies show these to exceed the variable costs related to increased amount of consumables used in a single-use design.

The costs of cleaning chemicals and water-for-injection (WFI) are often included in feasibility studies. These costs are seldom the deciding factor because they are usually low compared with those of other consumables and with the cost of capital in general. This analysis is perhaps counterintuitive because of the large volumes of resources involved in cleaning and rinsing. This apparent paradox occurs because the cleaning chemicals are common and relatively inexpensive, because WFI is not used for all cleaning solutions, and because WFI from an on-site generation and distribution system is much cheaper than WFI bought as a laboratory material. In an authoritative study on disposables costs, Barnoon estimates that $0.05/L for WFI costs is realistic for large-scale operations (2).

Estimates about reductions in operator time are sometimes introduced into the comparison, and typical values include a roughly 20% reduction for single-use systems (3). This number is somewhat anecdotal, however, because few published case studies exist. Although personnel costs are important, such estimates may be realistic only for single facility functions (e.g., washing and sterilization) but not for the entire facility because cleaning, sterilization, and maintenance are, after all, not constant activities. It should therefore be possible to allocate resources from other areas during peak load periods.

Environment and waste

The idea of discarding plastic bags appears intuitively wasteful, but disposal must be compared with traditional technology that requires cleaning and sterilization between batches. Recent studies estimate that single-use technology is 25–50% less carbon-dioxide intensive than is stainless steel (3, 4). Consuming and heating large volumes of water to clean and sterilize stainless-steel equipment is more energy demanding than producing and inactivating plastic bags, which can also be incinerated for energy recovery. Sinclair and colleagues notably demonstrated that automobile emissions from facility staff's daily commute were the overwhelming contributors to carbon-dioxide emissions (3).

The typical approach to solid waste disposal is to deactivate locally and then physically dispose of single-use equipment in an incinerator or landfill. As the amount of solid waste increases, waste storage, deactivation autoclave capacities, and transportation may be limited by the facility's physical boundaries. Depending on policies for the transport of material potentially containing live genetically mod-

ified organisms and process-containment requirements, an alternative is to handle solid waste as hospital waste and postpone the investment in deactivation capacity. The waste is then subject to stricter control and visual markings. A specialized vehicle takes the waste to a power plant (off- or on-site) for incineration, where some of the energy used to produce the plastic film is recaptured. Costs for this strategy can amount to about $100/metric ton of waste. The volume also affects the cost because of the number of trips necessary. This cost is relatively low because one could avoid installing a deactivation autoclave, although one must factor in the cost for additional handling. In one example, NNE Pharmaplan calculated that off-site incineration would enable production for five years before accumulated running costs outweighed the cost of investing in an autoclave.

Conclusion

The new single-use production paradigm shifts quality away from in-facility testing to supplier auditing and storage costs. These activities mainly take place before the equipment enters the production facility. Quality costs and waste costs are still not well described, but future work on the cost advantages of single-use technologies will address these aspects to a larger extent.

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