SINGLE USE (SU) TECHNOLOGIES IN BIOMANUFACTURING

North Jersey Section AIChE

Fall Kick-off - Meeting 1

September 24, 2019

YOUR PRESENTER:

- Peter Sibilski, P.E., CEM, FAIChE
- Plant Manager, Pharmetic Manufacturing Co., LLC
- B.S., Chemical Engineering - NJIT
- MBA, Technology Management - University of Phoenix
- Member, Industrial Advisory Board, NJIT Otto York Dept. of Chemical and Materials Engineering
- Work experience includes:
  - Diamond Shamrock – specialty chemicals
  - Occidental Chemical – specialty chemicals
  - Henkel Chemical – specialty chemicals
  - Olin Hunt – microelectronics chemicals
  - EI Associates – A/E consulting
  - BOC Gases – industrial gases
  - Schering-Plough - pharmaceuticals
  - ALZO International, Inc. – specialty chemicals

ATTRIBUTIONS

Some information presented on these slides was obtained from:

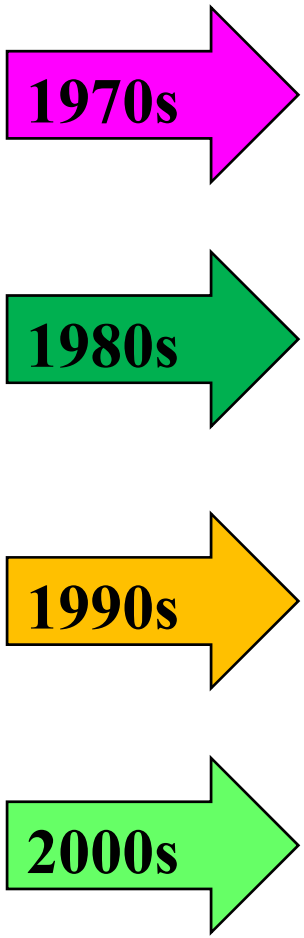
- **The Future of Single Use Components in Biopharmaceutical Production** – Matthew Olsen – Sartorius Stedim Biotech, Chemical Engineering Progress, July 2019 *(with permission)*
- **Single-Use Technologies in Biomanufacturing** – Anke Geipel-Kem (editor) Biomanufacturing, Nov 11, 2009
- **Single-Use Technology Integral to Advancing Biomanufacturing** – Nigel Walker, Nice Insight, Mar 9, 2016
- **Single-Use Technologies Changing the Biomanufacturing Landscape** – Eric Langer, Apr 4, 2011, www.bioplanassociates.com

- *…as well as almost 40 years of experience in the chemical process industry!*

What Is It?

- **SINGLE USE (SU) MANUFACTURING:**
  - Emerged about the mid-1980s, evolving from single-use systems which were gaining wider use in the pharmaceuticals industry, especially for the production of specialized, and/or small-batch drugs
    - » *This is the alternative to processes made of relatively inflexible stainless-steel vessels and reactors, hard piping, valves, and so on. Such a fixed system must be cleaned and sterilized, a relatively labor- and energy-intensive operation*
  - **Example:**
    - » *The PVC blood bags used for blood donations are actually more than just bags. They are examples of relatively simple single-use products. Initially, the bags replaced glass bottles but soon became available with a plastic tube or two, connectors, valves, and vials for taking samples.*

SU Manufacturing Timeline



Adoption of hospital bag technology for storage solutions. Single-use filters launched.

CMOs adopt disposable technology. Y-capsule filters and disposable filters launched.

Launch of aseptic connectors. Initial introduction of "plastic factory" concepts (media and hold-bags) & simple bioreactors.

Single-use sensor technology. Disposable chromatography & complex single-use bioreactors introduced.

Why the Movement to SU?

- **Strong growth in the demand for monoclonal antibodies and increasing sales of other biotechnology products**
- **Increasing titers**
  - *In the past, companies used titers in the 0.5 to 1 g/l range*
  - *Today, new processes are commercialized in the 2–5 g/l range and will likely near 10 g/l in the not-too-distant future*
  - *Companies are reporting well over a five-fold increase in titers in their commercial processes and higher values in pre-commercial processes, requiring even smaller bioreactors*
- **A growing market for niche products driving the need for smaller drug quantities.**
- **Contract manufacturers are expanding their markets**
- **Increased scrutiny by the FDA, *(e.g.: stricter safety regulations)***
- **The issue of sustainability and how it can affect processes and profitability.**

Market Drivers

- **Strong growth in the global biopharmaceutical market - from $162 billion in 2014 to $278 billion by 2020 - is driving investment in new facilities and expanded capacity/capabilities by both traditional biotechnology companies and conventional pharmaceutical manufacturers**

- ***Contract manufacturers are following suit…..***
  - *In early 2016, the global biopharmaceutical contract manufacturing market was estimated to be growing at an overall, healthy, annualized rate of 8.3% with capacity for mammalian cell culture and microbial fermentation production expected to increase by 14% and 16% by the end of that year*

Estimated SUS Market Growth

Table 1. Bioprocessing Systems Current Markets (Annual Revenue) and Growth in the Past and Upcoming 5 Years			
Products (revenue/year)	2013 Market	2018 Market	2023 Market
Bioprocess equipment, total market	$12 billion	$23 billion	$40 billion
Bioprocess equipment, upstream	$6 billion	$11.5 billion	$20 billion
Bioprocess equipment, downstream	$6 billion	$11.5 billion	$20 billion
Stainless steel/non-SUS	*$10.8 billion*	*$19.5 billion*	*$29 billion*
Single-use (SUS)	*$1.4 billion*	*$3.5 billion*	*$11 billion*
Non-commercial use (small/mid scale)	$1.3 billion	$3 billion	$9.5 billion
Commercial use (large scale/GMP)	$.1 billion	$.5 billion	$2.0 billion

BioPlan's estimates for SUS and related markets
American Pharmaceutical Review, October 23, 2018

Market Drivers

- **Many of the new facilities being constructed today are quite different from those built during the early days of the biopharmaceutical industry**
- **Advances in manufacturing technologies have led to as much as a 10-fold increase in productivity due to significantly higher titers**
  - *It is now possible to produce in a 2,000 liter reactor what previously required a 20,000 liter vessel, allowing for significant reduction in the scale for biopharmaceutical manufacturing facilities and associated capital expenditures*
- **A significant portion of the growth in demand for biologics is coming from emerging markets, and in many countries local manufacturing is required by the government**
  - *Technologies that can ensure consistent production in multiple locations are increasingly important*
  - *At the same time, demand for each individual biotherapeutic remains limited within a country, and thus technologies suitable for smaller production volumes are also needed.*

Market Drivers

- **In a recent survey by Bioprocess International on behalf of BPSA (*Bio-Process Systems Alliance, an industry group of single-use manufacturers and end-users*), the biggest market driver for switching to single-use technologies is the elimination of cleaning and sterilization cycles**
- **The survey also lists lowering manufacturing costs, increasing production speed and flexibility, and reducing contamination risks as factors spurring this market growth.**

Lower Manufacturing Costs

- **Single-use technologies can lower turn-around costs by reducing or eliminating the need for expensive stainless steel equipment and the associated expenses of installation and cleaning**
  - *Comparing single-use technologies with stainless steel for 1 g/l cell titers, a company can potentially realize savings of almost 50% in total cost of goods*
  - *As titers increase, companies can produce more product with smaller-volume bioreactors, which are particularly well-suited for single-use processes*
- **Additionally, a study "*The Environmental Impact of Disposable Technologies*", (*Biopharm International, November 2008*) found that disposables required:**
  - *87% less water*
  - *21% less labor (primarily by reducing CIP activities)*
  - *38% less space*
  - *29% less energy*

Enhanced Speed & Flexibility

- **Contract Manufacturing Organizations (CMOs) were among the earliest adopters of single-use technologies because the ability to turn around manufacturing operations quickly is vital to their success**
- **Interestingly, CMOs were more likely than branded drug manufacturers to adopt single-use technologies - 86% vs. 66%, respectively**
  - *This is attributed to the ease of use and the efficiency of these systems and devices when dealing with multiple products and bioprocesses that require fast turn-around times*
  - *Single-use systems provide CMOs with more flexible production capacity in terms of rapid switching between product campaigns and the ability to manufacture over a wider range of production scales*
  - *Implementing single-use systems and integrating them into manufacturing operations is, in fact, the single most important biomanufacturing trend or operational area that the industry must focus on, according to CMO representatives surveyed by BioPlan Associates.*

Safety

- Since single-use equipment can be pre-sterilized by the supplier prior to use, there is the potential elimination of classified environments from the manufacturing process
- Additionally, the reduced risk of cross-contamination helps companies avoid costly downtime and material waste

Other Benefits

- **Disposable technologies are particularly ideal for scaling down biologic manufacturing processes, which is a key trend in the biopharmaceutical industry**
  - *Single-use technologies are well suited for use in modular facilities designed to enable high-quality production of biologic APIs and formulated products around the world, including in places where traditional facilities cannot be constructed*
- **According to a 2015 report by BioPlan Associates, more than 90% of facilities use single-use/disposable technologies, and manufacturers and suppliers consider both disposable and stainless-steel options when planning their manufacturing strategies**
  - *Additionally, more than two-thirds of biomanufacturers and suppliers (69%) reported improvements in biomanufacturing performance at their facilities in the previous 12 months due to the use of disposable devices*

Other Benefits

- **Single-use technologies are seen as supporting flexible cGMP manufacturing and enabling efficient and rapid adjustment of production schedules and volumes and even system reconfigurations combined with ease of process replication and relocation to other global sites or transfer to contract manufacturers**
  - *These attributes also facilitate the implementation of key regulatory initiatives such as quality-by-design (QbD), the use of process analytical technology, and continuous processing*
  - *The ability to use a similar equipment configuration and the same materials for production equipment at the process development and commercial-scale manufacturing phases also simplifies process scale-up and can accelerate time to market*

Survey-reported Use of SUS

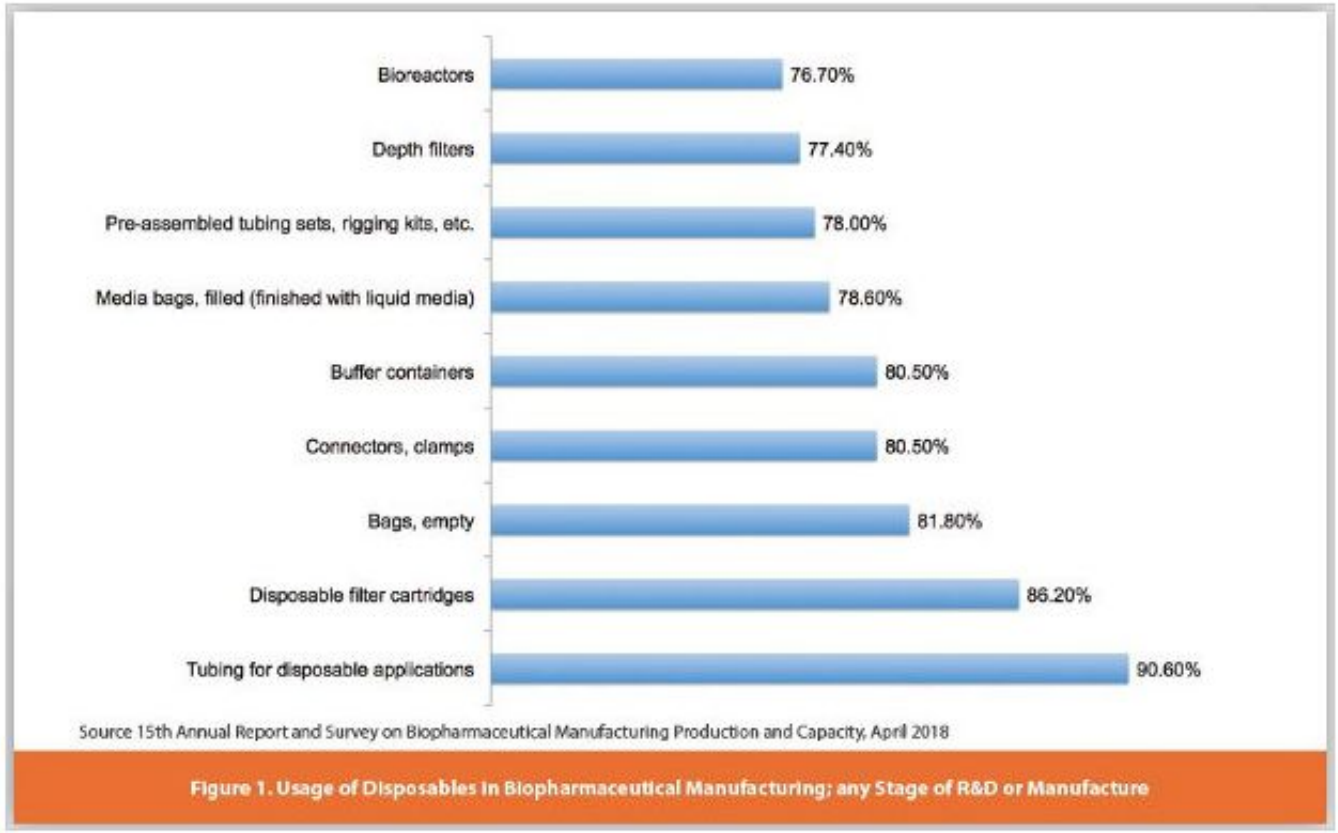


Figure 1 shows the average responses from developer survey respondents reporting use of various SUS equipment at their facility.

Single-use Bioreactor Example

- **A single-use bioreactor or *disposable bioreactor* is a bioreactor with a disposable bag instead of a culture vessel. Typically, this refers to a bioreactor in which the lining in contact with the cell culture will be plastic, and this lining is encased within a more permanent structure (typically, either a rocker or a cuboid or cylindrical steel support). Commercial single-use bioreactors have been available since the end of the 1990s and are now made by several well-known producers**

https://www.youtube.com/watch?v=OweV5mfhK20

Limitations to SU Use

- **There are limitations to single-use technology, and it is not always the most effective or economical solution**
- **Many companies take a hybrid approach, using a combination of disposable and reusable stainless steel/glass equipment**
- **In addition to economics, several other factors are considered in determining whether single-use systems are appropriate for a given project, including:**
  - *whether existing equipment is available*
  - *the timing and budget for a project*
  - *the potential need for future replication of the process*
  - *and whether the process will be performed in a multiproduct facility.*

Limitations to SU Use

- **There are limitations to single-use technology, and it is not always the most effective or economical solution**
- **Many companies take a hybrid approach, using a combination of disposable and reusable stainless steel/glass equipment**
- **In addition to economics, several other factors are considered in determining whether single-use systems are appropriate for a given project, including:**
  - *whether existing equipment is available*
  - *the timing and budget for a project*
  - *the potential need for future replication of the process*
  - *and whether the process will be performed in a multiproduct facility*

Limitations to SU Use

- **Various Risk Assessment techniques have been developed, for example:**
  - ***Technical Report Number 66 - Application of Single Use Systems in Pharmaceutical Manufacturing*** *- from the Parenteral Drug Association (PDA) describes a risk-based decision-making process for determining if implementation of single-use technologies is appropriate for a given process*
  - *Based on QbD principles, it involves a step-wise approach that considers factors such as the suitability and availability of particular single-use equipment systems/components, plus many different potential risks*
  - *If the answer to each question in the series is yes, then single-use technology is appropriate for the project, and as a bonus the reasoning supporting implementation of disposable systems is well documented.*

Upstream vs. Downstream Limitations

- **First, some definitions:**
  - ***Upstream*** *processes are those in which biological materials are either obtained from an outside source or inoculated and grown in culture, under controlled conditions, to manufacture certain types of products*
  - ***Downstream*** *processes are those in which the products are harvested, tested, purified and packaged*
- **While single-use bioreactors are widely used in upstream cell-culture-based biopharmaceutical manufacturing processes, disposable technologies for microbial fermentation are less well developed**
  - *Fermentations are generally higher volume, which can be an issue for disposable bioreactors*
- **Single-use solutions for common downstream operations are also more limited….**

Upstream vs. Downstream Limitations

- **For many downstream unit operations, large-scale single-use technologies that can handle the higher titers achieved upstream have not yet been introduced**
  - *Disposable technology is also finding increasing use in final formulation and filling processes for both non-sterile products and those that require aseptic processing conditions*
- **Suppliers of single-use technology systems are making rapid advances in developing effective downstream solutions, for example:**
  - *Various tangential flow filtration (TFF) devices are now commercially available that can be effectively combined with other downstream unit operations*
  - *Disposable, pre-packed chromatography columns have also been introduced to the market, and continuous chromatography systems (e.g. simulated moving bed (SMB), counter-current extraction) are being developed that have economics similar to single-use systems*

Upstream vs. Downstream Limitations

- **Single-use equipment manufacturers are also focusing efforts on the development of bioreactors for adherent cell manufacturing for cell-based therapies, small-scale bioreactors for scale-down modeling in the laboratory, and a wider array of disposable sensors for real-time monitoring**

What Are The Risks?

- **While single-use technologies provide many benefits, they also carry risks that tend to be magnified on the commercial-scale and are of greater importance when implemented at the final drug manufacturing stages**
- **One big concern is leachables and extractables from the plastics used in disposable systems**
  - *Many issues with leachables and extractables have been addressed; however, as single-use technologies are increasingly employed at the commercial scale and in manufacturing processes close to the final drug product, the risks they present increase*
  - *Regulatory scrutiny is significantly heightened when using disposable technology for final formulation and filling processes compared to media preparation or cell culture, and there is a need to demonstrate extractables / leachables performance*

What Are The Risks?

- **Change management is also an issue for single-use systems**
  - *Changes to reusable equipment are much easier to implement, largely because it can take much longer to assess extractables data and qualify modified disposable equipment*
  - *Both biopharmaceutical manufacturers and single-use suppliers must have rigorous change management procedures in place to ensure that disposable equipment consistently meets specifications for every application*
- **At present there remains a lack of industry consensus on what data should be provided by suppliers, particularly given that needs can vary depending on whether the disposal systems are being used upstream, downstream, or for final filling operations**
  - *The regulatory requirements are also rather vague and tend to be considered on an individual basis. Discussions are underway to address such concerns*

What Are The Risks?

- **The risk of being committed to a single supplier of disposable equipment has also created concerns in the industry**
  - *In most cases, components from one supplier cannot be used with those of another*
  - *This lack of interoperability often forces drug manufacturers to use only one supplier or to purchase duplicate versions of the same components*
  - *In addition to increasing inventory management costs, this situation creates supply chain security concerns*
  - *The trend today is consolidation and internal standardization on a set number of basic components that can be used to build the various configurations they require for different unit operations*
  - *In general, components/systems from suppliers that can guarantee dual sourcing through production at various sites are preferred*
- **In essence, suppliers of disposable equipment are as critical to ensuring that drug products reach patients as suppliers of key raw materials in terms of both reliable and on-time delivery and quality consistency.**

Addressing The Risks

- **Both interoperability and extractables/leachables are key topics under discussion by numerous industry groups and standards organizations seeking to find workable solutions for standardization**
- **The following organizations are actively involved in developing workable standards related to the use of disposable technologies:**
  - *The Bioprocess Systems Alliance (BPSA)*
  - *Biophorum Operations Group (BPOG)*
  - *Parenteral Drug Association (PDA)*
  - *US Pharmacopeial Convention (USP)*
  - *International Organization for Standardization*
  - *ASTM International, and the American Society of Mechanical Engineers (with its Bioprocessing Equipment (BPE) group)*

Addressing The Risks

- **BPSA and BPOG have joint User Requirement Specification and Change Notification Teams**
  - *The former is looking at quality requirements and product specifications, among other issues*
- **A PDA team has provided comments to ASTM as it works on its design verification standard**
- **ASTM is working on a standard for the determination and characterization of extractables from single-use materials with considerable input from BPOG and BPSA**
- **ASME, ASTM and BPOG are looking at leachables**
- **USP and ASTM are addressing sub-visible particles**
- **ASTM, ASME, and BPSA are working on system integrity testing issues**

Addressing The Risks

- **Many of these groups have published various technical documents and guidelines on these topics, for example:**
  - *BPSA developed a quality assurance template for establishing an agreement between a single-use supplier and biopharmaceutical manufacturer regarding quality consistency*
  - *BPSA's Quality Test Reference Matrices lists existing standards that are applicable to disposable technologies and should be referenced by suppliers in their quality procedures*
  - *BPSA also published the Guide to Gamma Irradiation and Sterilization of Single Use Systems and the Guide to the Observation, Measurement and Control of Particulates in Single Use*

Addressing The Risks

- **With respect to interoperability, there is discussion of developing standards that would enable a plug-and-play approach**
  - *Some suppliers are resistant to such standardization because they fear it will eliminate any opportunity to establish competitive advantage*
  - *However, many believe that such standardization would lead to greater efficiencies and lower costs, which in turn would encourage biologics manufacturers that have previously avoided disposable technology to adopt single-use systems and thus expand the market*
- **Specific areas identified for new product development efforts[1]:**

Product/service Area	Response Percent
Disposable products, bags connectors, etc	38.9%
Disposable product: purification	38.7%
Disposable product: probes, sensors, etc	36.9%
Chromatography products	34.5%
Analytical assays	32.1%
Process development (downstream) services	29.8%
Cell culture media	29.0%
Disposable product: bioreactors	28.6%

[1] Source: 8th Annual Report and Survey of Biopharmaceutical Manufacturing; Preliminary data, pub April 2011; BioPlan Associates, Inc. http://www.bioplanassociates.com/

Summing Up

- **The reasons for employing SU technologies in biomanufacturing are persuasive, however there are several challenges and concerns related to their use that still need to be fully addressed:**
  - *SUs can significantly increase the ongoing operating costs related to the buying and disposal of consumables*
  - *There are concerns with leachable and extractable substances arising from product contact surfaces, which may increase the risk of contamination*
  - *There are product sourcing limitations associated with purchases of single-use equipment*
  - *Consistent and uniform standards of quality, installation and use are still very much in the development stage*

Summing Up

- **Despite these risks, biopharmaceutical manufacturers ranging from small start-up companies to large product sponsors and CMOs are increasingly implementing disposables**
  - *Ultimately it is still unclear whether there will ever be a completely 100% stand-alone, SU-only biomanufacturing facility, or if future biomanufacturing facilities will be of a hybrid nature*
  - *Certainly, there is a strong case for 100% SU adoption in situations where the production capabilities are associated with multi-product, small-volume facilities which could also be a satellite of a larger plant location*
- **As companies strive to remain competitive in a global market, strategic implementation of single-use technologies has the potential to increase flexibility and overall output, decrease manufacturing costs, and reduce facility footprint, inventory and supply chain issues faced by the pharmaceutical industry today**

"There is no expedient to which a man will not resort to avoid the real labor of thinking."

Sir Joshua Reynolds

Psibilski@.ALZOUSA.com