Pharmaceutical Technology
Patricia Van Arnum
pvanarnum@advanstar.com, (732) 346-3072
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Biopharma Wants Better Upstream Bioprocessing Technologies

Large-scale biopharmaceutical manufacturing equipment for upstream product manufacture has changed relatively little in past decades. Although major improvements in cost-savings, flexibility, higher product yields from improved genetic and cell engineering, and widespread adoption of small-scale single-use bioprocessing equipment have occurred, innovation has been slow in coming for the equipment used, particularly bioreactors. Essentially all commercial-scale GMP biopharmaceutical manufacture is still done using fixed stainless steel bioreactors and equipment whose basic designs have remained largely unchanged.

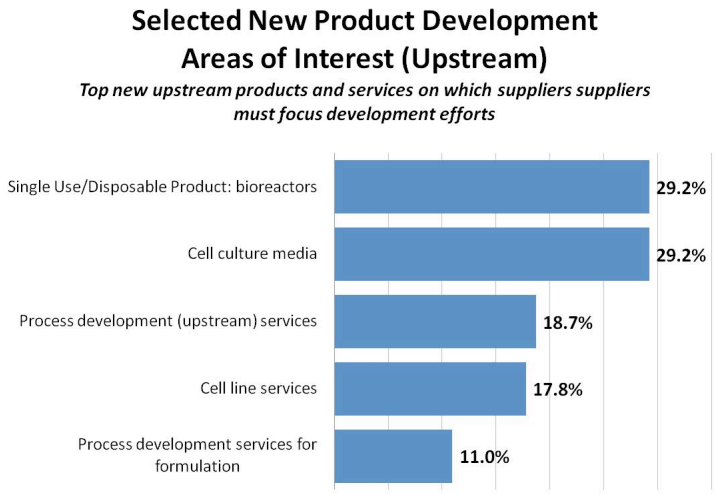
Our recently released *8th Annual Report and Survey of Biopharmaceutical Manufacturing Capacity and Production*(1) surveyed 352 global biomanufacturers regarding production bottlenecks, budget issues, use of disposables, downstream production, quality management and many other aspects. This year's data show the industry is demanding better processing, including both up- and down-stream processing improvements. On the upstream side, the global study showed that the industry is demanding new product innovation in single-use bioreactors, cell culture media, as well as for a variety of service areas.

Industry Wants Innovations in Bioreactors

The annual study shows that the biopharmaceutical industry recognizes upstream equipment innovations are overdue. Bioreactors are one of a company's largest bioprocessing expense. As an example of interest in alternative bioreactors, over two-thirds (68.1%) of survey respondents reported current in-house use of single-use bioreactors, and this percentage is growing especially in R&D and clinical scale production.

The industry is well aware that few highly innovative products, such as commercial-scale perfusion bioreactors and single-use large-scale batch-fed bioreactors have been introduced in recent years. Improvements in bioreactors, particularly for single-use, ranked along with purification equipment as the areas where bioprocessing innovations were reported as most needed, with 29.2% of respondents citing bioreactors (See Fig 1).

Fig 1



This lack of innovative products includes the major suppliers that dominate the bioprocessing systems market. Partly because of the strict regulatory environment where changes come slowly, even the single-use suppliers are focusing on relatively traditional bag-liner-in-a-steel-bioreactor single-use systems. These devices may lack truly novel innovation because of the difficulty in getting newer materials and devices into commercial operations, for regulatory reasons.

Much of industry's desire for improved bioreactors is related to the need for large-scale (e.g.., >1,000 L batch-fed), single-use/disposable bioreactors. Today, 1,000 L is currently the largest cost-effective size for disposable batch-fed bioreactors. Future areas for single-use bioreactor innovations may include unitary (single-piece) all-plastic, rather than plastic-lined, and even stainless steel-lined plastic bioreactors.

In our study, contract manufacturers (CMOs), with their rapid turnover of equipment need to be competitive, showed particular interest in improved single-use bioreactor systems compared to product developer/manufacturer respondents. Interest in disposable bioreactors also differed among regions, with the highest interest, 32.2%, in Europe vs. 26.9% of U.S. and 31% of rest-of-the-world respondents.

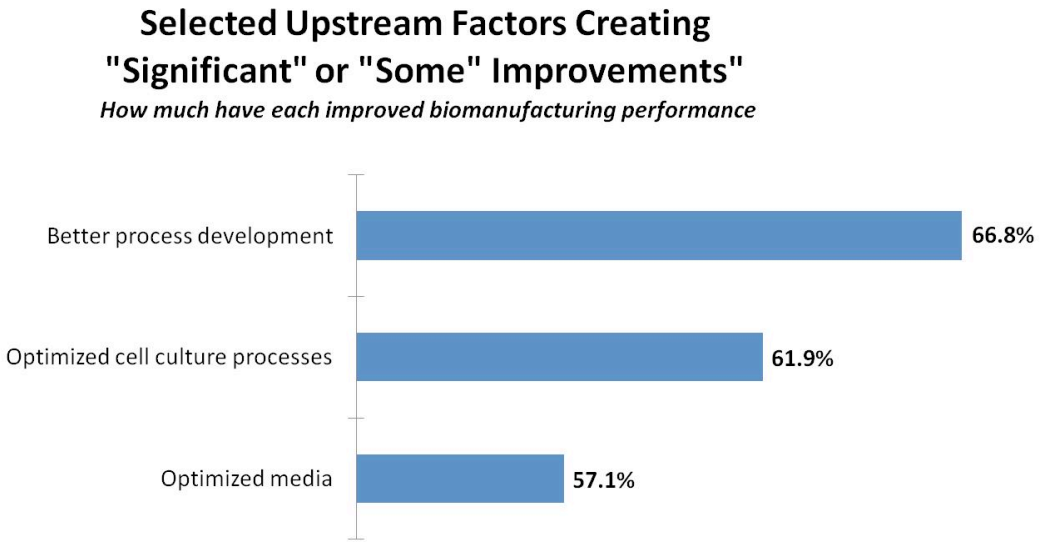
Help is on the Way: Suppliers' New Product Development

In addition to biomanufacturers, this year, we also surveyed 175 suppliers to the industry, and found that most are very involved in new product development activities. In fact, we measured 52 different areas where vendors are working on solutions. We found, for example, that single-use bioreactors, the hottest area of new product development, were being worked on in some way by 40.5% of respondents. Expression system platforms and cell culture optimization were also key areas in which vendors were investing in new product development. Thus, improvements and innovations can be expected from vendors sooner or later.

Last Year's Successes

To assess what facilities are doing *today* to improve their upstream processes, the study evaluated 15 areas where biomanufacturers were actively implementing performance improvements. We found that, in upstream areas, the greatest percentage of facilities were seeing 'Significant' or 'Some' improvement from "Better Process Development (with 66.9% indicating at least 'some' improvement as a result). "Optimized Cell Culture Processes" followed with 61.9%.

Fig 2



Perfusion Holds Promise, but Views Remain Dated

Perfusion bioreactors appear to be positioned to become the next major revolution in bioprocessing and single-use equipment, with perfusion equipment on track to compete head-to-head with conventional batch-fed bioreactors, even at commercial GMP scale. However, survey results shown the industry's views and knowledge of perfusion and its promise remain dated and rooted in the distant past when perfusion systems were actually fairly common.

Nearly all current bioprocessing today involves batch-fed bioreactors. Perfusion involves continuous slow feeding and removal of spent media along with the desired product with the host cells retained within the bioreactor by their being bound to bundles of capillary fibers, other membranes or retained in suspension in the bioreactor by special filters. While batch-fed bioreactors involve cells in dilute culture media suspension, perfusion bioreactors grow cells at ≥100 to 1000x-times higher concentration, with bioreactors commensurately smaller.

Thus, a small perfusion bioreactor over time and using the same amount of culture media can match or beat the product output of a much larger batch-fed bioreactor. FiberCell Systems reports it is

working on building desk-sized units that will have the equivalent recombinant protein production capacity of conventional 2,000-5,000 L bioreactors.

Perfusion is not new. Perfusion bioreactors were widely used for hybridoma culture, e.g. in the 1970s/80s, before antibody manufacture switched to batch-fed mammalian cell bioreactor manufacture of recombinant antibodies. Perfusion bioreactors were available from companies including Endotronics, Cellex, Biosyn and Biovest. Perfusion bioreactors today include those from FiberCell Systems and Zellwerk (marketed in the U.S. by Glen Mills Inc.). ATMI recently launched iCellis, the first large-scale perfusion bioreactor.

Although perfusion appears to be a viable new product candidate, the BioPlan survey shows that industry knowledge and attitudes towards perfusion remain largely out-dated. Among a list of 17 problems commonly encountered in bioprocessing, respondents consistently rated all of these as more serious concerns with perfusion vs. batch-fed systems. This included process complexity (66.1% for perfusion vs. 4.9% for batch-fed), and contamination risks (63.9% vs. 3.8%), It is exactly these and other concerns regarding perfusion are that already being resolved in perfusion as new bioreactors enter the market. As new products are launched in coming years, commercial-scale devices are likely to capture significant interest and establish new upstream solutions this industry is demanding.

References:

1) Langer, E.A., *Report and Survey of Biopharmaceutical Manufacturing Capacity and Production: A Survey of Biotherapeutic Developers and Contract Manufacturing Organizations*, BioPlan Associates, April 2011, 458 pages.

About the Author:

Eric S. Langer is president and managing partner at BioPlan Associates, Inc., a biotechnology and life sciences marketing research and publishing firm established in Rockville, MD in 1989. He is editor of numerous studies, including "Biopharmaceutical Technology in China," "Advances in Large-scale Biopharmaceutical Manufacturing", and many other industry reports. elanger@bioplanassociates.com 301-921-5979. www.bioplanassociates.com

Survey Methodology: The 2011 eighth Annual Report and Survey of Biopharmaceutical Manufacturing Capacity and Production in the series of annual evaluations by BioPlan Associates, Inc. yields a composite view and trend analysis from 352 responsible individuals at biopharmaceutical manufacturers and contract manufacturing organizations (CMOs) in 31 countries. The methodology also encompassed an additional 186 direct suppliers of materials, services and equipment to this industry. This year's survey covers such issues as: new product needs, facility budget changes, current capacity, future capacity constraints, expansions, use of disposables, trends and budgets in disposables, trends in downstream purification, quality management and control, hiring issues, and employment. The quantitative trend analysis provides details and comparisons of production by biotherapeutic developers and CMOs. It also evaluates trends over time, and assesses differences in the world's major markets in the U.S. and Europe.

NOTE: IMPORTANT TO INCLUDE THIS SO READERS UNDERSTAND HOW THE STUDY WAS CONDUCTED