Road Map to Implementation of Single-Use Systems
A BPSA White Paper for Manufacturing Decision-Makers within End-User Organizations

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The Bio-Process Systems Alliance (BPSA) is an organization of equipment suppliers, service providers, and users in the biopharmaceutical industry whose shared mission is to facilitate implementation of single-use technologies in biomanufacturing processes. A key focus of BPSA’s core activities is to educate users and develop guides that help safeguard the quality of drugs and therapies produced with single-use process technologies.

As an extension of its technical guides and white papers, BPSA realized the importance of developing a white paper that provides a high-level understanding of single-use systems to an audience of manufacturing decision-makers within end-user organizations. For an overview of what is contained here, please see the “Implementation” box on the next page.

Section One: Perspectives on the “New” Pharma Market
Single-use systems (SUS) are gaining wide use and acceptance in the biotechnology and pharmaceutical markets. As our first publication to address the topic from this perspective, we anticipate that this initial publication will be an evolving document that BPSA will address with future papers and more detail as the needs of the market evolve.

Why have SUS generated so much interest in the biotech and pharmaceutical markets? Fundamentally, the commercialization of new drugs and therapies occurs at only a fraction of a percent for every project that is initiated from an initial DNA molecule. Because the odds of a project going from concept to full commercialization are small, a need has been created in the market to test as many concepts as possible with the least amount of cost given the current market conditions in capital expenditures. No one wants to spend hundreds of millions of dollars on a facility that may never produce a commercial product. The business model based on discovering the next blockbuster drug is evolving toward a more personalized approach because it is becoming clearer every day that one pill will not cure all patients.

It is not often that we get to witness the beginning of a real paradigm shift, but preferences for SUS over traditional glass and stainless steel systems are unfolding. Stainless steel systems will not be completely replaced by single-use systems, but the benefits of single-use create many options to enable this transition, including the following:

- There is a need for greater flexibility, speed, and safety in development and production of drugs and biotherapies. As medical approaches become more personalized, a reduction in the “one pill fits all” mentality is already taking hold.
- Increased review criteria by the US Food and Drug Administration (FDA) are already reducing drug approvals.
- Less capital is available for research and development activities.
- Blockbuster drugs are a rarity now, and no one can afford the inefficiencies in discovery with high capital costs. Patent expiration and
SECTION TWO: WHAT IS SINGLE-USE?
As we look into the future of single-use technology and realize the benefits these components, devices, and systems can offer, understanding the past is critical. How did we get to the point of single-use implementation today, and what is the history behind these polymers and plastics and their benefits? When we understand where we often see single-use polymers used, what the key components are, and how they are traditionally supplied, we can make better sense of what the pathway forward looks like. This will also provide us with capabilities for bringing about faster solutions to currently incurable diseases.

History of Polymers in Biomedical Applications: Over the past few years, flexible polyvinyl chloride (PVC) bags have for the most part replaced the use of glass bottles for storing blood and its components. Blood bags enable greater sterility than glass in both the separation of blood components and the safer transfusion of components. With single-use blood bags, companies reduced contamination and the costs of washing, sterilization, and overall manufacturing. That led to increasingly wider use of blood-component therapies than of whole blood use, thus enabling more effective use of scarce donor blood.

As such PVC bags became more of a standard in the medical device marketplace for IV and intravenous blood/plasma applications, a natural evolution of this “new” technology spread into parallel markets. Individuals found new areas in which they could implement these systems — as storage containers for buffers, cell culture media, and cell harvesting, for example. SUS started to gain a greater acceptance, increasing the diversity of products manufactured with them and of redesigned processes based on shorter, multiproduct runs.

Benefits of Using Polymeric SUS: If we look at the benefits of polymeric materials over stainless steel, we find the following:
- Polymeric components used in container systems are comparable in strength, yet lighter and more cost effective than stainless steel (3).
- Using polymeric components in biopharmaceutical processes brings distinct advantages over stainless steel by reducing the risk of corrosion and long-term degradation of malleable parts.
- These materials also are chemically resistant (compatible with most acids and bases) and biologically inert for use with most biopharmaceutical products.
- The smaller footprint, greater flexibility in design, and lower costs — therefore, the ability to start up a facility at a fraction of the traditional cost anywhere in the world — also have contributed to the acceptance of polymers for these applications.

Furthermore, the United States Pharmacopeia (USP) Class VI-grade plastics are an ideal replacement for stainless steel, other types of metal tubing, and even glass for weight reduction, comparable strength/mass, chemical resistance, hardness, and low levels of extractables.

Benefits of SUS: Understanding that polymers can be comparable to stainless steel in the biopharmaceutical industry provides product solutions for improving operating costs, speeding validation cycle times, reducing contamination, and improving product yield. When we take a deeper look at the benefits single-use products and systems can offer, they can be broken down into four broad categories:

Cost Effectiveness and Economic Advantages: They reduce capital expenditures and facility footprints.
Safety and Quality: They reduce cross contamination, product loss, and cleaning validation while improving sterility assurance.
Operating Efficiencies: They reduce labor costs, facilitating implementation through faster batch turn-around and product changeover, improving process flexibility and speed to market.
Sustainability: They reduce use of water, utilities, and chemicals.
Vendor Availability: Sufficient, qualified vendors exist to supply and...
service SUS.

Section 5, “Economic Advantages of SUS,” covers the benefits of SUS in more extensive detail.

**SUS Parts and Components:** With the advantages SUS can offer, availability of single-use components continues to increase. Today’s SUS can contain one, all, or a few of the following products: tubing, filters, filtration in general, bags, fittings, sterile connections, sensors for monitoring pH, O₂, CO₂, pressure, temperature, and many other containers such as bottles, carboys, flasks, and centrifuge tubes. As the needs and requirements from FDA and other governing bodies grow stronger, the need to monitor process conditions also gets stronger, therefore setting up needs for more unique single-use products each day.

**SUS Applications:** Just as the number of available components has increased for SUS over the years, the areas in which such products are used have also increased. SUS have found their way into the biopharmaceutical market with buffer storage, media storage, and cell harvesting. Today, we see these same products used in manufacturing operations upstream (single-use bioreactors/fermentation and media preparation) as well as downstream (direct filtration, purification, formulation, and final fill). Moving forward, the same products are now being specified into new areas such as chromatography, mixing, seed train, and tangential filtration.

SUS can offer significant benefits in direct manufacturing and contract manufacturing operations and toward debottlenecking processing challenges. Adapting and implementing innovative single-use technologies will help make our industry more competitive in the new global economy.

**SECTION THREE: The Design and Business Case for SUS**

Some basic questions can help you begin to evaluate the role that SUS can play in your operations.

**How can you integrate SUS into existing clean-in-place (CIP) for your operations?** The many hybrid systems on the market help make the transition from traditional stainless steel systems to SUS. However, conversion of old systems to hybrid systems should be viewed only as an intermediate step if sufficient cost savings can be identified and if capital expenditures require such a change. Otherwise, it usually is best to design the flexibility and cost savings associated with SUS into a platform for new drug research and discovery.

**Are you trying to convert a legacy drug or new drug or vaccine in development because that will be a different “look” in implementation?** The type of system to choose will greatly depend upon the number of legacy drugs and therapies that your company currently manufactures. It is clear that no one wants to make a change to a process if its 510(k) has been recently submitted or the product has been approved and is making billions of dollars using a traditional system. New applications and products are the best bet for implementing SUS into your company. Many SUS providers can help provide additional detail on the difference between your past system experience and a new SUS platform.

**What are your needs regarding scalability?** If you are installing hybrid or single-use containers in the same “footprint” as a 10,000-L stainless-steel system, how will this affect your overall operating flow of personnel and materials/product?

**Do you have the option of designing a new facility that is 100% disposable based?** Modular facility designs are becoming increasingly popular; if you need to design for a multiproduct, multiscale facility, modularity may fit into your plans very well.

**Do you fully understand your application and what your product is going to be?** It is important to ensure that you aren’t embarking on an overkill or underkill with your design.

**What are your options for SUS implementation?** Options range from designing and developing your own SUS to purchasing a turn-key system.

**How do you make a business case?** SUS are good choices for CMOs and smaller biotechs. A product-lifecycle assessment (not looking only at steam-in-place, or SIP, and CIP) needs to evaluate the overall impact (e.g., disposal, environmental impact of cleaning water) of SUS implementation.

**How do you ensure business continuity — managing risks both upstream and downstream — during the potential change?** Supply chains and the security of supply are critical. You also need to address in a positive way the pushback from single-use vendors to standardize their offerings. At this point, what is meant by standardization has yet to be adequately defined. Companies should still explore options for dual sourcing.

**What factors influence your “make or buy” decision?** As mentioned, SUS fit in well with CMOs and smaller biotechs. Manufacturing with SUS is not as straightforward as it seems: Stainless steel manufacturing is commoditized to some point, whereas SUS manufacturing is specialty/limited to experienced/credentialed vendors because there are no BPE/ASME guidelines for plastics like there are for stainless steel.

**How Do You Identify, Evaluate, and Validate Vendors for SUS?** Does the vendor have experience? What qualities are you looking for in a vendor? Will the vendor provide you with a data package as to what it already has available? How do you ensure continuity of your supply chain? What systems does the vendor have in place in case of an interruption in supply? Will the vendor inform you if its own suppliers change? What are the pros and cons of dual sourcing?
**SECTION FOUR: SUS MARKET TRENDS**

As the market for SUS continues to evolve and grow, a number of changes are anticipated. The actual bioproduction landscape is changing through increased receptivity to biosimilar development, achievement of higher titers, and modifications in the way drugs are produced, especially through use of platform technologies. Many companies are moving away from their previous expectations of blockbuster drugs toward modular plant design and production of smaller lots. Efficiency improvements through inline dilution are resulting in an almost tenfold liquid volume reduction, so many earlier limitations in scalability no longer exist (1). Basically, if you can make the same amount of product and use only 10% of the liquid volume, there is no need to scale up to 15,000-L reactors when a 1,500-L reactor will suffice.

**Reference Point:** As a reference point, when making a new drug or therapy, a company can commit between $500 million and $1 billion dollars with no guarantee that the product will be relevant after three to five years.

**Paradigm Shift:** The bioprocess industry is seeing a paradigm shift similar to what occurred in the steel industry. Years ago large mills produced steel. However, the industry shifted away from large-mill production to miniature-mill production, and much of the market ended up going overseas where companies were not bound by existing infrastructure. The flexibility and smaller capital investment required made the mini-mills take over from the large mills. A similar shift is being seen in the bioprocessing industry today.

**Conversion Issues:** Some big biotech companies may find it hard to convert to new systems today because large capital expenditures (CAPEX) have already been committed. However, these companies may discuss a switch to SUS as new CAPEX become available. Pressure to cut costs, the shrinking of margins, and the increased global competition from low-cost regions are driving the conversion faster in parts of the world not already laden with $0.5–$1.0 billion facilities.

From the perspective of industry trends, SUS are today at the forefront of design and implementation of new processing lines and new product manufacturing. The costs associated with equipment purchase and set-up of “traditional processing” lines are similar to the costs associated with SUS. The key cost reductions are in operation of those lines once they go into production. Studies are showing that costs related to testing, validating, and implementing line preparation and reuse using traditional stainless-steel systems are proving to be higher than those using SUS for similar steps.

As current traditional manufacturing systems approach an age where significant equipment repurchase must be done or a line must be upgraded to improve efficiency or output, the transition to single-use manufacturing lines will increase. In addition, as the need to produce needed new drugs or therapies quickly (e.g., to produce H1N1 vaccines), the process flexibility and speed-to-market benefits of SUS will continue to grow in popularity.

As more suppliers of SUS become available, costs associated with SUS components will become even more attractive and competitive. The greatly increasing move toward SUS is attracting more SUS component suppliers and forcing present suppliers to expand capacity — all of which will be needed to meet increasing demand.

**SECTION FIVE: ECONOMIC ADVANTAGES OF SINGLE-USE**

Once your company has decided to investigate single-use technology for its manufacturing process, the good news is that major economic benefits can help justify implementation. These benefits have been validated and in some cases, originated by companies that have already used SUS in full production operations.

From the April 2009 edition of *BioProcess International*, Figure 1 depicts the top reasons to consider using single-use technology as part of your drug production process (4).

Eliminating cleaning requirements has been the leading factor in the shift to SUS over the past two years. SIP, which is a method in the pharmaceutical industry for in-line sterilization of processing equipment, is an expensive and labor-intensive process that companies can eliminate by adopting this new technology. An SIP process can take days to weeks to complete in compliance with a company’s validation plan for the FDA. That results in significant downtime while setting up new production lines up or switching to a new campaign. By eliminating SIP, companies see a savings in natural resources in addition to the economic benefits discussed here. No longer will you need to heat hundreds of gallons of water to clean legacy stainless steel equipment and to put that water into waste treatment facilities. Today, SUS offer a better solution that plays hand-in-hand with the trends of personalized medicine, rapid campaign turnovers, and green technology.

In a survey by *BioProcess International* (2), 72.9% of the respondents indicated that they achieved savings by using SUS.
technologies over other alternatives. One large pharmaceutical company saved 1,500 staff hours normally performed as part of the SIP process by using SUS rather than stainless.

Because all single-use surfaces that contact flow-path material throughout processing are replaced rather than steamed-in-place after each campaign, the risk of cross contamination is significantly reduced. This provides a strong appeal to regulatory and process personnel responsible for overseeing FDA validation. This reason alone can justify the switch to SUS. Some companies are moving to hybrid configurations with a mixture of single-use and stainless steel components. This tactic is influenced by comparing the economics of validation savings with the expense of converting subprocesses to single-use technology, delaying purchase of the most expensive pieces of SUS technology until they can be fully cost justified. In the BPI survey (2), 82.9% of the respondents are specifying some form of SUS into their process. Another consideration is that SUS also help eliminate the appearance (and associated costs) of false positives due to cross contamination because fluid-path components are used only once.

Working with single-use products rather than legacy stainless steel equipment also presents a savings in time — realized both at the time of initial factory or line startup as well as by shifts from one campaign to another. With current discussions involving pandemic outbreaks, single-use technology is an ideal solution for setting up production facilities or new production lines in a rapid-response deployment. Companies have displayed the ability to shift to a new campaign in a matter of days with SUS rather than weeks involved with cleaning and validating stainless steel equipment. This time savings has increased as facilities and even production lines have become multidrug focused rather than focused on making the same blockbuster drug at one facility for an extended period of time.

The capital involved in a new plant or expanded production capability is significant. In a recent large pharmaceutical case study comparing a stainless steel to SUS option, the capital investment for the traditional hardware operation was in excess of US$2M. Given the emerging trend for smaller, more flexible plants, process engineers are looking for investments that offer greater cost efficiency and shorter return on investment (ROI) payback periods. The traditional stainless steel facility can take up to eight years to be brought on-line from design through validation. Because the industry believes that most big blockbuster drugs are already in production, long-lead-time projects just don’t make sense in today’s competitive marketplace.

These economic advantages (and others not discussed here) explain the strong interest in SUS and why more than 60% of contract manufacturing organizations (CMOs) have readily implemented the technology. SUS has gone from a future technology to the mainstream in the course of the past year.

**Savings in Cleaning Costs:** The following example is provided of an anonymous pharmaceutical manufacturer who decided to evaluate and then implement SUS. This manufacturer realized savings in cleaning costs, reduced leak incidents, and reduced contamination.

A study was conducted on the internal cost assigned to cleaning and related validation. With permanently installed traditional systems, the company was required to follow highly documented and controlled standard operating procedures every time. Periodic and annual cleaning verification studies were required as well as periodic and annual cleaning validation studies. The company determined that by implementing SUS systems, internal cost savings site-wide on items related to cleaning and cleaning validation could be reduced by several million dollars annually.

**Reduced Leak Incidents:** Well-documented leak incidents using permanently installed traditional systems revealed significant lost revenue from mandatory leak incident investigations. Not only can an expensive batch of product be quarantined and eventually scrapped, but the labor required to complete an investigation can significantly affect productivity. A leak incident often demands personnel resources and time that can hurt production schedules and reduce the revenue/labor ratio significantly. This is often hidden lost revenue, but is lost revenue nevertheless.

**Reduced Contamination:** Procedures for cleaning and cleaning validation are designed to reduce the risk of batch contamination from substances or cross-contamination. SUS eliminates the risk of batch cross-contamination. Working with properly validated and audited SUS suppliers greatly reduces the risk of contamination from substances in the system. A single incident of batch contamination due to cleaning problems can cost as much as $10,000,000 in lost product. This does not include the cost of the necessary investigation.

**Section Six: Challenges of Implementation in Production**

Even with the documented operating and economic benefits provided by adopting single-use technologies, some facilities struggle to make the transition from traditional stainless steel systems. Figure 2 outlines the top reasons why some manufacturers have not yet integrated single-use technologies into their existing processes.

Although the percentages changed from 2008 to 2009, the largest barriers remained consistent. Here we address strategies for how your company could address each of these areas.

**No Experience:** A wide range of industry professionals are available to help companies that have limited experience implementing disposables. BPSA members both from supplier and end-user communities can provide valuable knowledge on justification and implementation of...
single-use into new or existing facilities. Design firms and consulting companies can also provide integration expertise. Vendors can be an excellent resource in their areas of expertise.

**Existing Investment in Stainless Steel:** Gaining the benefits of single-use technology does not require a complete conversion from stainless steel. Many companies have successfully combined SUS with existing stainless equipment to create flexible and cost-effective facilities that can manufacture a wide range of products.

**Process Scale Exceeds Disposable Technology:** Today there are limitations on the scale at which certain single-use technologies are available, especially as a process moves to volume production above 10,000 L. Two factors help address this concern. The first factor is the continued development and introduction of single-use components and systems with higher flow rates and holding capacities. Second is the trend toward higher titers, which allow smaller lot production (1).

**Concerns About Validation:** Many single-use technologies have been validated by manufacturers in upstream and downstream processes. BPSA has published best-practice documents for testing of connectors, tubing, filters, and films that can be used as a guide in developing appropriate validation procedures (5). Suppliers and industry consultants are available to help manufacturers validate components and systems.

**Extractable/Leachables:** Of strong interest and concern to the biopharmaceutical industry over the past few years, a great deal of work by both suppliers and end-user has gone into understanding and addressing extractables and leachables testing. BPSA has a technical committee specifically dedicated to leachables and extractables that has published articles and presented extensively over the past three years. For more information, contact BPSA (contact information is provided at the end of this article).

**Environmental Concerns:** Although the terms disposable and single-use can raise questions about sustainability, conversion to these technologies can actually reduce a company’s carbon footprint when compared with traditional stainless-based production (6).

**Concerns About Integrity:** Manufacturers must remain rigorous in their concern about the integrity of their entire processes to assure sterility and safety of final product. The overall growth in implementation of single-use components and systems testifies to the reliable manufacture of such systems. Thorough validation programs and vendor qualification are key aspects to assuring that you are working with high-quality products from reliable suppliers.

**Animal Origins:** Although not included in Figure 2, apprehension over BSE and TSE has led to concern over use of animal-derived components in manufacturing and processing of polymers that contact bioprocessing fluids. Animal-derived components in polymers commonly come from stearates rendered from tallow and used as processing aids to prevent polymeric materials from sticking to metal equipment during extrusion or molding. In response to related concerns, SUS are increasingly being constructed from animal-derived-component-free (ADCF) materials. When ADCF options are unavailable, polymer manufacturers should document that source and processing parameters for tallow-based additives meet or exceed EU standards (7).

Although potential challenges do exist in implementing SUS, most common barriers can be overcome by taking advantage of internal or external expertise. In addition to using supplier support, a number of manufacturers have hired or developed internal experts in disposable technology and even introduced corporate-wide blogs or Web pages dedicated to single-use technology.

**Section Seven: Work Continues**

By now you should have a clear understanding of the benefits of single-use technologies. Clearly there are many compelling reasons to implement SUS in your operations. You are very likely already developing a set of assumptions about the utility and advantages they provide.

The BPSA will continue to be at the forefront of single-use trends. The “For Further Reading” list highlights some documents already available on the BioProcess International and BPSA websites. Further studies and white papers will build upon the organization’s previous work toward developing guidelines about extractables and leachables, irradiation and sterilization, disposal, and component
test matrices.

REFERENCES


FOR FURTHER READING


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