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Single-Use/Disposables Technologies and Equipment Roundtable

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If a pharma company was looking to adopt single-use technologies for the first time – what advice would you give them?

Barbara A. Paldus, PhD: There are three key considerations:

- Consumable or single-use operating costs will far exceed the initial capital investment, so do not lock yourself into a single-source situation, especially on the bag films and tubing sets. Qualify at least two vendors for each unit operation of your processes to ensure security of supply chain and price. Consider using "universal controllers" for each unit operation to facilitate the interchange of bioreactors, filters, and chromatography columns.
- Transition as many process steps to single-use as early as possible in the development phase, in order to not duplicate process optimization and validation efforts. Growth or separation yields can be quite different in single-use equipment, so the earlier you know what works and what doesn't for your cell line and your product, the more informed decision you will make when planning a single-use pilot or production facility.
- Don't shy away from hybrid solutions, because certain downstream unit operations do not yet exist in single-use, especially for large-scale production processes. Select the production volumes that make sense at each process step, and create a best-of-breed solution. Many stainless skids work well with CIP sterilization and do not require significant plant infrastructure such as high pressure steam.

Eric Langer: Most biopharma manufacturers today recognize that single-use bioprocessing technologies provide significant manufacturing flexibility, and can get a therapeutic into clinical production at lower costs. The regulatory factors are also generally well recognized. But as yet, moving into larger, commercial scale is still evolving. For example, questions such as how a biologic may react to various single-use

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product contact surfaces, and related regulatory implications remain to be resolved. Despite these issues, single-use technologies are a mainstay of the industry. Those new to adopting these technologies are finding that near-term issues typically involve how to strategically implement them as part of a hybrid, stainless plus single-use manufacturing strategy.

Max Blomberg and Christian Julien: Engage your supply base early in the process and do so at multiple levels within the organizations. Successful single-use systems implementation, the benefits of which are understood, result in the end-user effectively outsourcing functions that with traditional systems were serviced via in-house capacity. This necessitates that the relationship an end-user has with a supplier not simply be transactional, but a relationship, and this requires interaction between a broad cross section of the two organizations.

Approach a single-use systems implementation with an eye towards the life-cycle of the process they are intended to serve. For example, if the single-use systems are being used in a PD, are they scaleable and appropriate for clinical trials and ultimately a production environment? Is the supplier of the single-use technology capable of supporting as much from a quality and supply chain robustness perspective? These are fairly basic questions, and certainly only a starting point in terms of a life-cycle analysis. However, if a single-use technology is to be employed in a manufacturing environment, successfully and for a long period of time, we should start with the end in mind.

Additionally, PDA TR 66 is an excellent resource to consult for implementation of single-use systems within pharmaceutical manufacturing. The document has a wealth of information drawing from industry and supplier SME's alike.

Michiel Ultee: First, select established manufacturers with a good reputation for quality, reliability and responsiveness in producing single-use technologies (SUT). Switching from a conventional stainless-steel system to SUT transfers some of the important cGMP equipment preparation, such as cleaning and sanitization to the supplier. Thus one relies on the supplier to ensure that the bags, tubing and associated SUT are clean and sterile, consistently produced and held in sufficient inventory to minimize supply delays. A full audit of the supplier is highly recommended. Secondly, storing SUT takes a lot of space. It's surprising, for example, to find out how much space a 2000L bioreactor bag takes up, even though it is folded up. Ensure that your facility has sufficient warehouse space to accommodate all the large bags, tubings, cartridges and other SUT.

Helene Pora: The most important thing is to be very clear about the scope of what the company is trying to accomplish - all the way from start to finish. The company needs to consider how critical the application is and then work with a supplier to identify a strong quality base. While it is much quicker to set up single-use technologies, the user must still allow time to qualify a supplier and for a potential audit. There are also other considerations, such as validation requirements (extractables and leachables, for instance) and risk assessments.

We see a lot of value coming from the QbD approach, which helps companies by establishing a proven, market-driven process and design that delivers results. End users are able to think about validation and quality in parallel with the design of their facility, so they are able to take full advantage of the time-saving benefits of single-use technologies.

Surendra Balekai: Most pharmaceutical drugs are chemical formulations as compared to biological drugs that are proteins. The chemical compatibility of the formulation with the single-use film (bioprocess container) as well as the product contact time/conditions are the most critical to consider in the adoption of single use technologies for a pharma company.

What processes are easiest to transition to disposable technologies and why?

Paldus: Media mixing and buffer preparation unit operations are the easiest to transition to disposable technologies because the processes are very robust and do not involve significant real-time measurement or control. The single-use vessels employed most mimic their stainless steel counterparts in geometry and functionality so that process transfer to single-use can occur rapidly. Because change-over of the solution composition is frequent in mixing applications, the single-use liners and bags present an immediate advantage as they are sterile and prevent any form of cross-contamination from batch to batch.

The next easiest process to transition is cell culture as again the bioreactor vessels and sensors have been modeled on their stainless steel predecessors. While process automation is more complex in cell growth than in mixing applications, control solutions exist today that put single-use skids on equal footing with their sterilizable counterparts. In fact, overall titers in single-use bioreactors are increasing to levels that allow for higher yields in smaller vessels volumes today. Moreover, the flexible configuration of single-use bioreactor bags provides an advantage in the development of continuous processes in single-use over stainless steel.

Langer: The most common single use technologies involve components such as bags for buffer, tubing, connectors, etc. for fluid transfer. These are likely the easiest to transition technologies. The

most rapidly growing areas include higher-end applications like mixing systems, bioreactors, and downstream purification technologies like membrane adsorbers.

Blomberg and Julien: The most common and historically accurate answer is upstream processes or those where the associated risk complexity of the application is relatively low (e.g. buffer or media preparation, bulk liquid fluid transport/shipping, and UF/DF concentration). While there is certainly some truth in this, we typically say that the easiest processes to transition to single-use systems are those where the demonstrated gain to the end-user is most pronounced. So while there are certainly gains to be made in buffer and media prep areas, ergo fairly frequent early adoption within an organization in these areas, there are also substantial gains achievable in, for example, final fill and finish assemblies. As our industry develops treatments targeted toward more narrow population bases, the need of filling infrastructure that can support multiple products and rapid changeover has created a scenario where the implementation of single-use systems in this operation demonstrates a substantial gain. This is obviously about as far downstream in the process as you can get, which is an example of why the historically accurate response no longer rings true today.

Ultee: Buffer storage in disposable bags in movable totes is now standard practice, and easy to implement. Bioreactors are another common area for SUT, but require additional considerations in terms of type of agitation, size and impeller design. Cartridge filters for clarification and solution filtration are also easy to adapt, as they are essentially plug-and-play.

Pora: You can see this through the history of single-use because, naturally, the easiest to adopt solutions become accepted more easily. When it comes to bioprocessing, buffer and media prep are the easiest immediate transitions, whether on a smaller or larger scale.

Balekai: Powder storage, mixing applications at appropriate conditions (pH and temperature) and and applications in the formulation, filling, and bulk shipping areas are some of the easiest to implement single use technologies.

What are some best practices for integrating disposable technologies with stainless steel equipment?

Blomberg and Julien: Implementing a hybrid systems approach can breathe new life into existing infrastructure and also provide substantial operational gains. Further, there is certainly still a place for greenfield hybrid systems implementations. (Samsung's facility in South Korea is a great example of this.)

Operator safety and product integrity are crucial considerations in the design phase of hybrid systems. In general, the implementation of GEP (Good Engineering Practices) by a seasoned applications engineering team is highly recommended to achieve a design that is fit for its intended purposes.

Ultee: Using disposable bioreactors in the scale-up or seed train to a larger stainless-steel bioreactor is a best practice across much of the industry. The cell cultures are expanding as they proceed to larger and larger vessels, and relatively simple rocker-type or wave bioreactors are easily implemented for this use.

Pora: The most critical element is your footprint constraint, and following closely behind that is connectivity. The facility must be laid out in a way that the equipment can not only be accommodated but also connected.

Another key element of integrating traditional and single-use technologies is the interface and whether the setup is application dependent. These will help drive the layout and will help streamline the sterility needs/activities. And, of course, no matter what the setup is, operator training is always important. Users of the technologies need to be fully trained to optimize results.

Balekai: There are a number of connectors available that help integrate with stainless steel equipment in non-sterile conditions and can be sterilized in situ. In unavoidable conditions, some of the critical transfer sets can be autoclaved and tube welding/sealing processes can be adopted.

Currently, disposable technologies are primarily used for biopharmaceutical production. Do you see their use expanding into other dosage forms? If so, what might that be and why?

Langer: Disposable technologies are moving into all areas of bioprocessing, including chromatography, and even fill-finish operations. The objective for many companies is to establish a (near) fully single-use facility. At present, such a facility for mainstream commercial scale bioprocessing does not (yet) exist. But the linking technologies are being rapidly developed.

Blomberg and Julien: Absolutely! Production processes that can benefit from the same drivers that led to adoption in the biopharmaceutical space are already evaluating single-use systems. In some cases adoption is going to require advancements in fluid contact materials (e.g. engineered polymers) to facilitate enhanced chemical compatibility. PVDF-based biocontainers were introduced to aid in this expansion and are chemically resistant to aliphatic and aromatic hydrocarbons, and halogenated solvents, enabling the adoption in liquid dose manufacturing processing for bulk chemical fluid management. Polyethylene-based biocontainers, the contact material of choice for predominantly aqueous based biopharmaceutical manufacturing, are not suited for these applications.

In other cases, adoption will simply require new form factors to facilitate processing on different scales with different materials. Biopharmaceuticals adopted single-use systems to decrease capital investment associated with new production capacity, increase operational flexibility, and ultimately speed their time to market. These same drivers don't exist for well-established or high volume products, but where new small molecule production processes require these attributes, single-use systems are certainly a consideration.

> The future of disposable technologies will involve the development of non-reactive, cheap, strong, and fully scalable devices that meet expectations of regulators.

Pora: Due to the nature of biological products, single-use technologies often make the most sense. This is because integrity and sterility become so much more critical with living drug products. While they are not limited to the production of a single type of product or dosage form, we tend to see a great contribution in injectables, which are gaining popularity.

Balekai: So far polyethylene films have proven to be best suited for biologicals. Especially when we talk about product contact surfaces with drugs, safety in terms of extractables and leachables become high priority. In the future, if there is film that is inert and has a more robust chemical compatibility, its application in the pharma industry will be a tremendous potential for all sterile injectables.

What do you see as the future for disposable technologies?

Paldus: At Finesse, we see the future for disposable technologies as quite bright. The shorter lead times, easier operation, and consistent yields that result from a transition to single-use will continue to drive the conversion to single-use. Having witnessed the early adoption cycle (2006 to 2011), we believe that single-use applications in mixing and cell culture are now firmly entrenched, and will continue to expand for orphan drugs to biosimilars. As downstream technologies evolve, filtration and chromatography steps will follow in adopting of single-use platforms.

In the last three years, most of the large consumable vendors have updated their films to minimize not only leachables and extractable profiles, but also by-products from the multi-layer film tie layers. Many suppliers have introduced at least one new film indicating progress in producing higher purity materials for both bags and tubing sets. We see ongoing development and evolution of these materials as the community understands the requirements on these plastics better and optimizes them for bio-processing.

Langer: The future of disposable technologies will involve the development of non-reactive, cheap, strong, and fully scalable devices that meet expectations of regulators. Many of the unit operations are available as single-use today, but until a fully disposable plant is available at relatively large scales, and that regulators can accept, the growth in this industry will continue to be rather linear; when the parts are in place for more integrated SUS facilities, then a geometric growth and adoption curve can be expected.

Blomberg and Julien: The adoption rate for single-use systems will continue to increase as the industry matures and expands the capabilities of what can be accomplished therein. Industry maturation is a broad term, but is meant to include areas such as increased regulatory comfort with the technology through the adoption of standards and evolving relationships between end-user and the supply base.

We see the alignment of single-use systems (manifested as simple fluid contact surfaces) and automation platforms (manifested as smart integrated infrastructure), as a major driver in the adoption of single-use systems, as this expands overall processing capabilities.

Innovation paired with a QbD enabled material-science based foundation will also help expand single-use technology development and adoption in traditional pharmaceutical platforms. This is also true of biopharma processes, which seek to use the cleanest materials that chemistry can provide, and makes them receptive to newer/cleaner polymer formulations, such as PVDF-based biocontainers, which expand single-use applications beyond the previous limits of PE-based biocontainers.

Ultee: Due to the stringent demands for high purity in biopharmaceuticals, and the sensitivity of cell cultures to trace impurities, the manufacturers of disposable technologies have had to improve the purity of their plastics significantly, a trend that is continuing. Specifically, the raw materials used in SUT are becoming more inert and of higher purity. Plastics are a huge market and vary widely in composition and consistency. Much of the production goes into large volume uses such as the automobile industry, where trace amounts of solution leachables would not be a concern. Secondly, I foresee further expansion of disposable technologies into downstream processing, especially with the use of disposable membrane separations replacing traditional chromatographic columns. Capacities and capabilities of membrane-based separation devices have improved markedly and will be further expected to make inroads into traditional protein separation methods.

Pora: As we look toward the future, the proof of concept has already happened, and single use is becoming widely adopted. Now, we are working towards standardization so that companies have a better idea of how best to optimize single-use technologies. The industry is moving towards commercial implementation and, at Pall, we are taking that one step further as we develop our continuous commercial processing portfolio.

Balekai: The foundation for disposable technologies has been laid and there is significant development happening in associated components, such as sensors, connectors, tubing, etc. In the last two years there has been significant adaptation of SUT in downstream processing. Once the development is complete, and products are released; they will prove their dependency and reliability. Disposable technologies are here to stay and expand.