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TRENDS & DEVELOPMENTS IN BIOPROCESS TECHNOLOGY

Standards-Setting for Single-Use Equipment in Biopharmaceutical Manufacturing:

An Update on Progress, and the Impact of Standards Implementation

By ERIC S. LANGER

Introduction

Only a year ago, the lack of standards for single-use equipment systems (SUS), as covered in this journal[1], was cited as inhibiting growth in the bioprocessing industry. The need to establish more standardized approaches for single-use devices' design, quality, and leachables/extractables that regulators and industry end-users could accept was slowing the acceptance rate of these novel devices.

In our current study, the *9th Annual Survey of Biopharmaceutical Manufacturing*[2] we find a resumption of growth in the adoption of single-use devices. Our study indicates that part of this is due to increasing budgets for bioprocessing technologies, and the other part is due to advances in standards-setting for the industry.

This year's survey revealed that biomanufacturers (69.1%) are restricting the adoption of SUS due to lingering concerns about leachables and extractables (L&E) in the plastics from which disposable equipment is manufactured. While there continues to be a lack of generally-accepted standards for acceptable levels for L&E or other design and quality aspects for SUS, very significant advances are being made by industry vendors, end-user groups, and regulators (in *Discussion* section). This article summarizes trends in standards-setting and how this movement is affecting overall SUS adoption.

Methods

As part of our survey[2], we questioned key bioprocessing staff associated with 15 areas of biomanufacturing operations. The annual industry report provides analysis and a composite view from 302 responsible individuals at biopharmaceutical manufacturer and contract manufacturing organizations (CMOs) in 29 countries. The survey also encompassed an additional 185 direct suppliers of materials, services, and equipment to the industry.

Each of our yearly surveys analyze trends such as single-use and disposables in detail. We identify variations according to industry segment, process step, as well as geography. The study covers issues including current capacities and future constraints, expansions, budgets, developments in downstream purification, quality management and control, hiring issues, employment, and training. A quantitative trend analysis provides details and comparisons of commercial production by biopharmaceutical developers and CMOs.

The study also evaluates patterns emerging over time and assesses differences in the world's major markets: the United States and Western Europe.

In addition, this article assesses major trends in standards-setting for SUS through interviews with subject matter experts (SMEs) in this field. Specific comments from SMEs are included in the *Industry Experts' Discussion* section.

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Results

In this article, we will present data from the *9th Annual Study* on how evolving benchmarks in the development of standards for SUS devices are affecting the bioprocessing industry. We will also discuss: (a) standards-related factors that are restricting any full-scale adoption of single-use devices; (b) end-users' degrees of satisfaction with vendors in multiple areas, including their use of standards; and (c) which organizations' decision-makers are expected to be responsible for setting the standards.

Standards-Related Factors Impact on SUS

We asked respondents to indicate the factors limiting their implementation of single-use devices. This year, we identified 26 different factors, of which four directly or indirectly relate to standards-setting (Figure 1). As mentioned, L&E continue to top the list with nearly 70% of the industry indicating concern. Similarly, material incompatibility ranked highly followed by the absence of L&E regulatory guidance, and the lack of testing standards.

Despite the repeated appearance of standards as a constricting factor in SUS adoption, we found that this was not considered the most critical factor. Respondents were separately asked, "*Which is your MOST important reason for not increasing use of disposable technologies?*" Their responses were diverse. L&E was the primary concern for 14.4% of respondent. Surprisingly, "*no clear regulatory guidance on leachables and extractables*" was a critical factor for only 4.4%. Even less urgent, "*lack of uniform standards for testing and measuring*" was a primary concern with only 1% of respondents.

SUS Vendor Satisfaction with Standardization

This year we measured 13 areas of vendor satisfaction related to single-use devices. Interestingly, the percentage of respondents indicating they are "satisfied" or "very satisfied" with their vendors' standardization dropped by more than half to 21.1% (Figure 2). This finding is remarkable because during the prior five years, this attribute declined only one or two percentage points per year, until this year. The reason might be that more biomanufacturers are now actively evaluating SUS devices themselves in more areas, and are using them at larger scales (*e.g.*, for later-stage clinical supplies manufacture). When end-users experience difficulties incorporating such devices into their clinical and commercial-scale operations, due to lack of standards, they will rate this factor increasingly lower.

In addition to the question of vendor satisfaction, we asked about the importance of each of 13 attributes to determine the gaps between what is being delivered by SUS vendors and what is important to end-users. By assessing the relative importance of an attribute and comparing that to the level of satisfaction (or dissatisfaction) with vendors in this industry segment, we can identify and quantify gaps between the quality of service and products offered, and the importance of each attribute.

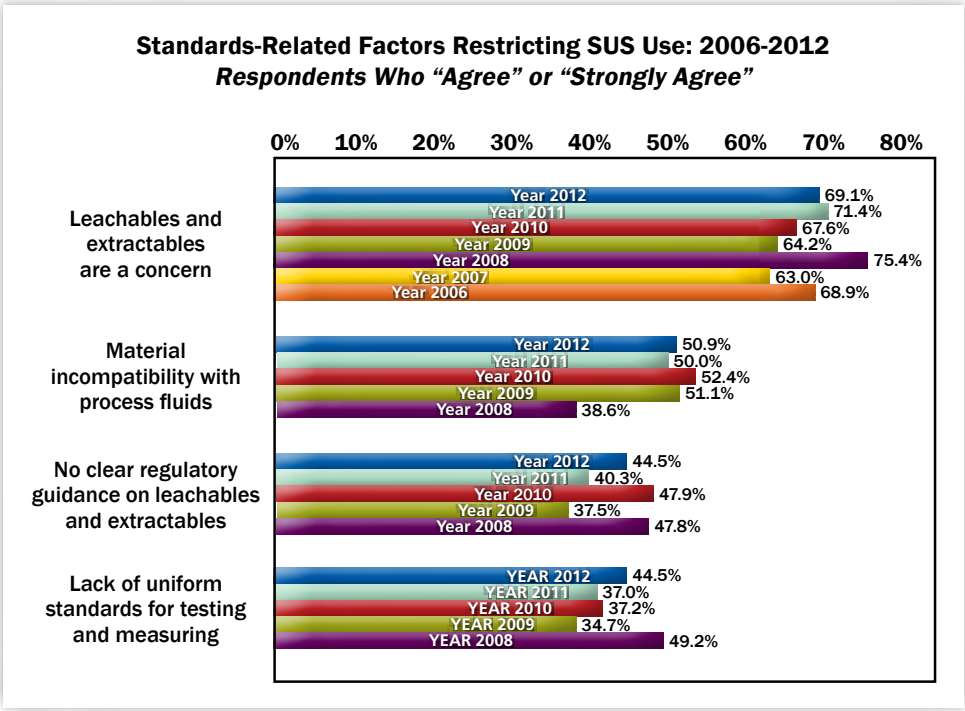

FIGURE 1.

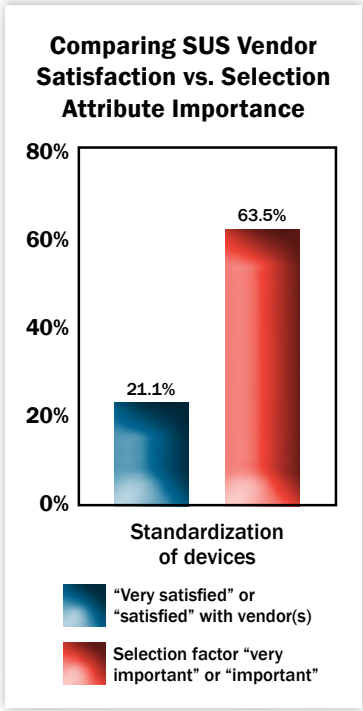

FIGURE 2.

This year, the gap between satisfaction and importance was substantial with an almost 43% point difference. In comparison, the largest gap was in vendors providing L&E data that regulators will accept (a 54% point gap).

Organizations Expected to Set Standards

Many organizations are taking a role in the development of standards associated with the biopharmaceutical industry. When end-users and suppliers to the industry were asked who should set the various standards associated with single-use equipment, we received a surprisingly broad variety of responses. Because multiple organizations can be responsible for standards-setting, respondents were able to indicate more than one group. End-users indicated that the top organizations they expect to be setting standards for single-use devices include: (1) International Society for Pharmaceutical Engineering (ISPE)[3] (41.6%) and American Society of Mechanical Engineers (ASME)[4] (20.8%); (2) Parenteral Drug Association (PDA)[5] (19.8%) and International Conference on Harmonisation (ICH) [6] (18.8%) for L&E standards; and (3) ICH, PDA, and International Organization for Standardization (ISO) (all 11.9%), and Bio-Process Systems Alliance (BPSA)[7] (9.9%) for standards in component manufacturing (quality) (Figure 3).

We also compared the perceptions of suppliers and end-users in terms of who should be setting standards for various aspects of SUS devices. This year, there was significantly more general agreement among the two groups regarding who should be setting standards for design and engineering standards, with ISPE and ASME taking the lead with relative consistency (Figure 4).

Standardizing Single-Use Designs

Also, this year, we asked respondents to identify areas where they expect vendors to standardize their devices more actively. Not unexpectedly, connectors were the area where users sought the most standardization (Figure 5). This would permit interconnectability between various components and different vendors' devices. Overall, this plug-and-play approach may increase the adoption rate of single-use systems but would require a degree of coordination on the part of global vendors (with most having to abandon their proprietary connection systems in favor of those from competitors). Connectors were "important" or "very important" to over 92% of respondents. Similarly, materials used in bags and tubing were high on the list of products for vendors to standardize. This would help to facilitate the development of regulatory documentation.

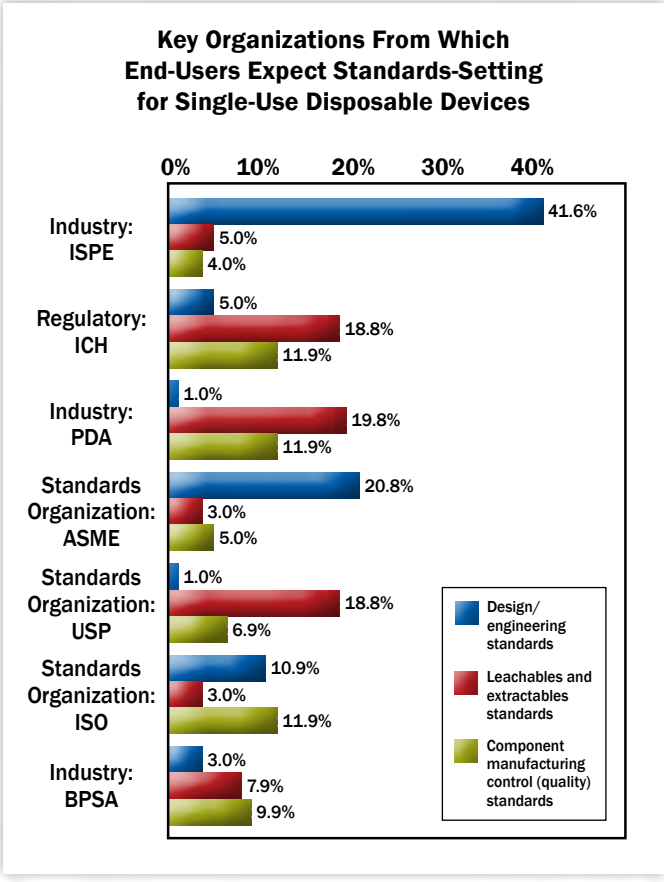

FIGURE 3.

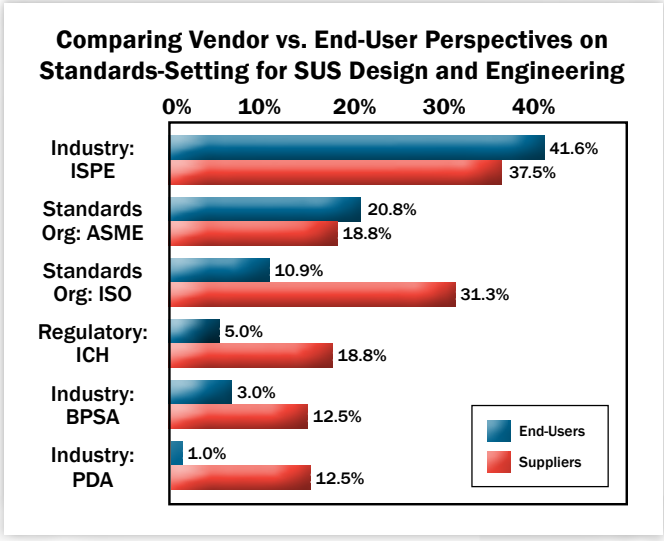

FIGURE 4.

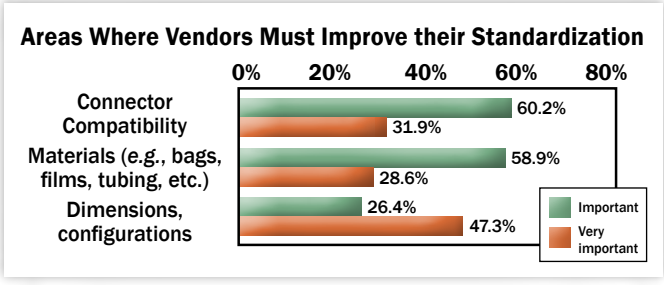

FIGURE 5.

Discussion

Until recently, biomanufacturing had been done predominantly in fixed, stainless steel equipment, even at clinical scale. This is changing and the last 10-15 years have seen the emergence of single-use devices made of plastic that now perform all manufacturing operations for a lower initial investment with faster turnaround times.

Perhaps as a result of these advances, industry pressures for setting standards are increasing. Yet, even the definitions associated with standards-setting are not fully agreed on. Jerold Martin, Senior Vice President at Pall Corporation, BPSA Chairman of the Board, co-author of numerous PDA and BPSA guides and standards for American Society for Testing and Materials (ASTM) International[8], ISO[9], and ASME BioProcessing Equipment (BPE)[10] states, "*It means one thing to 'standardize' on a particular component, design, method, or practice, but that is not the same thing as a recognized industry 'standard' that specifies a particular design or methodology.*" Even with reverse-engineering (copying), in the absence of a published standard for a design, not all standardized devices are interchangeable. One example would be the tri-clamp flange-style of hygienic fittings. Martin notes, "*Industry consensus and reverse-engineering came first and then it took another ten years for ASME BPE to publish a true 'standard' for dimensional specifications and tolerances.*"

To date, no actual standards have been developed for any single-use component. Martin notes that BPSA Guides, PDA Technical Reports, ISPE Good Practice Guides, and US Food and Drug Administration (FDA)[11]/European Medicines Agency (EMA)[12]/ICH Guidelines are not standards but rather provide recommendations and focus on best practices for the use of SUS. Legally-recognized industry bodies that write official standards applicable to bioprocessing include the United States Pharmacopeial Convention (USP)[13], European Pharmacopoeia (Ph. Eur.)[14], ASTM, ASME-BPE, and ISO. Of these, only ASME BPE is developing a standard for single-use manufacturing. The content tends to be generalized and related to best practices more than design standards for specific components. The one exception, says Martin, is the ASME-BPE subcommittee revision of the hygienic fitting (tri-clamp) standard to better accommodate molded polymeric adapters.

The industry continues to find selection, qualification and validation of single-use components a challenge. True standardization would help reduce the need to assess different materials and designs. This would also tend to shift responsibility for some design aspects such as materials selection from device developers to standards-setting bodies.

Industry Experts' Discussion of Standards-Setting

SUBJECT MATTER EXPERTS:

We asked key experts in bioprocessing with knowledge of the impact of standards to comment on the recent trends and discuss the future of the industry. Experts included:

- ***Jay Ankers***, Principal at LifeTek Solutions, and Chair, ASME BPE
- ***Paul Priebe***, Director, Fluid Management Technologies, Sartorius Stedim Biotech North America
- ***Jerold Martin***, Senior Vice President at Pall Corporation, Chairman of the BPSA board
- ***James Dean Vogel, PhD***, Principal Engineer, President and Founder, The BioProcess Institute

INTERVIEW SUMMARIES:

(1) Development of standards for single-use devices in bioprocessing has moved forward steadily over the past few years. However, work is still needed.

a. What have been the most substantive recent advances in standards-setting?

Jay Ankers: The most significant advance in the last five years is the concurrence and agreement by developers, inventors, and producers of single-use devices and materials that industry-accepted standards at this early phase in their development are needed. End-users need uniformity and control in the production of the devices and materials they use in their processes but the industry needs new technology and development of novel designs. We are, as a group at ASME BPE, finding that balance. Specific examples are standards around the leachables and extractables as well as the particulates generated from use of polymeric materials and other nonmetallics. Level of sterility of single-use devices and their materials is as important as it is for stainless steel and other multi-use materials.

Jim Vogel: Extractables and leachables have led the way for standards. The BPSA, ASME BPE, PDA, ASTM, and ISPE, all have active teams working on this. The BPSA first published their recommendations in 2010, ASME BPE enhanced their content for their 2012 edition, PDA has held workshops and are drafting a document, ASTM has a document, and ISPE is planning to include it in their Disposables Baseline Guide.

Paul Priebe: The biggest advance regarding standardization is the beginning of a substantive

dialog between the end-user community and the supplier base. To that end, the BPSA will play a definitive role in the coming years to foster this dialog and ensure that the energy on this topic continues. BPSA will not become a standards writing body, but rather will bring the industry together on the right topics within the best standards writing body to bring the particular area of standardization to realization.

Jerold Martin: The most substantive and impactful advances in best practice standards in the past two years have come from the BPSA Guides on Quality Test References, Extractables and Gamma Irradiation originally published in 2008–2010. PDA, ISPE, and ASME BPE are making advances in developing complementary best practice guides that will be published in the coming year.

b. What areas remain the most challenging in terms of establishing meaningful standards?

Ankers: Single-use technology (*i.e.*, materials, shapes, component designs, etc.) are proprietary and by design, they are relatively easy to change, replicate/copy, improve. Developers need to maintain their intellectual property to protect the competitive edge they deserve. End-users, by a large margin, will not choose to develop a process around other's proprietary designs and materials and put their supply chain in the hands of one supplier. These two competing needs create a roadblock to the standardization of cost-effective, single-use materials, components, and complete systems.

Vogel: The first challenge is to continue discussions. There is concern about the term "standards". It means different things to members of the single-use community. End-users want a level playing field to evaluate different options, and vendors want to preserve their competitive advantages. We need to do the right things to help the industry evolve to best meet the needs of patients. The second challenge is to develop agreement on how to compare options. Standard testing methods, acceptance criteria, etc., would assist the end-users' ability to compare different offerings. Single-use technologies have unique limitations and cannot always utilize existing methods (*e.g.*, pressure testing). Methods include:

- A standard panel of routine buffers/solvents which represent the majority of process applications.
- Particulate expectations and capabilities: the BPSA is leading this discussion to address what are the requirements of the end-users against what are the capabilities of the vendors.
- Integrity—how to define the integrity of a SUS is important. They are not as robust as traditional steel systems and can easily be damaged in setup. This is more of an integration of vendor and end-user quality systems.

A third challenge is connectors. Many vendors have their own connector and do not permit inter-connectivity.

Priebe: There is a lot of enthusiasm on the topic of standardization but no consensus yet on a definition of what we mean. We can talk about standardization of qualification tests, specifications, technical designs, technology, or materials. Each area has benefits but also presents the potential to stifle innovation. We need to build consensus between the end-users and suppliers on what we mean by standardization, which area should be worked on and what area should be left alone for now.

Martin: While best practice standards (*sic*, recommendations) are being developed, design standards will be the most challenging. For example, sterile connectors, unlike the tri-clover hygienic flange connector, are based on patented technologies that cannot be established as "standards" until patents expire and the users come to consensus on which design should be the standard. Standardization (either written or otherwise) of biocontainer film formulations and 3D/tote geometry will also require industry consensus before suppliers can standardize. To date, it has been difficult for users to even standardize (establish consensus) internally on system components and configurations within or across facilities. Suppliers cannot make those choices for them, though even suppliers would prefer to reduce the number of components and configurations that must be built.

(2) When SUS standards are implemented:

a. How will they specifically affect bioprocessors' decision-making, etc?

Ankers: Standards will shorten the time a developer of a novel material or design can benefit from their invention. However, it also shortens the amount of time it takes an end-user to qualify a supplier. Standards tend to have a more positive effect on the end-user than they are for the truly "novel idea inventor."

Vogel: Standards will allow a level playing field. Product offerings can be compared side-by-side and decisions can be based on sound business and science reasoning.

Priebe: The standardization to be taken on in the early work will likely be the easiest to implement with the least IP held by the supplier base that solves real implementation hurdles. This "low hanging fruit" is what we need to pick first, to learn how to do this work, build trust and then move on to tougher topics. The best standards are the ones that prevent the reinvention of the wheel with no added value. Good standards will allow bioprocessors to focus their energy on the value-added activities of GMP implementation of single-use technologies faster and at less cost than multi-use technologies. My view is that standard qualification methodologies and specification formats is an area where we could readily achieve something that would simplify implementation for end-users. This would prevent an end-user from inventing his or her own method of evaluating a single-use technology for fitness for use and get right to a quick assessment based upon a standard data package.

Martin: Those users who are reluctant to implement single-use due to sole sourcing and supply concerns may be more willing to adopt it if multiple suppliers can be qualified more easily. For those already committed to single-use, it will lower their anxiety in the choices they've made and about supply chain robustness.

b. How will SUS standards benefit the industry as a whole?

Ankers: Standards have the effect of putting uniform quality and potentially safer materials and devices into the hands of end-users. This is true for both production scale and development scale. The side effect may be that small inventors and suppliers will not be able to profit from their work, making development of novel ideas less interesting (less profitable). And small companies often have some of the best ideas.

Vogel: Standards will allow the industry to mature. It will become an industry based on the ability to evaluate performance. Standards will define what is important and how to measure performance. This will free up the technologists at both vendors and end-users to apply single-use technology to address the process issues which they are uniquely able to do.

Priebe: The underpinning benefits of single-use technology have been proven many times over and it has now become the default choice for many applications. In the past, we spent a lot of effort justifying the decision to go single-use. That doesn't happen so often anymore. Now we need to shorten the implementation timeline and allow a real expansion of existing processes using multi-use technology. This combined with implementation in new processes will trigger a growth rate of the SUS industry that is double or triple the baseline growth rate of biopharma.

Martin: For users, multiple sourcing of standard components provides more security of reliable supply and cost-competitiveness, can reduce qualification and validation effort and expense, as well as reduce inventory costs. Suppliers can benefit by reduced production costs of system variants. On the other hand, standards for component design and materials will inhibit future innovation and may be premature at this stage of implementation.

Summary

The development of standards for single-use devices in bioprocessing is critical to the advancement of these novel devices. Over the past five years, developers, inventors, and producers have increased their dialog and have recognized the need for a balance between the end-users' demand for greater uniformity and the suppliers' need to protect and foster innovative technology and better designs. Documents and recommendations are being developed by numerous organizations to provide this balance.

However, many areas of standards development remain challenging. Single-use designs are proprietary and developers need to protect their intellectual property. Yet end-users will not accept becoming locked into a single supplier even if a particular vendor has the best design and product. Thus, the industry continues to wrestle with building a consensus between the end-users' need for consistency and the suppliers' need to avoid stifling of innovation.

As SUS standards are implemented, there is general agreement that they will positively affect both end-user decision-making and will likely increase adoption of innovative devices. Standards will shorten development time for novel materials and designs and will shorten the time for end-users to qualify new suppliers — leading to more and better (healthy) competition. Standards will allow more effective product comparisons, reduce repetitive inventions by competitors, and simplify GMP implementation of single-use technologies. SUS standards will benefit the industry as a whole by establishing uniform quality and performance which will help enable better process monitoring, reduce validation costs, and shorten end-user implementation timelines. This will increase growth rates for the SUS industry and ultimately permit more cost-effective biologics manufacturing by more drug innovators at more facilities around the globe.

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