A growing throw away culture

Pall Allegro 3D biocontainers designed for large scale applications

Eric S Langer, president and managing partner of biotech marketing research company BioPlan Associates, highlights changes in attitudes to disposables use in biopharmaceutical manufacturing

The use of disposables in biopharmaceutical manufacturing continues to advance globally. In fact, from BioPlan Associates' newest industry study, *The 6th Annual Report and Survey of Biopharmaceutical Manufacturing*, the concerns over adoption have rapidly become less strategic, and more operational and commercial.

This year's study elicited data on 10 critical areas associated with biopharmaceutical production from 443 production executives at drug developers and CMOs in 39 countries. A major area in the study involved the changing role of disposables in manufacturing.

This year, decision makers' objections to disposables have declined both in 'quantity' and importance. For example, respondents were asked about their most important reasons for not increasing their use of disposables.

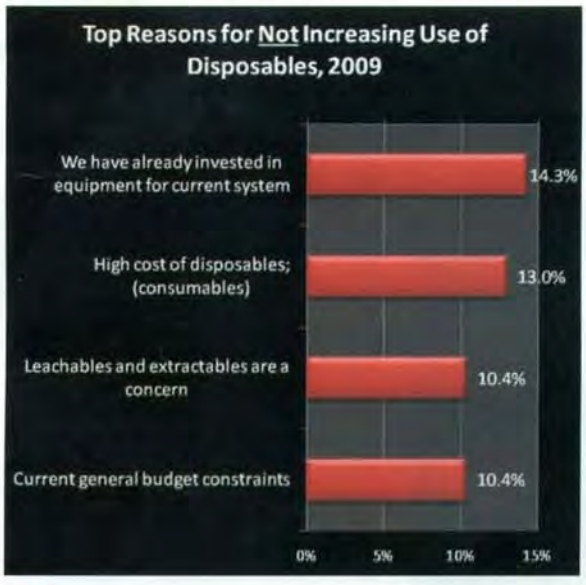


Figure 1

Factors such as how regulatory agencies would treat leachables and extractables (L&E) issues have consistently been near the top of the list. Last year these regulatory worries for restricting adoption of disposable manufacturing were a primary concern to 16.6% of biomanufacturers. This year, that percentage has dropped to 10% (see Figure 1). In addition, last year, the 'Lack of disposable equipment that meets process requirements' was a major concern, as was 'Breakage of Bags and Loss of Material.' This year, these issues were essentially no longer primary concerns to respondents.

greater acceptance

The key trends suggest greater acceptance of disposable products. In fact, three of the top four issues were cost- or budget-related, rather than technical. This is a clear indication that the industry has become comfortable with disposables for biomanufacturing applications. The question now seems to be one of cost-effectiveness for specific applications.

In fact, the top concern, 'We have already invested in equipment' (which is something of an 'If it isn't broken, why fix it?' attitude toward disposables), has dropped since last year from 19% of biomanufacturers down to 14% this year. This may indicate an increasing receptivity toward disposables even in current facilities.

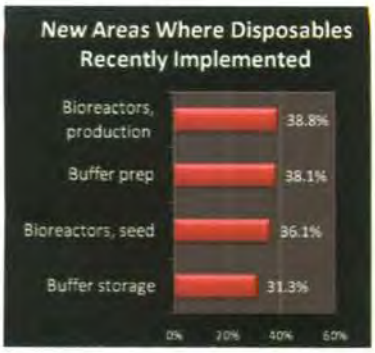
However, as one can imagine, the bigger the company, the less likely it is to be interested in converting to a disposables facility. In fact, 73.3% of large biomanufacturers indicated that investments in current equipment would inhibit their use of disposables to some degree, compared with only 49.5% of mid-tier biomanufacturers.

increased adoption

We also found that disposables were being adopted in new areas of biomanufacturing at an increasing rate, especially for some of the more technically advanced disposables. For example, production bioreactors were newly introduced to 39% of respondents' facilities over the past 12 months (Figure 2). Somewhat surprisingly, 30% of large biomanufacturers have introduced production bioreactors within their facility during the past 12 months. These are likely to be at the process development scale.

When comparing newly implemented disposables usage in the US vs Western Europe, there are some significant differences. In the US, 47% of respondents indicated they were currently using disposable production bioreactors (at some stage within their facility), compared with 28% in ▶

Figure 2



◀ Western Europe. Seed bioreactor usage was consistent between the US and Europe.

Newly implemented buffer storage is carried out in disposables by 31.2% of US facilities, compared with 39.6% of Western European facilities, and 16.7% of facilities elsewhere in the world. Buffer prep is done using disposables at 45.3% of US facilities, and at 35.9% of Western European facilities. Mixing using disposable technologies is somewhat less common in the US (12.5%) than in Western Europe (20.8%).

current usage

Our study also measures over time the overall prevalence of disposables. Acceptance and prevalence of disposables in the industry is rapidly increasing as companies gain experience with these devices. This is reflected in our respondents' current usage of single-use/disposable systems in biopharmaceutical manufacturing. "Disposable filter cartridges" were the most commonly listed disposable items, noted by 94% of our respondents (equal to last year's usage data).

Most of the other popular items also were small or common ones, such as connector clamps and depth filters. On the whole, however, the survey responses suggest that almost every kind of disposable has penetrated the market broadly, althought not necessarily deeply.

Fully 61% of respondents reported using at least one disposable bioreactor, and 74% reported using buffer containers, and 56% were using a disposable mixing system. Even for filled media bags, acceptance in at least some part of the production network was reported by 59% of those surveyed (48% in 2005).

Compared with the results of earlier annual surveys, the current study results also reflect the rapid rise of the disposables market. For example, over the six years that the study has been implemented, the use of sampling systems has risen from 0% to 67% this year; while the use of bioreactors has risen from 21% to 61%. Clearly most of the industry has begun to broadly accept disposables, as is seen by the increasing use of disposable bioreactors, membrane absorbers and other key production components.

disposal of disposables

Waste disposal of single use products is an increasing concern. Because biological waste cannot simply be sent to local landfill, companies are finding incineration or other sterilisation and recycling processes costly and burdensome. More than 23% of biomanufacturers were finding that disposal of disposables was causing a reduction in their overall usage. In fact, 51% of biomanufacturers, and 41% of contract manufacturers indicated that waste disposal was having at least some impact on their operations with respect to reduced usage of disposables.

Figure 3

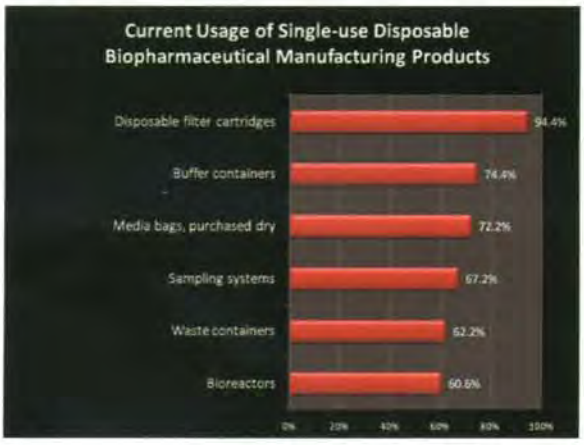


Figure 4

Some of the comments associated with waste disposal include:

- 'We pay for disposal based on weight, therefore very important'
- 'Incineration is the only real way of dealing with this, new methods need to be developed for the disposables we are incinerating'
- 'The use of disposables must have a positive...environmental impact (the method of disposal, raw materials in manufacture of technology, etc) to justify their widespread use'
- 'Need to incinerate, finding the vendor for the same is difficult. I think the seller should take back the used disposables or else help us in proper waste disposal'
- 'Need to fit "green" philosophy and reduce carbon footprint. From what I have read disposables lower environmental impact due to lower staffing (transport) and cleaning requirements'
- 'Disposables should be collected as special waste and incinerated to generate heat/energy'
- 'Balance Disposable disposal vs CIP waste impact'
- 'Recycling of single use disposables would be an issue we'd like to see addressed even with additional costs built into overall materials costs'
- 'Disposables represent a good compromise by reducing requirement for cleaning (energy-consuming, time-demanding and waste water treatment required before discharging in the environment) while ensuring high product quality and optimisation of capacity utilisation'
- 'Disposable suppliers should be actively involved in the development of waste disposal processes'

The survey identified 25 reasons that respondents considered to be factors in deciding on the use of single use technologies. This year, the top reason continues to be to 'Eliminate cleaning requirements', noted by 88% as being Important or Very Important (50% indicated this as 'Very Important' both this year and last). Following were 'Decrease risk of product cross contamination (83% this year, vs 78% last year). Then 'Reduce time to get facility up and running' (79% this year, 74% last), and 'Reduce capital investment in facility & equipment' (78% this year, 73% last year).

leachables & extractables

We identified 26 possible reasons why manufacturers may be restricting their use of disposables. Topping the list, with more than 64% of respondents indicating that they agree or strongly agree, was concern over 'leachables and extractables' (L&E). The level of anxiety over this was higher than for other issues, but it was lower than the 75% figure indicated last year.

Another L&E regulatory-related issue, noted by nearly 38%, was 'No clear regulatory guidance on leachables and extractables'. This suggests that biomanufacturers and CMOs continue to be concerned about the L&E issue, but that it may be diminishing over time as companies and regulatory agencies become more acclimated to dealing with these factors.

It may be that decision-makers in the industry may be more aware and sensitised to this issue as the use of disposables rises. Further, they may be more

Survey Methodology:

This sixth in the series of annual evaluations by BioPlan Associates yields a composite view and trend analysis from 443 responsible individuals at biopharmaceutical manufacturers and contract manufacturing organisations in 39 countries. The methodology also encompassed an additional 140 direct suppliers of materials, services and equipment to this industry.

This year's survey covers issues such as: current capacity, future capacity constraints, expansions, use of novel expression systems, use of disposables, trends and budgets in disposables, trends in downstream purification, quality management and control, hiring issues, employment and training. The quantitative trend analysis provides details and comparisons of production by biotherapeutic developers and contract manufacturing organisations (CMOs). It also evaluates trends over time, and assesses differences in major markets in the US and Europe.

Pall's Allegro 3D biocontainers come in 100L, 200L and 500L sizes

aware of the FDA's growing interest.

Most manufacturers and vendors recognised that testing disposable devices for leachable and extractable contaminants in biomanufacturing is difficult, given the infinite variety of conditions such as contact times, pH and a myriad of others. So, given those difficulties, who should be doing the analysis and L&E testing?

With 82% of our respondents indicating they agree that 'vendors should generate L&E data, and validate', this suggests a need and opportunity to vendors. And although 47% indicated that they expected to generate their own L&E data for 'Phase III or commercial applications,' 22% indicated that they would pay 25% more for disposables if they came with useful vendor-generated L&E data. In fact, 9% would pay 50% more.

Regardless of whether such an additional fee for L&E data would be justified for all products, clearly there is some value in testing. Vendors may find financial benefits in addressing this problem.

Testing for leachables and extractables is becoming an important function in its own right, but it can be challenging. A substance that might not leach in many months in an ordinary system can start coming out during stability testing, or in different temperature or pH conditions, or after a longer period of contact. Providing accurate results may require testing within each given application or system. As a result, some 35% of respondents this year expressed concern about a 'lack of uniform standards for testing and measuring.'

Figure 5

Figure 6

other issues

After the L&E issue, the greatest factor restricting expanded use of disposables, cited by 63% of our respondents, is 'Breakage of bags and loss of production material.' The bag breakage issue was noted by 55% last year, up sharply from the previous two years' surveys (44% for 2006, 35% for 2005).

After that, it is the cost issues (noted by 61%). However, the highest objections came from the CMO respondents, where 70% agreed that cost of disposables (consumables) was a reason for restricting disposables usage. This compares with 59% of biomanufacturers who found price was a major argument against disposables.

Other concerns limiting the use of disposables among respondents include a fear of becoming too dependent on a single vendor (52%).

According to Dr John Liddell, head of Process Science at Avecia Biologics, getting buy-in at typical biopharmaceutical facilities for the use of disposables is often an applications issue. 'Making disposables sufficiently flexible for application to different process types, as well as to a larger range of unit operations is important. Examples of where flexibility may be necessary include different bag ports and numbers, different filter types, different mixing requirements, unit operations such as chromatography control systems and microbial fermentation.'

disposable use by CMOs

Across the board, CMO respondents reported at least the same, and almost always greater use of disposables. Areas of CMO dominance include mixing systems (69% for CMOs vs 39% for developers), filled wet media bags (60% for CMOs vs 44% for developers), bioreactors for scale-up and clinical production (66% for CMOs, vs 34% for biotherapeutic developers), and membrane absorbers (51% for CMOs vs 33% for developers).

The attraction of disposables for CMOs is fairly clear. Because CMOs need to switch between different clients and must minimise cross-contamination risks, the use of disposables makes it easier to create distinct production campaigns. Single-use items also make it easier to assign and pass on costs to individual clients.

The survey makes clear that the use of disposables is rising but potential users are reporting serious environmental, disposal, safety and regulatory concerns and practical limitations on their use. Many new disposable products are in the pipeline, from bioreactors, to probes, to downstream technologies, sensors and other innovations. The story is still unfolding, but the trends show disposables are fully embedded in today's biomanufacturing environment. ■

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