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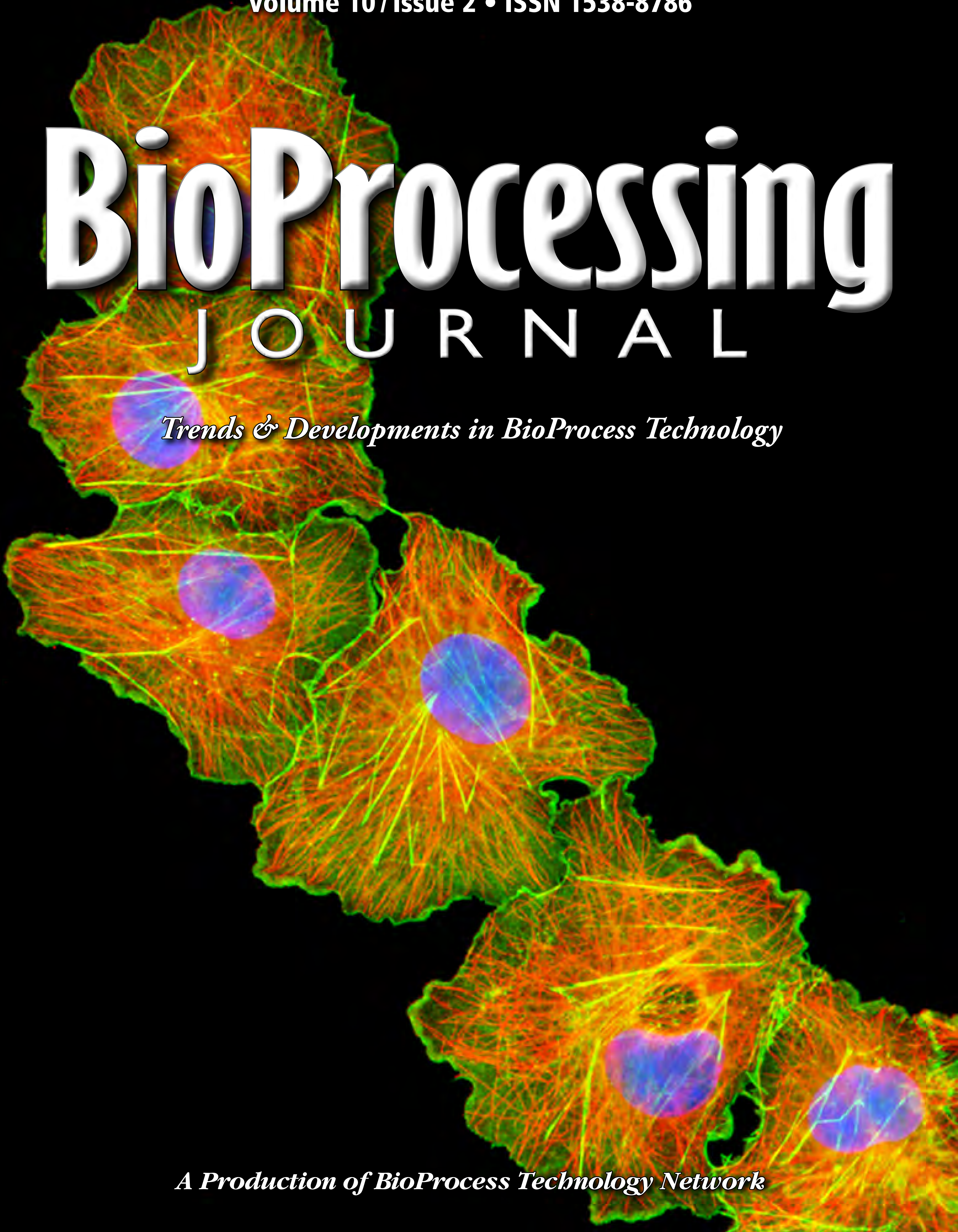
Trends & Developments in BioProcess Technology



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BioProcessing JOURNAL
TRENDS & DEVELOPMENTS IN BIOPROCESS TECHNOLOGY

Disposable/Single-Use Equipment in Biopharmaceutical Manufacturing: *Global Standardization Is An Absolute Necessity*

By ERIC S. LANGER

Introduction

Single-use systems (SUS) have been employed in biopharmaceutical manufacturing for over 15 years. Consistent year-to-year growth has been seen both in the total volume of sales and the number of manufacturing steps in which SUS are being used. It is projected that the majority of commercial-scale biologics manufacturing will be done in disposable equipment in the near future because of improvements in SUS design and innovation.

These devices can significantly reduce capital costs (for example, stainless steel vessels), eliminate equipment cleaning and sterilization, improve turnaround times, and reduce concerns about microbial contamination within a production facility. As reported in this year's *8th Annual Survey of Biopharmaceutical Manufacturing*[1], however, the rate of growth in SUS use may be slowing. Contributing factors are: 1) the economy; and 2) the need for more consistent product standardization (*e.g.*, design, quality, and leachables/extractables [L&E]) data that regulators and industry end-users can accept with confidence.

The 2011 survey analyzes in detail the trends in usage of single-use and disposable biomanufacturing equipment. It identifies variations according to industry segments, process steps, as well as geography. Aside from the economic factors and structural changes in the industry, the major reason cited for the latest trends in SUS adoption is a lingering concern about possible leachables and extractables in the plastics that could alter or contaminate the final biologic product. Consistent with this is the fact that the majority of SUS are found in scale-up and clinical production, versus commercial manufacture.

There are currently no explicit standards for leachables and extractables in SUS. The purpose of this article is to broadly summarize the effects this may be having by reviewing industry responses to questions posed in the 2011 survey. Included are thoughts on whether to integrate the information already out there, what agencies should establish industry-wide standards, how they are typically set, and who should be testing products to ensure standards are being met.

In our research, we find that industry suppliers are seeking guidance from regulatory authorities to better define expectations regarding single-use technology. Many commercial-scale facilities are waiting and watching for details about the relatively few organizations who have indeed begun producing fully-licensed products—at commercial-scale—using SUS.

Some end-users as well as vendors are suggesting that the industry should consider other models and industries where standardization is required. It would be useful to see how these groups have arrived at a common understanding that contributes to regulatory and quality acceptability as

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well as device interoperability. In other industries such as internet network connectivity, accepted design standards clearly define a common base upon which vendors should work. It is from this point that supplier innovation and competition can focus around design, usability, and better technology.

Methods

As part of our *8th Annual Survey of Biopharmaceutical Manufacturing*[1], we questioned key personnel associated with 15 areas of biomanufacturing operations. The final report provides analysis and a composite view from over 352 responsible individuals at biopharmaceutical manufacturers and contract manufacturing organizations (CMOs) in 31 countries. The survey also encompassed an additional 180 direct suppliers of materials, services, and equipment to this industry. This year's survey covers issues including: 1) current capacities and future constraints; 2) expansions; 3) trends and budgets for disposables; 4) developments in downstream purification; 5) quality management and control; and 6) hiring issues, employment, and training. Quantitative trend analysis provides details and comparisons of commercial production by biopharmaceutical developers and CMOs. It also evaluates trends emerging over time and assesses differences in the world's major markets, the United States, and Western Europe.

Results

The 2011 survey reports the high usage of SUS in biopharmaceutical manufacturing with items like disposable filter cartridges being employed at some stage in R&D or production by well over 90% of respondents. Survey results going back to 2006 show significant growth in the application of SUS systems at all stages of R&D and production with the greatest increases seen with membrane adsorbers (26%), bioreactors (22%), and mixing systems (19%) with compounded annual growth, respectively, over the six-year period. This upward trend is seen for all SUS systems, as shown in Figure 1. Looking at the year-on-year growth, however, it is clear that the rate is slowing or stagnating for SUS across the board (2011 survey, data not presented).

Implementation of SUS

When single-use systems first entered the market, they tended to be small-scale and used predominantly by R&D. This is no longer the case, however, with items like single-use bioreactors, and downstream purification devices and chromatography columns becoming available in sizes that are practical for use in clinical-scale, and even commercial-scale manufacture. Bioreactors also now span the size range from benchtop units to 1,000 and 2,000 liter capacities. These facts, together with improved upstream productivities (*e.g.*, cell lines producing higher titers) mean that commercial manufacturing processes done entirely in disposable equipment are likely to increase in the near future. Despite this, data from the 2011 survey show that individual SUS devices are employed mainly in process development and scale-up (data not shown).

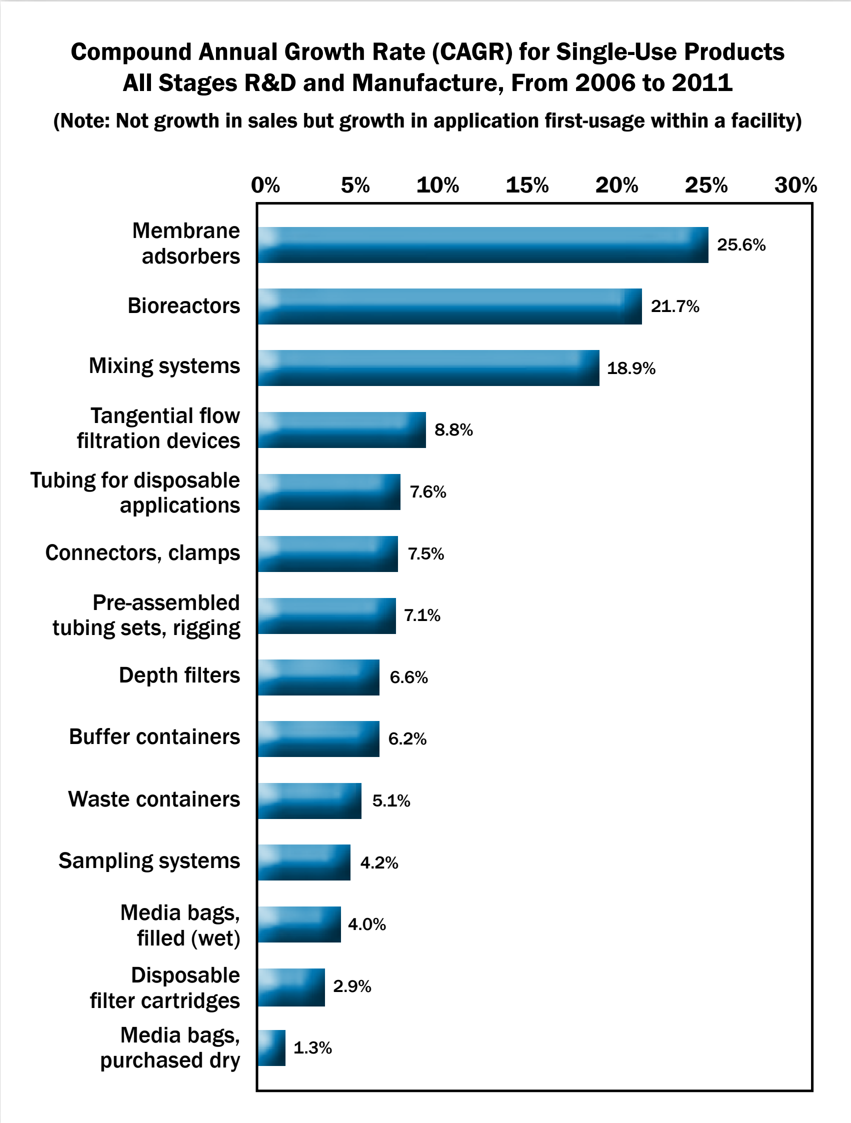

FIGURE 1. Average annual growth rate for disposables from 2006 to 2011.

Factors Limiting Adoption of SUS

We sought to identify the factors most likely to restrict the use of disposables by biopharmaceutical manufacturers. Of the 26 items mentioned, the most frequently cited was a concern about "leachables and extractables", selected by over 71.4% of respondents (an increase over the previous two years). Next came "breakage of bags and loss of production materials" (63%). These factors, along with issues such as "we do not want to become vendor-dependent (single-source issues)", which was noted by 55.8%, relate to the need for greater benchmarking and standards-setting within the industry.

Since SUS directly contact the biopharmaceutical product, apprehension about the possibility of leachables and extractables is understandable. Some vendors are providing data to address regulatory concerns and remove the burden on the end-user of performing lengthy and frequently expensive studies. But in the absence of agreed and accepted standards for doing this testing, end-users are predictably cautious and may still feel the need to do their own testing within their own systems. Among respondents to the 2011 survey, those concerned with the later stages of production were more inclined to do their own testing as the perceived financial risks are greater once the process approaches the final product. Their position might be modified, however, if testing standards were established and implemented by SUS vendors.

Relevant Existing Standards

Regarding leachables and extractables, the role of SUS in manufacture has similarities to that of pharmaceutical excipients (for which the regulatory guidance is also somewhat ambiguous). But with containers and closures, there is a body of regulations and standards.

Disposables also have both raw material attributes (*e.g.*, lot tracking and certification of quality) and equipment attributes (*e.g.*, engineering specifications and drawings, and specific materials of construction). Standards exist covering these aspects, and both the standards organizations and the industry are working to modify them to apply to SUS.

Who Should Set the Standards for SUS?

Most in the biopharmaceutical industry recognize the need for standardization in design, production, and use. However, developing those standards is a complex process in which many organizations take a role including regulatory agencies, industry associations, and standards organizations. A number of these have offered support in developing standards for SUS (*e.g.*, the Bio-Process Systems Alliance [BPSA][2]). The picture is further complicated in that multiple sets of standards are needed for: 1) standards for engineering and design; 2) leachables and extractables; and 3) component manufacturing control (quality).

In light of this complexity, it is not surprising that there was considerable diversity in the responses to questions about which organizations should be responsible for formulating standards for disposables. There was further variation when the respondents were subdivided into end-users and suppliers. The top selections are shown in Table 1. The results most probably reflect a generally poor understanding of what a standards setting body is. For example, the International Conference on Harmonisation (ICH)[3] — chosen by substantial numbers of end-users and suppliers — is an organization focused on "active pharmaceutical ingredients" without any direct relation to the functions of SUS.

In our study, we found that both end-users and suppliers

TABLE 1. Responses to the question: "Which organization(s) should be responsible for setting the various standards for SUS in biomanufacturing?"

RESPONDENTS	DESIGN AND ENGINEERING		LEACHABLES AND EXTRACTABLES		COMPONENT MANUFACTURING CONTROL	
End-Users	ISPE	29.9%	ICH/USP	19.7%	ICH	24.8%
	ASME	19.7%	PDA	16.1%	PDA	8.0%
	ISO	11.7%	FDA	10.2%	BPSA	7.3%
Suppliers	ISPE	37.6%	FDA	36.2%	FDA/ISO	33.3%
	ASME	35.5%	ICH	28.4%	ICH	22.0%
	ISO	21.3%	USP/PDA	24.1%	EMEA	20.6%

NOTE: Percent of respondents in each segment (end-user and supplier) that believe standards should be set by the respective organization.

preferred that the International Society for Pharmaceutical Engineering (ISPE)[4] and the American Society of Mechanical Engineers (ASME)[5] groups provide standards for design and engineering aspects but weren't clear on who should set standards for leachables and extractables. They opted for regulatory bodies (*e.g.*, FDA[6] and EMA[7]) whose function is to provide guidelines rather than establish standards. For component manufacturing control standards, suppliers suggested the FDA or the International Organization for Standards (ISO)[8], whereas end-users chose ICH.

The Standards-Setting Process

It is suggested the industry focus more on industry organizations (comprised of makers, suppliers, and single-use component users) who better understand the challenges associated with design, engineering, leachables/extractables, and implementation of appropriate quality control standards. They should become the leaders in developing and setting the needed industry standards.

In fact, standards routinely originate from the industry organizations and the consensus standards (ASME BioProcessing Equipment [ASME BPE][9] and the Association for the Advancement of Medical Instrumentation [AAMI][10]), and not the regulatory authorities. The consensus standards look to the regulatory authorities and industry organizations to start the process with regulations (*e.g.*, CFR 211.65[11]) and guidelines (*e.g.*, the ISPE Baseline Guides[12], for established and best practices and guidelines). AAMI's standards are increasingly being referenced for sterility assurance of gamma-irradiated components and the ASME BPE for material and component testing.

Unfortunately for this fast-moving sector of the industry, the process to agree on best practices, guidelines and standards takes time for writing, public comment, and publishing.

Who Should Be Responsible for the Testing?

This year's survey determined that 90% of respondents "agreed" or "strongly agreed" that "vendors should generate leachables and extractables data, and validate." This represents an increase from 82% over the past three years. However, that this number declined in relation to later stages of manufacturing where 55.1% said they expect to generate L&E data themselves for Phase III or commercial applications. This likely reflects biomanufacturers' need to reduce regulatory risks associated with leachables and extractables. As noted above, however, this expectation would likely be modified once generally-accepted standards for SUS are adopted.

As far as meeting the costs of testing for L&E, a significant majority of respondents (62.2%) said they would pay 10% more for their disposable equipment if the vendors supplied useful data, and 21.8% said they would pay a whopping 25% more.

Design and Engineering. For setting design and engineering standards, the ISPE edged out ten others by both end-users (29.9%) and vendors/suppliers (37.6%). The ASME followed with 19.7% of end-users, and 35.5% of vendors/suppliers (Figure 2).

Leachables and Extractables. ICH and United States Pharmacopeia (USP) were equally indicated by end-users (19.7%) as the organization best suited for establishing standards in biomanufacturing. Among vendors/suppliers,

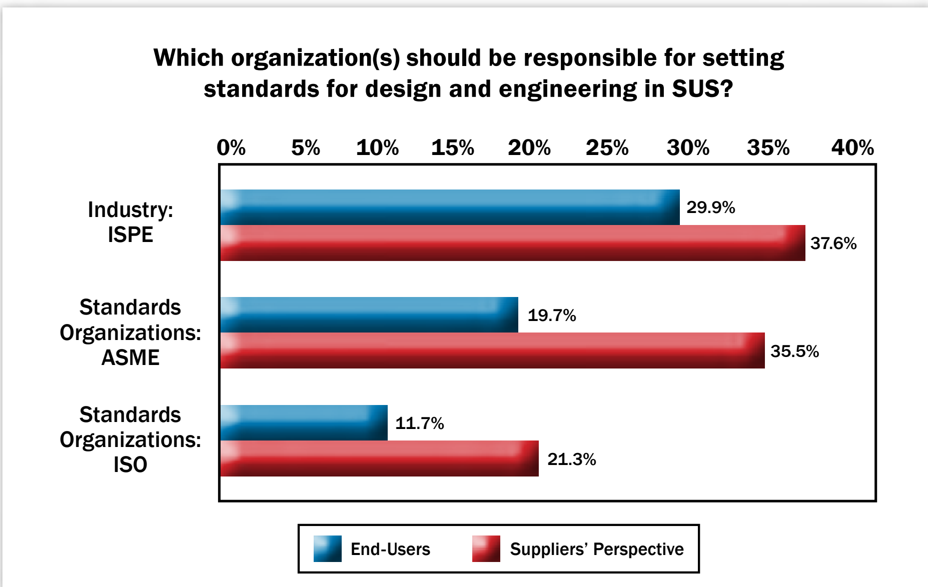

FIGURE 2. Standards-setting for design and engineering—organizations expected to set standards.

28.4% felt that ICH should be responsible for L&E standards, and 24.1% voted for both USP and PDA (Figure 3).

Component Manufacturing Control (Quality). For manufacturing controls, the regulatory body ICH was indicated first among end-users (24.8%) with PDA at a low of 8%. Among vendors/suppliers, 22% stated that ICH should be responsible for the component quality standards. BPSA was noted by 7.3% of end-users and 19.9% of vendors (Figure 4).

Discussion

To date, biomanufacturing has been done predominantly in fixed, stainless steel equipment. Significant capital investment is required to build this equipment and it has to be cleaned and sterilized between runs. The last 10–15 years, however, have seen the emergence of single-use devices (disposables) made of plastic that can potentially perform all manufacturing operations for a lower initial investment. And since there is no cleaning involved, users can achieve faster turnaround times. Already in use by a significant portion of the industry, there is every reason to believe that disposables will increasingly move into commercial-scale manufacture industry-wide.

The current SUS bioprocessing supplies market today is generally limited to smaller bioreactors and other equipment used to support biopharmaceutical manufacture during product development, clinical trials and other product testing. This is because there are relatively few commercial-scale, single-use bioprocessing operations at this time. A high demand for disposable supplies is not there yet. Also, the plastics used in SUS must be proven to be comparably safe to stainless steel-based bioprocessing before any significant changeover can take place. The FDA and other regulatory agencies will expect product applications to include state-of-the-art information relevant to contact plastics' toxicity and long-term safety.

Many drug manufacturers, particularly the larger ones who are the major players in the SUS market, will continue to primarily use stainless steel bioprocessing equipment for commercial manufacture until they can perform adequate due diligence regarding the known and potential hazards associated with SUS contact plastics. What is needed includes: 1) basic toxicological/safety assessments including basic information about plastics' chemistries; 2) breakdown products; 3) known and potential contaminants, unreported additives and manufacturing aids; 4) the actual and potential interactions of these agents with the product; and 5) related toxicology testing and safety assessments. None of these are currently available to biopharmaceuticals producers by SUS manufacturers across the board.

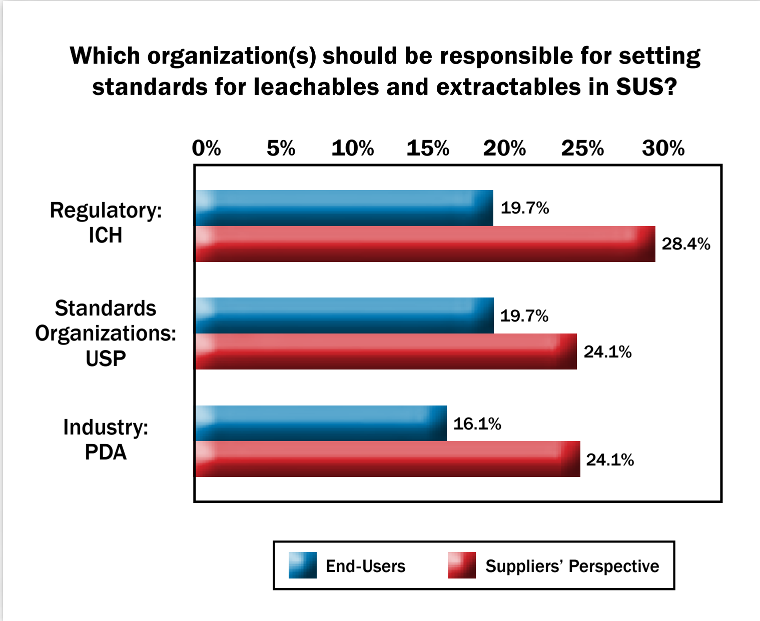

FIGURE 3. Standards-setting for leachables and extractables — organizations expected to set standards.

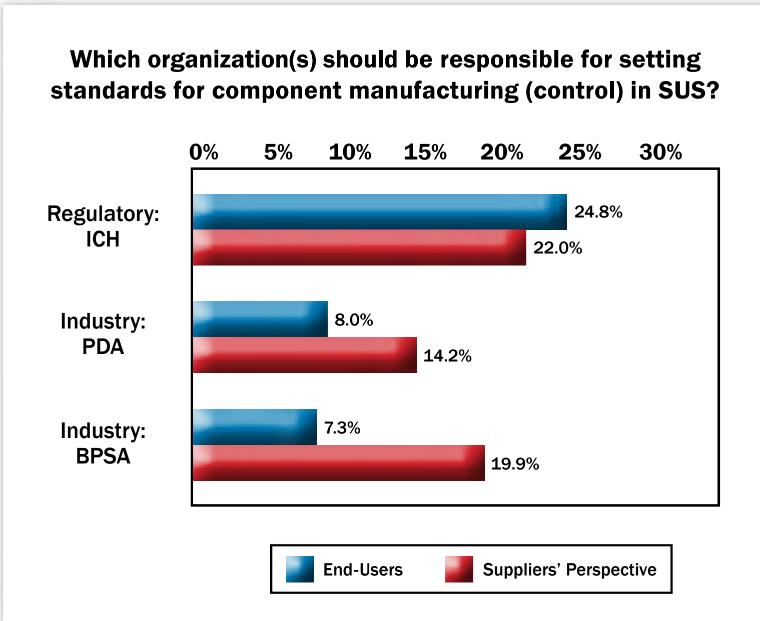

FIGURE 4. Standards-setting for component manufacturing (quality) — organizations expected to set standards.

Entirely disposable upstream processes that can support commercialization are quickly becoming a reality, and now companies are focusing on cost-effective downstream single-use innovations. Even the older, more conventionally-built facilities are considering modifying their infrastructure to support disposables for hybrid, plastic + stainless steel production.

Industry Participants Agree

According to **Jonathan Royce**, BioProcess Marketing Program Leader at GE Healthcare Life Sciences (Uppsala Sweden), there may be too much weight placed on developing proprietary technology in the industry: "There is no true standardization on plastics or connectors. Compared to stainless steel, single-use technology is a complex combination of different polymers, different connection types, and unclear standards." Royce feels that more leadership from the end-users might facilitate standardization of SUS technologies.

Similarly, **Katherine Ulman**, Associate Scientist, at Dow Corning (Saginaw, Michigan USA) recognizes that confusion about setting standards may be limiting growth, and that standards setting should be focused more on both "suppliers and users of single-use components who better understand the challenges associated with design, engineering, leachable/extractables, and implementation standards to be leader(s) in developing and setting their industry standards."

Time will be needed to resolve these issues. Consulting Engineer **James Dean Vogel**, P.E., BioProcess Institute (East Greenwich, Rhode Island USA) notes that the field is quickly evolving and becoming more complicated. "Unfortunately for this fast-moving sector of the industry, the process to agree on best practices, guidelines, and standards takes time for writing, public comment, and publishing."

The lack of well-defined standards for SUS is limiting their implementation, but establishing standards for single-use systems will resolve slowly, just like stainless steel and fittings standards, which took decades to be adequately defined. However, today's plug-and-play type equipment requires more flexibility when establishing standards. Additional standards centered on addressing basic materials compatibility, manufacturing control and consistency, and supply chain security for end-users' drug process documentation are critical.

Decisions surrounding the adoption of new SUS technologies will ultimately be easier when consensus is built around essential standards elements. At that point, suppliers will find the resources to focus more on improving technologies within a rational, standardized framework.

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