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Feature Article

Users Are Sold on Single-Use Systems

Survey of Adoption Trends Shows Burgeoning Usage Across All Sectors of Industry

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Disposable components in biopharmaceutical manufacturing are continuing strong growth, especially in production areas like buffer storage and mixing systems.

This is according to BioPlan Associates' "5th Annual Report and Survey of Biopharmaceutical Manufacturing," in which we probed issues among 434 industry biomanufacturers and CMOs regarding their use of, and resistance to, disposables at all stages of biomanufacturing.

Since we began measuring usage in 2005, the trend has been for more usage, in more applications, with stronger expectations from vendors to provide more variety, better-tested, and less expensive products.

Some of the disposables issues covered in this year's international study include: growth rates, disposables usage by application, newly introduced disposables, downstream operations, leachables and extractables issues, reasons for increasing use, factors for restricting use, current spending and budget growth, use in commercial-scale manufacturing, and satisfaction with vendors.

Why Disposables?

Single-use disposable components have become an increasingly common feature at biopharmaceutical facilities over the past five years. They can be used for: propagation of cell culture organisms; preparation, storage, and transfer of process solutions; the storage and transfer of intermediate or bulk product solutions; and the transfer of raw materials including media and buffers. Disposables usage has been driven largely by a need to reduce cleaning requirements and the associated time, validation, and cost factors.

Annual Growth for Disposables

In the study, we evaluated growth rates for 14 disposable applications. *Figure 1* shows annual increase in market penetration (that is, market share gain, not growth rates) for the top five applications. The graph indicates the jump in the percentage of facilities now using these products.

The fastest growing acceptance for these products is in preassembled tubing sets and mixing systems. Today, there are more products available and more experience in their use. Sampling systems have matured as well, as people begin to recognize the benefits. Membrane absorbers and bioreactors reflect a trend of going to a fully disposable process.

According to Vladimir Kostyukovsky, Ph.D., senior director of manufacturing at Artisan Pharma, "What is new in bioreactors is that there are now a number of stir-tank reactors that have been tested in the last couple of years and are being more readily accepted."

When comparing trends over the past two years, we found large jumps in a number of disposable areas including the use of membrane absorbers, which jumped 62.3 percentage points in market penetration over two years from 12.9% to 66.7% (an annual growth rate of 127%). In addition, mixing systems usage grew from 19.4% in 2005 to 73.7% in 2007 (a 54.3 percentage point increase, and an annual growth rate of 94%). Bioreactor usage grew from 21% in 2005 to 59.4% in 2007 (a growth rate of 68%).

Stage of Production/Application

Expectedly, disposables in 2007 were found to be used mainly during scale-up/clinical production. Some of the key data included

the use of sampling systems, which were used by over 50% of respondents in their commercial-scale production.

Bioreactors are now used by 27.5% of respondents in some way in their commercial-scale production. Faster growth for clinical-stage manufacturing was expected because in commercial stages it is more difficult and costly to switch due to regulatory considerations. However, sampling systems are some of the easiest to implement and are relatively easy to switch.

Newly Introduced Applications

We evaluated 12 newly introduced or implemented disposable applications. From the survey, 47.5% of respondents said the use of disposables for buffer storage was newly introduced or implemented at their facility during the previous 12 months.

Other disposables that have been newly introduced were buffer prep (by 40.3% of respondents), filtration (39.6%), and media storage (33.1%). Both solution preparation and storage involve the same functional area. Thus, if a decision was made to store buffers in plastic, it may be a logical step to also make them in plastic.

Leachables and Extractables

Respondents were asked a number of questions regarding leachables and extractables (L&E) in disposables. We found that 74.3% agreed or strongly agreed that, “vendor should generate L&E data and validate the data.” That number, however, declined in relation to later stage manufacturing, where 41.1% said they “expect to generate L&E data myself for Phase III or commercial applications.”

This likely reflects biomanufacturers’ need to reduce regulatory risks associated with leachables and extractables at later stages of production. Even at late-stage clinical production and commercial production, more than half of biomanufacturers expect vendors to be generating data on leachables and extractables. Significantly, nearly a third also indicated they would pay 25% more for their disposables if they were provided such data.

Reasons for Increasing Use

We identified 28 reasons for the increasing trends toward the use of disposable and single-use system components. *Figure 2* shows the top five reasons.

The primary reason biopharmaceutical developers and CMOs use these products are to eliminate cleaning requirements (cited by 50.5% of respondents as “very important”). Second was “decreasing risk of product cross-contamination,” indicated by 40.6%. Third was “reduce time to get facility up and running” which was indicated by 37.6% as being “very important.”

Three-Year Comparison

There are several reasons for the increased use of disposables over the last three years (2005–2007).

The criteria that biopharmaceutical manufacturers and CMOs give for potentially increasing their usage of disposables are changing. This may reflect a maturation of this segment as the industry becomes more aware of attributes and benefits.

“Eliminating cleaning requirements” now holds the top position, with 50.5% of respondents indicating it as a very important reason for why they choose to use disposables. This compares with 54.9% in 2005 and 55.5% in 2006.

A surprising number of factors showed marked decreases in importance as well. This may be the result of the industry becoming accustomed to the use, risks, and benefits of disposables.

One of the most interesting results is that “decrease risk of cross-contamination” dropped from the top spot in 2006, with 58.9% indicating it was a very important factor, to 40.6% of respondents in 2007. Interestingly, none of these respondents felt that “reducing initial installation time” was a very important factor in their decision to use disposables. This was a decrease from 27.3% in 2006.

Most Critical Reason for Increase

When asked to indicate the most critical reason for using disposable technologies, respondents said that, “eliminating cleaning requirements” was the single most important factor (16.8%).

“Reducing capital investment in facility and equipment” was the second most critical reason for using disposable technologies (15.2%), although it ranked fifth when participants were asked to rank the reasons for using disposables. This could be a function

of where respondents were regarding stages of facility expansion or construction.

Reasons for Restricting Usage

We tested 17 reasons why biopharmaceutical manufacturers and CMOs might not expand their use of disposables. *Figure 3* shows the top five. The primary concern was over leachables and extractables where 75.4% of respondents agree or strongly agree that L&E issues are restricting the use of disposables. This compares with 63% of respondents last year. Part of this is the result of the increased use of disposables, which has, in turn, increased awareness and FDA interest.

The second greatest concern was the fact that participants had "already invested in equipment for current system" (65.2% agree or strongly agree). Other factors included:

- becoming vendor-dependent (single-source issues)
- breakage of bags and loss of production materials
- investment in validation
- lack of uniform standards
- regulatory guidance on leachables and extractables
- lack of cost data

CMOs vs. Biotherapeutic Developers

The primary reason both CMOs and biotherapeutic developers might not expand their use of disposables was concern over L&E issues (70.6% for CMOs and 75.9% for biotherapeutic developers).

When comparing differences between CMOs and biotherapeutic developers, a significantly greater number of biotherapeutic developers indicated that the primary reason they would restrict expanded use of disposables is because they have already invested in equipment for their current system (67.9% for biotherapeutic developers vs. 37.5% for CMOs). This is likely because CMOs can generally be more flexible; they can also pass many of these direct costs on to the client. Lack of lifetime operating cost data comparing stainless steel to disposable options is more of a concern to biotherapeutic developers.

Other differences between CMOs and biotherapeutic developers were found, from "lack of disposable equipment that meets process requirements" (where CMOs were more concerned), to "material incompatibility," "lack of clear guidance on leachables and extractables," and "breakage of bags" (where biotherapeutic developers were more concerned).

Current Spending

Bioreactors tend to be one of the most expensive disposable items, and they were the item on which respondents spent the most in 2007. On average, respondents spent $212,959 per facility annually on these products. This is a change from last year's top item, which was "media bags—filled wet" on which facilities spent an average of $164,313 in 2006.

Annual Growth in Spending

We measured annual growth in spending for 14 common disposable devices (*Figure 4*). The fastest growth rate in per-facility spending was for mixing systems, which was reported to have increased 239% over the past 12 months.

Other fast-growing areas were membrane absorbers, media bags—purchased dry, and disposable filter cartridges. Much of this increase has been the result of more systems becoming available and greater confidence and experience in those currently on the market. This has also caused the shift from prefilled bags and dry bags.

Budget Increase

To determine where the greatest increase in spending on disposable and single-use systems will occur, we asked respondents to indicate which type of disposable devices they plan to budget the greatest increase for over the next 12 months.

The single largest budgetary increase for disposable components will be in bioreactors over 100 liters. This was indicated by 16.6%

of respondents, and suggests an industry focus on extending the scale of disposable bioreactors at least into scale-up production. Buffer bags, 100–500 L, were the second largest area of budgetary increase.

Satisfaction with Vendors

We tested end-users' perception of eight attributes associated with disposables, including quality, product selection, and service received from vendors. This may point out potential areas of dissatisfaction that could impact adoption rates for disposable technologies.

A majority, 75.6% of respondents, indicated that for quality of product they were satisfied or very satisfied. This also points out that a quarter of end users are not fully satisfied with quality. Regarding strength of the product, 62.8% were satisfied or very satisfied. Not unexpectedly, regarding cost of products, only 24.7% indicated satisfaction. This is consistent, however, with price analysis in other industries.

Summary

The industry's concerns regarding disposable products continue to center on how leachables and extractables associated with disposables may affect their specific project or system. Further, over half of respondents indicated that they would restrict their usage of disposables if forced to rely on a single vendor.

Standardization could improve the overall rate of adoption for these products. Downstream disposables are moving toward greater industry acceptance in most manufacturing areas. Once this is achieved, more companies, both CMOs and biotherapeutic developers, are likely to increase use of disposable technologies as they increase their ability to fully integrate overall production processes.

This study suggests that, as new biomanufacturers and new products enter the industry and products pipeline, disposable options are becoming a fundamental part of the decision process.
