The ROI Case

Economic Justification for Disposables in Biopharmaceutical Manufacturing

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Biopharmaceutical manufacturers are increasingly making production decisions based on return-on-investment (ROI) calculations. Single-use systems and disposables are two such areas for which ROI benchmarking information is being sought to make manufacturing decisions. Disposables use in biopharmaceutical manufacturing has grown steadily, as shown in a recent worldwide report and survey of 187 biopharmaceutical manufacturers and contract manufacturing organizations' capacity and production (**1**). That survey quantified reasons for the increasing trend toward use of disposable systems and components and revealed continued interest in the use of disposables. However, interest has not always resulted in purchases of single-use equipment. Part of the reason, according to the survey, is a lack of economic data.

Disposables suppliers are expanding their product lines, developing new products, and creating customized configurations. This has been part of the reason for increased growth. Suppliers also are beginning to quantify the benefits of converting fixed elements of biomanufacturing systems to single-use systems. Users of disposables and single-use systems are becoming increasingly comfortable with the concept; in fact, only 3% of respondents reported they used no disposable components in their biopharmaceutical manufacturing today. So what's the future of disposables, and how should biomanufacturers determine whether single-use components are right for them?

A Function of Economics: According to the report, the growth in use of disposables will be a function of economics. Disposables can provide distinct, measurable benefits in a manufacturing setting. However, because each biomanufacturing setting is different, the associated monetary value will also be different.

Trends in Single-use

Estimates made by makers of single-use systems put the growth rate in use of disposable bags, containers, and tubing at 10%–20% annually. Single-use systems are used in essentially all aspects of biopharmaceutical manufacturing: production, storage, transfer, filtration, purification, and separation of biotherapeutics.

Determining Value-in-Use: By now, most biomanufacturers are familiar with the major benefits of these systems, including decreased risk of cross contamination, elimination of cleaning requirements, and reduction of facility start-up time. What they're not necessarily familiar with is the economic value that these benefits bring to their specific operations. To determine actual "value-in-use" requires additional data the demonstrated economic benefits of using one system over another, direct and indirect costs of shifting between methods, and valid estimates of risks associated with manufacturing processes. A first step in making these return on investment (ROI) calculations is determining what is currently being used.

(WWW.PHOTOS.COM)

What's Being Used

According to the report, the most common disposables by far are filter cartridges (78%), followed by media bags purchased dry (65%). However, as mentioned, each situation is different. For example, use of tubing sets at CMOs is running at 67%, whereas only 50% of biopharmaceutical developers use them.

Need for Economic Data: "Single-use systems and disposable components have not been overwhelmingly adopted partly because they are a relatively novel approach to manufacturing, and the economic data on their use has not been objectively presented, as yet," says Denise DeTommaso, marketing manager at SAFC JRH BioSciences, a supplier of disposables to the industry. The industry is very invested in stainless steel, so transforming biomanufacturing processes will entail more than just replacing steel with plastic; it will mean changing the way manufacturers think about processing (and related changes in regulatory approaches) and how that balances costs. In some cases, engineers will need to start from scratch to design systems that take advantage of the

benefits that disposables can offer — and changing processes is expensive and time consuming.

Stepwise Acceptance — and Innovations: Today, the market acceptance for disposables is typically achieved stepwise, component by component, rather than through complete replacement. Most single-use product manufacturers help their biopharmaceutical customers transition to disposable products first with peripherals involved with storage and transportation. HyClone, a well-known producer of single-use systems including media-filled disposable bags, got into the business by producing bags for its own use. It began selling those same bags to customers, which became a natural entry into the single-use market. Customers got used to bags and saw that they performed well within their own systems, did not break, and were convenient to use. They began to consider expanding such use into single-use fillers, filters, and tubes and have slowly graduated to more sophisticated hybridized disposable-plus-stainless steel systems, sampling systems, and even bioreactors.

"We're now moving into a phase where disposable units are processing vessels," says Leland Foster, CEO of Fisher Scientific, parent company of HyClone. According to Foster, single-use bioreactors are the next big thing that the market is looking for. To fill this need, HyClone and Baxter have codeveloped a single-use bioreactor based on conventional stir-tank technology. This is in addition to a single-use mixing vessel that HyClone already has on the market.

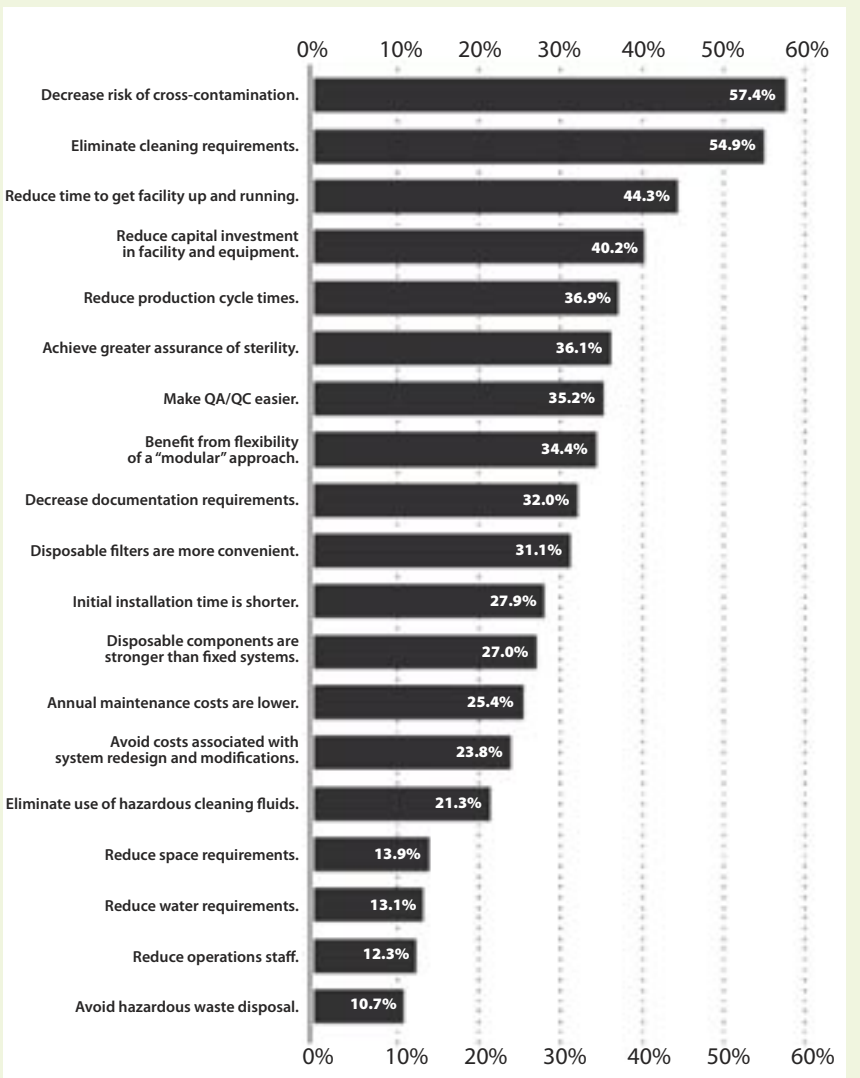
Decreasing Cross Contamination Risks: Biopharmaceutical manufacturers say that the most convincing reason for moving toward disposable and single-use system components is the decreased risk of cross-contamination (indicated by 66% of CMOs and 45% of biopharmaceutical manufacturers) (Figure 1). A second compelling (related) issue is elimination of cleaning requirements between batches (indicated by 55% of respondents). Eliminating the need for clean-in-place and steam-in-place equipment and the validation required to use the same tank for different batches decreases the cost of infrastructure and the time between batches, making for a more efficient process. The question of course, from an ROI perspective, is just how much these effects will have on a company's bottom line.

Maximizing Efficiencies: Contract manufacturer Xcellerex is an example of how an entrenched user of single-use systems approaches this novel technology. It has realized the benefits and limitations of disposables and has designed its systems to maximize efficiencies.

"We've built entire manufacturing plants around disposables using single-use bioreactors, holding tanks, media and buffers, tubing, process components, sensors, and so on," says Geoff Hodge, vice president of process development and technology at Xcellerex. "Nobody is 100% disposable unless you are at extremely small scales like 10 L or less."

Xcellerex's FlexFactory production line is entirely turnkey and transportable. It includes a scalable disposable stirred-tank bioreactor, disposable stirred-tank mixing systems, and downstream operations in modular units. It also includes paperless electronic batch records with additional on-line process and GMP (good manufacturing practices) quality/compliance control that catches operator error, providing higher batch success rates. The entire production line can be built, operated, and validated at Xcellerex and transferred to a customer's facility, compressing the overall time to install GMP manufacturing capacity by at least 50%. Determining the value of that compressed time is where ROI comes in.

Figure 1: Reasons for increasing use of single-use/disposable system components (Source: *Third Annual Report and Survey on Biopharmaceutical Manufacturing*, www.bioplanassociates.com)



Hard Costs

As a starting point for establishing an ROI case, hard costs to evaluate in biopharmaceutical manufacturing include

Capital

Material costs

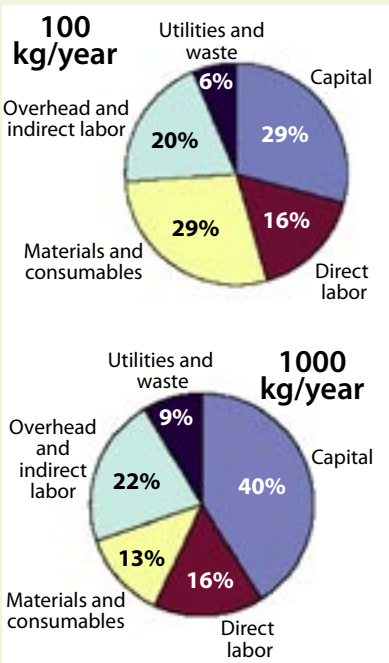
Direct labor costs

Indirect labor costs

Overhead allocations

Utilities

Figure 2: The majority of biopharmaceutical manufacturing costs are "fixed" (SOURCE: THOMAS C. RANSOHOFF)



Calculating ROI

The market is clearly not ready to simply throw out steel systems and replace them with plastics. From the survey, looking at the reasons biomanufacturers are restricting their use of disposables, 55% of respondents cited "We have already invested in equipment for current systems" as a significant reason for restricting use of single-use or disposable system components. The market, especially for larger biomanufacturers, will remain primarily steel-based until sound economic and strategic justifications are presented to decision-makers.

"From a process economic perspective, an end-user must determine whether these capital and cleaning savings justify the higher consumable and other costs associated with the use of disposable equipment in their particular circumstance," says Thomas C. Ransohoff of BioProcess Technology Consultants, Inc., a coauthor to the BioPlan survey.

Needed — Real-World Data: Further, 50% of respondents to the survey indicated that the lack of lifetime operating cost data on the difference between stainless steel and disposables options was restricting their adoption. This reveals a need for real-world data and case-studies on successes so that decision-makers can make informed assessments on expanding their use of disposables. Without such benchmarks, biopharmaceutical companies and CMOs will be slower to adopt disposables because they will be less able to determine the cost-benefits of implementing disposable options.

Suppliers to this industry are beginning to recognize that presenting a justifiable, valid ROI case to their biopharmaceutical clients is increasingly important. Such cases are based on real-world data. Life science suppliers face customers who are more demanding; pricing pressures are increasing, and margins are contracting. In fact, according to a recent study of life sciences purchasers, 70% require an ROI analysis for investments of $25,000 or greater (2).

Some suppliers have responded by incorporating ROI claims into their sales and marketing materials. However, unless those claims are backed by data collected independently, without bias, and in a way that demonstrates actual cost-savings, the claims are frequently discounted or discarded by decision-makers.

Return-on-investment and value benchmarking, however, are frequently moving targets, especially in clinical applications, where it can be difficult to determine the distinct "hard money" returns. But determining these data points is critical. Operating costs in biopharmaceutical manufacturing are typically grouped into the following categories: capital, material, direct labor, indirect labor/overhead, and utilities. This is a starting point for establishing an ROI case for disposables.

The Special Challenges of Complex Processes: ROI can be especially hard to define when dealing with large, multiyear, multifaceted projects that are complex to implement or have cost-savings areas that are difficult to determine. Further, assessing the impact on a complex process of changing a single variable can require careful cost-assessments and a solid research plan. As the scale of a manufacturing operation increases, the "disposables equation" does not move linearly. As an example, in an analysis of operating costs for a monoclonal antibody process that increased in scale from 100 kg/yr to 1000 kg/yr, Ransohoff's group concluded that capital costs decreased from 40% of total costs to 29% (Figure 2). Such data points would need to be included in any ROI calculation.

BioPlan Associates, which has developed benchmarking data and spreadsheet models for determining ROI for life sciences decision-making, generally finds that without validated benchmarking data, it is difficult to assign believable value to the savings a technology can provide, especially a new technology. The processes are complex and often do not lend themselves to easily determining how a novel technology, such as disposables, will reduce costs.

For that reason, justifying investment in new technologies often is a tough sell, and such projects can have a difficult time taking priority over other capital projects. However, new data (still being developed) will help decision-makers calculate return on investment and enable some manufacturers to pitch new technology projects more effectively, even when the return for pricey systems is difficult to pinpoint.

So How Do You Determine ROI?

ROI involves "crunching numbers" and assigning value to both tangible and intangible cost savings areas. Calculating return on investment requires benchmarking and establishing value to specific activities and costs. Some "hard dollar" activities can be directly calculated based on hourly wages, cost of goods, and other cost-accounting factors such as allocation of a full-time employee's activities to a specific task (not always easy to do, especially when that task crosses over to other cost centers); utility costs allocated to discrete tasks,

The market is still looking for CASE STUDIES that show how and where implementation of disposables perform best compared with steel over a long period of time.

or costs of raw materials (see the "Hard Costs" box). Cost avoidance, such as reduction in capital expenditures, must also be allocated.

Other costs are less tangible. Such "soft dollar" activities include assigning a value to "risk of contamination" for example, or to "quality components" when the downside might be the loss of a multimillion-dollar batch due to failure of a simple component. Reducing errors through ease-of-use or effective training on disposables has value. So does determining the value of becoming 10% more efficient: Do you eliminate 10% of your workforce or increase your output "X" percent? Intangibles tend to be hot-button issues, and allocating costs to them is not a trivial exercise.

Tips for Developing an Effective ROI Case

Understand how to measure ROI.

Create an easy-to-use, flexible spreadsheet tool that reflects most configurations.

Be confident in the benchmarking data used to calculate your ROI.

Use clear, simple calculations

Avoid any unsubstantiated calculations that undermine the credibility of the analysis.

Where estimates are used, note how numbers were derived, and any error limits.

Continue collecting benchmarking data, postimplementation, to evaluate your model with your own data, improve its accuracy, and gauge success.

The more hard numbers, the more concrete the decisions, and the greater the courage executives will have in their own convictions. Clearly delineating between the tangible and intangible ROI calculations can make decision-makers more comfortable, particularly for novel technologies.

Using proprietary assessment tools for making ROI-based decisions such as time-and-motion studies, side-by-side comparison assessments, next-best-alternative options, and others can be used to assign hard numbers to less tangible factors. If tangible and intangible costs are documented and explained in depth, including the inherent limits of error in the data, then decision-makers can take calculated risks based on their knowledge of the accuracy of the ROI calculator. Industry cost data research can create a framework for calculating ROI, and it can give managers critical data for their own cost justifications.

Research on new technologies, by definition, is light or nonexistent. And that is what makes ROI calculations a challenge for both suppliers and purchasers. Such research, though, is critical because it helps determine the math when calculating ROI. Decision-makers are sometimes forced to assign estimated values to intangibles. The wider the estimates or the greater the number of intangibles, the less accuracy those tools provide.

Most companies include a strategy component and long-term business considerations in their decision rather than base decisions exclusively on short-term ROI calculations. Regardless, knowing the ROI that an implementation plan will provide over time strengthens the decision process and establishes a value to a decision. Showing that value makes it easier to sell to upper management and ultimately helps simplify decision making and related strategies associated with purchases.

ROI Benefits of Single Use

Single-use systems reduce operating costs and decrease capital investment by eliminating the elements traditionally used in stainless steel systems. But the cost of disposables over the life of a project can add up. Ransohoff notes that "the primary economic driving forces for disposable process technology are reduction in capital costs and in the costs associated with cleaning multiuse equipment." Additionally, by reducing the need for long-lead capital equipment and cleaning validation, the use of disposables can save time, which directly translates to economic benefits.

Some vendors point to these benefits as the most compelling ROI case for disposables. "It will never be cheaper to use stainless steel," according to Bob Smith-McCollum, of Stedim. "Cleaning and validation are expensive." He adds that disposables also save water. In the Stedim model, 82% of the expense previously spent on water is saved. "Waste water could become a limiting variable in the future," he says, because it needs to be treated before it goes to the municipal system. Stedim's cost savings model estimates that overall cost savings of using a single-use system is nearly 40% when compared with stainless steel systems.

What Are the Major Stumbling Blocks for Disposables?

In addition to the lack of economic data, the relatively slow adoption rates of single-use systems today may be the result of unaddressed concerns about the technology. According to the BioPlan report, the primary reason why biopharmaceutical manufacturers and CMOs might not expand their use of disposables were their concerns over leachables and extractables (69%) and loss of production materials through breakage of bags (58%).

"The obstacles to incorporation of disposable process technology in biopharmaceutical processes include characterizing extractables and the risk of product loss due to failure (bag breakage)," says Ransohoff. "The costs for these activities should be included in an economic analysis as well as other costs related to using disposable technology, such as the potential for increased warehousing requirements and waste disposal costs."

Some vendors are focusing on the trend toward animal-free components, based on regulatory concerns. Although translating these concerns to an ROI case for purchasers can be a challenge,

strategic issues are involved. "[Animal free] went from a curiosity to a major issue," says Tom Murphy, chief executive officer of TC Tech, a supplier to this industry. "This is the future."

Addressing leachables directly, Denise DeTommaso of SAFC JRH says that "there are so many thousands of products that can be put in contact with disposables. You have to do specific testing for specific products. By now most manufacturers have done pretty extensive testing on leachables and extractables. If a customer presents us something that has not been tested, we will test it to confirm its usability in our systems."

Reader Tips

Making the ROI case should be based on a purchaser's manufacturing situation and need. As such, any ROI model must be flexible enough to accommodate different situations, yet simple enough so that individual elements of the model are understandable and believable. At the heart of any ROI model are benchmarking data. Vendors can and should help generate and share those data points (see the "Tips" box).

After implementing a single-use system, manufacturers should continue evaluating the efficiencies and economies of the system. This will help gauge success and identify new cost structures. The data allow manufacturers to improve the accuracy of their original cost estimates and ensure the accuracy of future calculations. Measuring after implementation and comparing that to benchmarks made using stainless steel will also validate the original analysis. The market is still looking for case studies that show how and where implementation of disposables perform best compared with steel over a long period of time.

Using an ROI model can simplify evaluation of benefits versus costs for many purchasing departments and process development groups. Vendors work closely with their customers' engineers and purchasing departments to ensure that disposables are appropriately designed and that their potential benefits are properly assessed. Requests for proposals (RFPs) should be written to allow vendors to recommend solutions that achieve the efficiency goals disposables are capable of providing. ROI calculations can be used to compare design performance, especially when vendors' proposals differ significantly upfront. The most cost-effective design might not be the cheapest. A biopharmaceutical disposables manufacturer that understands the overall production process may recommend more efficient ways of designing a system. But because RFPs often come from purchasing departments, vendors are responsible for revisiting the design to ensure that it delivers the most value at the least cost.

Getting the most out of their vendors is a goal of all biomanufacturers, but because the need for information is great and availability of performance data is sparse, partnering with vendors to share data is even more critical with novel technologies such as disposables. Purchasers should take advantage of vendors' consultative approach to ensure they are getting the best long-term value and ROI.

The use of disposable systems is on the rise. However, like any technology, doing your homework and aligning your business objectives and engineering requirements to the capabilities of the product will, in the end, determine whether or not these systems are right for you.

Reference

1 Black JV, et al. *The 3rd Annual Report and Survey of Biopharmaceutical Manufacturing Capacity and Production.* BioPlan Associates, Inc.: Rockville, MD 2005; www.bioplanassociates.com

2 Kotler Marketing Group and Information Industry Association. *2004 ROI Current Practices Survey: Enterprise Results*; www.kotlermarketing.com/resources.

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