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Disposables/Single-Use Roundtable

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For biopharmaceutical manufacturing have single-use technologies finally become the standard for manufacturing these types of products?

Bikash Chatterjee, President and CSO, Pharmatech Associates: With outsourcing as a core component of most drug development programs, deeper understanding of the risks and advantages presented by Single Use Disposables (SUDs) has catalyzed their adoption. This technology has indeed become the industry standard for most early development programs, shifting the risk from the processing side to the CMC side in terms of characterization and risk management. SUDs tout the potential for significantly lower capital cost, although the variability in these deployments depends upon the compliance tolerance of the organizations.

Brian Follstad – Director, Upstream Process Development, Catalent Biologics: Single-use technology has become more prevalent, and many companies adding capacity are choosing single-use technology for flexibility and risk mitigation. Single-use systems will mitigate risk of product carry-over for multiproduct facilities as well as mitigate facility risk from contamination events. There are still instances where stainless steel might be desirable, particularly for batches larger than 4,000L or for processes with regulatory submissions containing data only from stainless steel batches.

Emily Schirmer – Director, Downstream Process Development, Catalent Biologics: Additionally, for large volume, high titer processes, single-use downstream technologies become limiting. Vendors are aggressively working to close this gap. For companies targeting individualized medicine therapies or smaller patient populations, the manufacturing model moves to smaller footprints with higher frequency, which can drive the desire for a single-use facility.

Robert Dream, Managing Director, HDR Company LLC: Single use technology (SUT) is gaining high traction in the biopharmaceutical manufacturing domain, but, there is much to be done to give the end-user/manufacturer and regulatory agencies an acceptance to make it the standard for manufacturing biopharmaceuticals.

The manufacturers of SUS supply the end-user with information regarding the material qualification and the suitability of SUS/SUT for respective use. The regulatory requirements for the material qualification of SUS are set by EU-GMP Guide, and US-FDA, 21 CFR 211.65(a). It is necessary here to ensure that the interactions (extractables/leachables, adsorption, by-products or decomposition products) between the product and the SUS will have no effect on the quality of the active agent/pharmaceutical to be produced. These specifications, however, do not apply to the overall biotechnological process, but to the end-product. In addition to these legal requirements, compliance with the guidelines provided in pharmacopoeias must also be observed.

Eric Langer, Managing Partner, BioPlan Associates: Single-use bioprocessing technologies are, according to our 15th Annual Report on Bioprocessing, clearly a leader in adoption at clinical and pilot scale bioprocessing. With over 85% of the industry indicating that major unit operations are now designed using SUS devices, for these applications, SUS is the primary manufacturing strategy at this scale. Two key issues going forward include: 1) Will the percentage of the clinical pipeline currently being manufactured in early-stage SUS devices ultimately migrate to stainless steel in late-stage clinical production,

or will the bioprocessing continue to be done in scaled-up (larger) SUS devices. And 2) whether recent improvements in titer and other production efficiencies can ultimately mean that the required large, commercial-scale production quantities can be met using plastic SUS devices, which are currently limited to 2000L (or multiples of that using parallel manufacturing in additional 2000L bioreactors, etc).

Max Blomberg, Director of Operations, Meissner Filtration Products: Single-use systems are not the standard, but they are a standard consideration. This is an important distinction to make because not all unique combinations of product, process, scale, and lifecycle stage derive the same benefits from single-use technologies. To suggest that they have become the standard infers that as an industry we are not evaluating the best marriage between the aforementioned variables and available platforms. In many cases, single-use systems are the best option. However in other situations, hybrid or conventional (aka "traditional") systems may present the best fit. This said, they have certainly become a standard consideration when performing such an analysis, and this exemplifies the maturation of single-use technologies.

Joseph Chartier, Fluid Management Technologies, Sartorius Stedim North America Inc.: Yes, single-use technologies are the standard in many capacities for biopharmaceutical processing. Benefits of single-use have been proven, which is shown by the usage in processes from historically low-risk applications (media and buffer prep) to much more critical applications (drug product/fill finish). This expansion of use verifies the proven reliability ad benefit of single-use.

Vincent Lam, Product Specialist, Fermentation Technologies, Sartorius Stedim North America Inc.: In general, single use is becoming more of a standard for new biopharma applications since it drastically reduces the initial capital invNutestment to reach an IND. This is especially true for mammalian applications, however there will be legacy processes and unique industries that will still prefer stainless steel solutions. In order for single use to be truly ubiquitous within the industry, there must be a standardization of components that allow for interchangeability of single use parts within unit operations.

Alex Kakad, Product Marketing Manager, AdvantaPure®: Single-use technologies are continuing to gain adoption in the bioprocess industry for new drug processes. Many legacy processes continue to use traditional stainless manufacturing equipment.

As single-use technologies have become more mainstream, have you noticed any unforeseen benefits or disadvantages to using this technology? Can you elaborate?

Chatterjee: The ability to anticipate challenges with SUDs is often directly proportional to the rigor applied to the risk management process in their selection and design. SUDs move the Extractables and Leachables discussion and focus from the primary container back to the manufacturing process. This escalates the rigor required by the supplier to demonstrate that the material and processing of these SUDs are consistent and inert. First, it is up to each organization to determine what level of oversight is required to ensure this. Second, bag integrity presents its own set of challenges to demonstrating and managing. In a risk analysis for an organization looking to replace their monoclonal antibodies (mAb) intermediate bulk containers (IBC) with SUDS to remove the shipping and cleaning costs, we identified over 200 failure modes. 15 of these were related to CMC and were not addressed in their program. This is an indication of how complexity increases exponentially with such systems.

Follstad: Manufacturers should consider potential impact of waste due to the need for plastic components. However, single-use technologies can be beneficial when considering the amount and types of chemicals used for stainless steel cleaning procedures. One disadvantage continues to be the risk of cell lines or biological products responding negatively to the films used in single-use technologies. However, this risk continues to decrease with manufacturers offering films with low extractable and leachable profiles, for example Aegis™.

Schirmer: There is an inherent risk to the supply chain to design and procure single-use assemblies that are fit for purpose in manufacturing facilities. For contract development and manufacturing organizations (CDMOs), single-use technologies enable a flexible approach to transferring processes internally and externally and allows the facility to adapt to a wider range of product titers in the bioreactors.

Dream: Despite widespread use and acceptance of SUS in bio-pharmaceutical production processes, users are currently faced with challenges as follows;

- There are no defined, pharma-grade polymers.
- The qualification and validation data of all producers are variously compiled and informative. Often not all additives are specified.
- There are no regulatory requirements for SUS for the overall biotechnology process, only for individual SUS at best (e.g. for filters) and for end-products, consequently, the requirements for inspections by authorities are not defined for the individual production steps.
- For a complete review, a universal approach for all SUS is required. In addition to bags and filters; this also includes tubing, tube connectors, membranes, etc.
- Within the individual clinical phases, the same SUT should be used whenever possible to highlight its suitability
- In general, there have been few risk analyses for SUS
- Development is proceeding at a rapid pace for base materials (plastics) of SUS and its processing
- The requirements for SUS can vary widely, depending on the length of time of contact with the SUS, the importance of individual extractable substances for each process or surface-active substances such that influence an extraction
- There are no evaluated analytical methods with acceptance criteria for leachables and extractables

These challenges originate primarily from materials and the associated qualification and validation of SUS (Single Use System) and the processes arising thereby. Hence, pharmacopoeias describe tests for polymers (EP: 3.1.x, USP <87>, USP <88>, USP <381> or USP <661>), but they present these as screening tests. However, not all polymers from which SUS can be made have been entered in the pharmacopoeias.

Langer: A significant benefit to global healthcare in general is the ability to rapidly deploy a modular and/or single-use facility in emerging

regions. This makes it easier for countries like China to produce needed biologics in regions that would not be likely to have the ability to construct and commission a GMP quality biologics facility. By some estimates, over 30% of all cancer patients now live in China. According to our 2nd Edition Advances in Biopharmaceutical Technology in China, as China's economy continues to expand, the access to these life-saving medicines are not just going to be a luxury, but will become a healthcare policy issue, and domestic consumption of biologics will continue to grow along with the country's GDP. Essentially, as China is now the world's largest retail market (beating out the US in 2019), much of that disposable income is likely to be diverted to healthcare in the near future. SUS bioprocessing is going to play a vital role in this transformation.

Blomberg: While there are a host of specific technical points that could be made here, we believe that one of the primary sources of unforeseen, or perhaps overlooked, benefits and challenges is the augmented role of the supply base when single-use technologies are employed in a process. At the risk of oversimplifying things, this stems from the realization of what a biomanufacturing company is really outsourcing when using this technology. Considerations in this regard include engineering, sterilization validation and even facilities management. As an example, in the case of the latter, whereas with conventional processing systems a biomanufacturer's facilities and/or engineering group was responsible for ensuring equipment uptime, when single-use technologies are used, this now depends, to some degree, on the availability of single-use systems from the supply base. There are benefits associated with outsourcing some of this responsibility; however, also challenges which we have seen manifest themselves in e.g. relatively larger warehouses for facilities that predominantly rely on single-use technologies. This can of course be mitigated via a reliable single-use technologies supplier and JIT delivery.

Sharon Koesnadi, Field Application Specialist, Fluid Management Technologies, Sartorius Stedim North America Inc.:

The benefits of single-use are well understood. Time to market & downtime reduction, Cost reduction on upfront investments, Reduction of risk of cross contamination, ease of use, no SIP/CIP, which creates more flexible facilities.

Disadvantages - Supply Chain aspects from both the supplier and end-user sides. With many designs being custom for specific customer and specific applications, this results in tens of thousands of components and custom part numbers. This can create very complicated change control, supply chain and component qualification processes.

Single use technologies have historically been utilized in a very manual process, without many automation controls. As the industry evolves further, this will be increasingly required and requested from end-users.

As single use technologies are utilized in more critical applications, where the drug product itself is being stored, shipped or processed, higher requirements for risk mitigation are being driven by the industry. Increased assurance of integrity of containers is necessary the further downstream in a process single use is used.

Understanding the biocompatibility of single use systems with process solutions also needs to be understood. Impact of extractables on cell lines/patients is critical.

For companies who are environmentally conscious the question of how to properly dispose of the plastics and its long term effects on the environment is still yet to be explored

End-users need to have a system in place to minimize these risks and vendors need to have a process in place to control these aspects for long term single-use success.

Kakad: The ease of cleaning and validation concerns is continuing to drive single-use adoption in the bioprocess industry.

In your opinion are there certain type of companies that derive the most benefits from single-use technologies? What types of companies are they, and what types of products do they manufacture?

Chatterjee: With the growth of virtual biotech, CDMOs may well reap the greatest benefit from these systems. The flexibility these systems provide can translate to higher client throughput. In a market that is starved from capacity, this is a compelling benefit for both service providers and drug sponsors alike! For CDMOs in particular, the ability to reduce capital investment in processing tanks and associated utilities and infrastructure and pass along the cost of consumables to their customers, is a significant operating advantage.

Schirmer: Single-use technologies can be a good fit for multi-product sites, including CDMOs, because of reduced logistics to changeover between molecules and the need to adapt various processes into a single facility. Single-use CDMOs can support small- to mid-scale processes for a range of products and cell types. Large scale manufacturers that employ single-use technologies can adapt to uncertain or variable market demand for their portfolio of commercial products.

Follstad: For small or emerging biotech firms, the single-use technologies can be a benefit in terms of decreasing the time and resource expenditure for bringing a molecule to the clinic. The time decrease is from minimal change over, maintenance, and cleaning studies as well as more flexibility for varying modality pipelines.

Dream: Companies that derive the most benefits from single use are those that seek to incorporate the following in their operation;

- Cost reduction
- Easy disposal
- Increase in productivity
- Less energy demand and water use
- Time saving
- Reduced risk of cross contamination

Biopharmaceutical companies in general use SUS extensively in R&D and preclinical, as well as companies that can afford to manufacture in a smaller scale, up to 3000 L.

Langer: As noted, the facilities in emerging regions are the ones focusing more on SUS as their manufacturing strategy. In China, WuXi currently has the world's largest SUS capacity as a contract manufacturer. In our analysis, Top 60 Biopharmaceutical Facilities in China, we find that capacity is growing at over 20% annually; faster than in most developed regions. Further, the great majority of facilities, since they don't have legacy stainless steel, are focusing on SUS at clinical scale, with intentions to expand to commercial scale in SUS, as well. Just considering the biosimilars pipeline, it is clear that bioprocessing in SUS devices at commercial scale is feasible, given that most biosimilars makers need not plan for huge kilo quantities. This is because there can be up to 8

biosimilars competitors for each reference product, and such regional demand may be met using SUS devices.

Blomberg: We believe this is less company specific and more predicated on product/product lifecycle. Products which are moving through clinical or into commercial, or those where production demand can be met by a limited number of campaigns within a given year, are examples of where great benefit can be achieved via the use of single-use technologies. In these two examples, benefits are derived from taking advantage of new manufacturing techniques without dealing with the burdens of change control (associated with changing from conventional systems to single-use for established products), and closed system processing that many single-use enabled production processes provide, which eases the challenges associated with running a multiproduct facility.

This lens does tend to identify certain types of companies who would benefit from single-use technologies, such as contract manufacturing organizations and those who are just starting up production facilities. However, it doesn't preclude other types of companies who would derive the same benefits from single-use technologies as leveraged towards, for example, their new product pipeline.

Joseph Chartier, Application Specialist Manager, Fluid Management Technologies, Sartorius Stedim North America Inc.: There are benefits for most biopharmaceutical processing companies. Depending on where they are in production or development, speed to market, cost reduction or decrease in capital investment are key benefits. Multi-product facilities and CMOs benefit most significantly with rapid process/product change-over. During development and as processes scale up, single-use technologies can minimize the costs of capital expenditures.

Vincent Lam, Product Specialist, Fermentation Technologies, Sartorius Stedim North America Inc.: Many companies from various industries would benefit from single use technologies. Any emerging company that wishes to reduce their initial capital investment for capacity to produce material would benefit. Organizations that run a variety of processes and products within their facilities would benefit from the self-contained systems and reduced turnaround times that single use offers. Processes that involve a high safety risk such as virus production would benefit from single use technology.

Kakad: Some new biomanufacturing facilities are being designed and built to only use single-use technologies. They are not equipped with sufficient wifi to adopt traditional stainless manufacturing techniques.

Gregg Donovan, Product Marketing Manager, AdvantaPure®: Another type of company benefitting from the use of Single-Use technology would be the CMO's (Contract Manufacturers), who are able to produce a batch run for an end user and dispose of the Single Use System quickly and environmentally soundly.

From lab-scale to manufacturing scale – single-use technologies are found everywhere. Is there a specific phase of biopharmaceutical product development that benefits the most from single-use technologies? Can you provide any insights?

Chatterjee: Industry has moved comfortably to SUDs between batch sizes of 50l to 1000 liters, with newer technology increasing the working volumes to 2000 liters. As a result you see these systems broadly used in early development and through pilot plant including scale-down model validation.

Follstad: All phases of development benefit from single-use technologies, but the largest benefit would be in GMP production. In early phase development, single-use technologies allow for the efficient manufacturing of products with minimal facility investment.

Schirmer: Additionally, single-use facilities offer flexibility to changing pipeline priorities. In later stage development and as the process scale increases, single-use technologies can continue to be employed to allow for seamless scale up.

Dream: It is believed that the SUT for production of protein-based therapeutics will not continue to grow at the same rate it has. As described earlier, it is necessary to expedite the standardization efforts for SUS/SUT, to overcome the limitations and to further develop them. This is especially the case for the field of sensors with respect to process-relevant measurement parameters as well as the scale of instruments and devices for depth-, ultra- and diafiltration, chromatography and filling. If there is success in these areas, complete single-use production systems and hence the "Single-Use Factory in a Box" will be that much closer to a reality. Biotherapeutics of the newest generation will be important in shaping the further development of SUT. These are produced with autologous (produced naturally in the body) or allogenic (produced extraneous to the body) human stem cells or T-cells and therefore are also known as Cell and Gene Therapeutics. These cell and gene therapeutics are the most important product segment in personal medicine. More than 200 cell therapeutic agents are in the clinical trial stage, because, cell and gene therapies are still in their infancy compared to established manufacturing of protein therapeutics, innovative equipment and new technology are urgently required in order for it to reach commercial success.

Langer: In general, the majority of SUS devices are found at clinical-scale, according to our 15th Annual Report and Survey. However, some common devices, such as bioreactors, perfusion devices, and waste containers are more prevalent at process development scales. This suggests that usage is often based on the application. But in any case, SUS, even at commercial-scale is making advances.

Blomberg: I would suggest this is one of the biggest paradigm shifts associated with single-use technologies in the last 10 years. The answer to this question as little as five years ago would likely have been pre-clinical or early phase development, but today there is no hard cut over where single-use technology stops being a key enabler to biopharmaceutical development and manufacture. This, of course, includes the caveats that certain products and process scales may best be supported via hybrid or conventional systems.

Bobbi Allen, Product Specialist, Fluid Management Technologies, Sartorius Stedim North America Inc.: While all scales and manufacturing stages can derive benefits from Single Use Systems, Clinical phase production is especially attractive for a number of reasons. Speed of design and delivery of the manufacturing equipment is reduced while lowering the overall cost compared to the stainless equivalent. Clinical production is inherently temporary, so dedicating stainless equipment to these phase of manufacture results not only in WbD (Waste by Design) but increases costs and time the time needed to generate clinical material. By minimizing CAPEX requirements the overall business risk of clinical trial failure is mitigated.

Matthew Olsen, Product Specialist, Fluid Management Technologies, Sartorius Stedim North America Inc.: Single-use technologies offer improvements at all scales but the most compelling offering is in the area of manufacturing. The cost savings from SIP and CIP validation removal and reduction of plant utilities is really overwhelming. The increased ability to rapidly iterate on a process or completely switch molecules produced in the same suite by simply replacing single-use assemblies is also a very compelling reason for adoption of single-use technologies, especially for Contract Manufacturers.

Kakad: All phases of manufacturing benefit from adopting single-use technologies. GMP areas benefit most from the reduced need for cleaning and validation while lab and pilot scale areas typically benefit most from the ability to get products and processes up and running with a short lead time.

Donovan: Agreed: all phases both upstream and downstream benefit from the adoption of single use systems. With end users now seeking larger, more complex single use systems that are deemed sterile (Sterility Assurance Level 10 to the minus 6 per VD Max25), facilities can get further downstream very quickly.

Looking ahead, do you see any quantum leaps in single-use technologies, or just a steady stream of incremental improvements?

Chatterjee: So far, the area that has been the slowest to move to single use is fill finish because of the complexity of existing equipment. Even so, the advantages of doing so could be significant if the number of components that needed to be cleaned and sterilized were reduced to single use. I would look for advances in SUD technology to continue to expand into this space in the not too distant future.

Schirmer: There have been quantum leaps in adapting single-use technologies to perfusion processes in terms of large increases in productivity. Continued development of single-use technologies will continue to enable the biologics industry with respect to speed to clinic and adapting commercial facilities for variable market demands. Single-use facilities are the most feasible approach for the individualized medicine industry and can be flexible for the idea of one-reactor for one patient.

Follstad: There are new technologies emerging all the time that increase titer and improve efficiencies during development. Examples include Berkeley Lights' Beacon® Platform for cell line development, Sartorius' ambr® systems for process development and characterization, and major advancements made in continuous processing. These technologies can make smaller scale production practical for an increasing number of molecules, potentially leading to increased adoption of single-use technologies.

Dream: Predictions for healthy growth in demand for biologic drugs are driving many manufacturers, including branded and biosimilar drug producers and contract manufacturers, to invest in new production facilities. These state-of-the-art manufacturing sites often look quite different from traditional plants. Rather than massive permanent stainless steel reactors, biopharmaceutical companies are opting for much smaller, typically 2000 L disposable bioreactors. Many factors are influencing this move to single-use technologies, not least are the benefits they provide, such as reduced capital expenditures, reduced risk for cross-contamination, and greater flexibility to meet changing market needs.

The global biopharmaceuticals market was valued at $162 billion in 2014 and is estimated to grow at a compound annual growth rate (CAGR) of 9.4% from 2014 to 2020 to $278 billion by 2020, according to Persistence Market Research.

Langer: The bioprocessing industry is highly regulated, and new technologies are slow to introduce. Novelty that has not been introduced at commercial scale (not just pre-clinical, or even clinical scale) are slow to mainstream. Regulators need to be convinced of safety, and bioprocessors need to be shown the economic benefits of even a revolutionary new technology. Any new material that may have drug product contact needs to be considered a risk. So incremental improvements have, and likely will be, the way most SUS device suppliers improve their SUS technologies. There are some areas, such as personalized medicines, cell therapy, etc. where there is a lack of appropriately scaled devices, and where automation in SUS devices is not yet available. In these areas, there may be quantum leaps in SUS technologies, but this will likely be due to design and other technical advances, rather than new materials.

Blomberg: In an industry as risk adverse as ours, the idea of quantum leaps is a bit daunting. We, however, believe that advancement of single-use technologies will substantially outpace anything which could be described as incremental improvements. These advancements will include substantial enhancements in the level of integration with automation, novel sensor technologies, compatibility with continuous manufacturing and new solutions that provide a step change in the level of robustness delivered for the most demanding bioprocessing applications. For example, we will likely see greater adoption of more robust, single-use solutions for the freeze/thaw of bulk drug substance as a way to help reduce processing costs and increase operational flexibility. Advancements in these types of commercially available systems have opened up processing flexibility for 100 L and beyond.

Joseph Chartier, Application Specialist Manager, Fluid Management Technologies, Sartorius Stedim North America Inc.: I don't foresee quantum leaps forward at this point. A steady evolution in product development, increased automation and better waste management are the likely future drivers. In addition, more standardization is likely to be implemented as a driver for both suppliers and end-users. Application-based standards and platforming single use assembles has been growing in interest in recent years.

Neil Johnson, Field Application Specialist, Fermentation Technologies, Sartorius Stedim North America Inc.: In general single use technology would advance through incremental improvements. The main areas where improvements may accelerate would be the realm of single-use sensors and process analytics. The key areas of improvement would be on-line control of critical quality attributes, supply of consumables, and smart single use assemblies.

Kakad: There are some areas of single-use that are seeing quantum leaps in technology development. One example is the area of ultra low temperature storage and transportation. There are many new single-use materials being developed and launched into the industry that allow drug product to be safely processed and stored down to -86 degrees C.