

## Disposables: Biopharmaceutical Disposables as a Disruptive Future Technology

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**Users and vendors convene at an IVT meeting on disposables to discuss the potential of single-use technology in bioproduction over the next 10 years.**

Jun 1, 2007

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If the prognostication and crystal ball-gazing at a recent meeting organized by the Institute of Validation Technology (IVT) on disposables is any indication, the future of single-use components in biopharmaceutical manufacturing processes is likely to become increasingly diverse and attractive. The meeting, "Disposable Technologies for Biopharmaceutical Manufacturing" held in February in Alexandria, VA, included an interactive breakout session, co-chaired by the authors. Both users and vendors projected how disposables may affect bioproduction over the next 10 years. Meeting participants identified how disposable technologies can do far more than reduce cleaning requirements and minimize risks of cross contamination. They can also help save money, manufacture products previously unprofitable, and be used in areas not otherwise considered.



### CHANGING SITUATION

The biopharmaceutical manufacturing industry has accepted disposable components in manufacturing in the same way that food services and other industries have; disposables are seen as effective and useful tools to be adopted within each manufacturer's system. The regulated nature of biopharmaceutical manufacturing, however, and the associated risk of using new technologies on multimillion dollar batches of pharmaceutical ingredients, differentiates it from other industries.

Though some early visionaries had projected rapid conversions to fully disposable manufacturing facilities, these components have been integrated into production facilities ad hoc rather than using a whole-systems approach, and disposables usage has grown only moderately. This stepwise integration, which started more than a decade ago with basic filtration components, tubing, and connectors, has progressed to include media and buffer bags, and is now moving on to disposable bioreactors, mixing devices, sampling devices, and disposable probes. The regulatory and operational fears associated with the use of disposables early on have rarely materialized.

As current technologies develop, decisions to use disposables are being based on factors such as whether they are compatible within a given system or if they make sense economically. Typical issues of single-source vendors are emerging. For example, companies may be more reluctant to use disposable bioreactors until there is sufficient competition. In comparison, similar concerns are not seen with filters, since competition is greater and these components are well established.

Today, most disposables are used for process development and clinical-scale manufacturing. There might not be any substantial growth in the use of disposables until they break into the production of licensed products at commercial scale. For this to occur, regulatory strategies will be required for changeover from hard-piped systems to disposables. Because legacy systems are unlikely to shift to a disposable approach, expansion in the use of disposables will happen only for current pipeline products, not the existing ones. A major exception may be vaccines, where pressure for new technology drives greater use of single-use components.

Leachables and extractables, a current regulatory concern in the industry, is an issue vendors heard over 15 years ago regarding filters. At that time, as today, disposable components, including filters, required extensive testing to ensure compatibility. Changing conditions required product-and system-specific analysis. Such product compatibility testing will likely always be required for most disposable products. Still to be decided is whether vendors should take responsibility for leachables testing, whether industry should improve methods of

analysis, or whether should vendors evaluate ways to improve the products themselves.

In the future, increased levels of partnering among vendors and users regarding leachables and extractables will be needed. Vendors will be expected to identify types of extractables in their products and simplify the process for manufacturers to identify sources and types of leachables.

## **THE ROAD AHEAD**

Most participants at the IVT meeting tended to agree with industry analysts, and do not expect disposables to radically change the way biopharmaceuticals are made in the near future. There will continue to be reliance on stainless, fixed common-use assets and equipment trains. Areas of potential use for disposables include upstream and downstream systems, filtration, tubing and components, fill-finish, cell therapy, and other applications. Some applications in disposables, however, have the potential for radically altering production strategies. The meeting participants also discussed potential opportunities for disposables to improve future biopharmaceutical manufacturing.

### **Offshore Manufacturing**

Some industry observers feel that disposables could have an impact on where biopharmaceuticals are made geographically. "In developing countries that may be capable of producing biogenerics, as the worldwide need for large molecule therapeutics grows, some active pharmaceutical ingredient (API) manufacturing will likely move offshore," said Lee Karras, senior vice president of pharmaceutical operations at AAIPharma. "This situation is already the case in the small-molecule arena. As such, you will eventually see large multiproduct facilities overseas that rely on disposable technology, especially in multiproduct equipment trains, so that their assets are best utilized and production costs minimized."

### **Improved Storage in Space-constrained Environments**

Dedicated compounding tanks used in parenteral manufacturing in a multiproduct facility need to be stored when not in use in an area that is clean and free of potential bioburden contamination. Disposables, in contrast, store more easily and efficiently than portable dedicated tanks. "Companies are moving toward storage into clean areas with high-efficiency particulate air (HEPA) control," says Karras. "These areas are costly to build and maintain. Disposable bags and tank liners can be stored in double or triple over-wrapped bags, flat and stacked in a lower cost general warehouse. When needed, the over-wrapped bags or liners can be taken into a clean area and unbagged in succession as they are moved into cleaner areas ultimately exposing the bags and liners to only the desired level of cleanliness."

### **Greater Flexibility for Small-scale Operations**

Disposables will become an enabling technology for the production of small-scale products, according to Roland A. Heinrich, PhD, vice president of bioprocess R&D at Millipore. "Flexible production opportunities in small to medium scale will give opportunities to small start-ups to commercialize earlier...or allow them to negotiate better with their large manufacturing partners," he says.

### **Personalized Medicine and Disposables**

The nature of cell and gene therapies make disposables a logical manufacturing approach. Visti Wedege, manager of cell culture products at Nunc A/S, says, "Disposables are becoming a critical component in achieving the promise of safety in personalized medicine. Disposables will ultimately provide a safe patient manufacturing and delivery solution by minimizing the potential for cross contamination. For the same reasons, disposables will likely prove to be a more cost-effective approach because the responsibility for cleaning and validation will move out of the clinic, as part of a cell therapy procedure, and to the component manufacturer." Bioreactors and other disposable elements produced under current good manufacturing practices (cGMP) enhance the overall convenience and safety of cell therapy procedures.

### **More Multiproduct Facilities**

Millipore's Heinrich also considers the application of disposable technology in multiproduct manufacturing settings a prevalent trend. Not all products need large volume manufacturing. Hence, multi-product manufacturing in one suite using disposables will allow high capacity utilization. In addition to multiproduct facilities, Heinrich envisions modular manufacturing done in a "rapid factory" based on disposable, prevalidated units that can be deployed quickly. These would be capable of producing products safely in areas without proper infrastructure; for example, they could be used to manufacture vaccines in underdeveloped regions.

### **Lower Costs for Additional Capacity**

Both contract manufacturing organizations (CMOs) and biotherapeutic manufacturers will be able to squeeze

more capacity into the same utility infrastructure by using disposables. "Some facilities may be able to double the capacity without impacting the majority of the utilities in the coming years if disposables are deployed in unit operations," says Tim Vickers, president of Project Planning and Delivery, Inc. (PP&D). "This will help keep incremental add-on costs lower than if they just added steel tank manufacturing capacity."

### **Reduced Seed Train Requirements**

Vickers also sees seed trains as an area that will impact production. These trains now comprise disposable components only. Expect as much as 2,000–3,000 L to be optimal use, as the ergonomic disadvantages increase and the net present value advantages diminish at larger scales.

### **Disposables May Allow Contract Manufacturers to Provide Unique Services**

In five years, according to Vickers, we will see an increase in the number of boutique contract manufacturers. "Disposables will allow the establishment of contract start-ups," he says. "Many will flourish because lower capital expenditure is required and they will operate at scales that are optimal for disposable use. These CMOs may provide unique services, such as cytotoxics, because they will not have to worry about tank-to-tank changeover issues from dissimilar products, for example, changeover from baculovirus expression to protein expression in mammalian cells."

### **Disposables Use in Animal Health**

Disposables are likely to be used more often in the manufacture of animal health products, i.e., those regulated by USDA, not FDA. As a result, here is the potential to lower the barrier of entry to the animal health industry. At present, this industry pours substantial capital into clean facilities, so a closed system may be very attractive. Today, disposable manufacturers do not seem to be concentrating their R&D or product development in animal health areas. This may represent a possible market for disposables.

### **Accelerated Production in Developing Countries for Export**

According to Holly Haughney, vice president of marketing at Pall Life Sciences, Biopharmaceuticals Asia, "Validation of cleaning in biopharmaceutical manufacturing can require a considerable amount of work for the submission for a new drug to the FDA or EMEA. In developing markets, such as India and China, where it is necessary to meet these requirements of the US and European regulatory authorities if manufacturers expect to enter the lucrative export market, the use of disposable systems provides a benefit in the reduced amount of testing and documentation for cleaning validation." Some industry analysts point to the potential to limit expensive infrastructure as a way to move toward "transportable factories." Disposables may possibly support efforts in developing markets such as China, India, Korea, and Brazil. Initially, hybrid systems may make production there more practical, perhaps in 5–10 years. Disposables may also facilitate local production of biologics by reducing the staffing requirements for talented employees that can produce regulated products. A fully disposable-oriented facility could probably reduce headcount.

### **Vaccine Manufacturing**

New viruses like avian influenza have increased the need for speed and safety in vaccine production. Disposable technologies can provide an advantage in these areas. For some products, according to Hélène Pora, PhD, marketing director of biopharmaceuticals at Pall Life Sciences, 70% of development and production time involves quality and safety controls. In vaccine production, potent microorganisms upstream in the process can present contamination risks and slow development. Disposables address these issues and can reduce the steps required to separate and purify conjugate vaccines. Disposable technologies can also be used in polishing steps where disposable membrane columns can remove contaminants more rapidly than resin-based chromatography can.

### **Improved Plant Safety**

Disposable manufacturing technologies can provide plant safety benefits. According to Robert Blanck, market manager at Millipore Corporation, "Disposables in the future will improve safety. Some areas in which this is already occurring include new gamma pre-sterilized flow paths, reservoirs, storage containers, filters, and connecting devices being developed that improve plant safety by making sterile parts free of operator intervention. Separating the operator from the product improves operator safety. This may be particularly valuable to the manufacture of products such as cytotoxics."

### **Rapid Downstream Purification**

New types of mixed-mode chromatography sorbents will make protein purification faster and cheaper. Chromatography is efficient and versatile and such products address downstream production bottlenecks caused by new technologies which have been adopted upstream in biopharmaceutical production. The ability to

purify different kinds of molecules allows users to develop platform technologies that can reduce the number of process steps. Mixed-mode sorbents can distinguish proteins that have similar or close isoelectric points. The ability to adjust selectivity will provide for a wide range of applications, including monoclonals, vaccines, enzymes, and plasma fractions.

### **Disposable Filling Lines in Fill–Finish**

According to Millipore's Robert Blanck, disposable filling systems will change the way fill–finish is done. They will allow faster filling-line implementation, easier validation, and improved sterility. The disposal of product contact surfaces will reduce downtime between filling campaigns and provide added product safety. The operator intervention in aseptic connections and components is eliminated up to the tip of the filling needle. This is particularly relevant for filling cytotoxic or biohazard components. Such disposable components can be installed in 15 minutes, compared with conventional filling operations, where set-up times may exceed eight hours. For R&D or clinical-fill operations requiring the fast development of products, or production "fill-and-finish" operations requiring improved filling efficiency and enhanced product safety, disposable filling technologies are expected to expand.

### **Fill–finish for Non-sterile Environments**

AAIPharma's Karras also feels that because disposables offer faster changeovers and require less-dedicated equipment trains, they make sense in fill–finish applications for parenteral manufacturing. "We may see a greater move toward disposable filling needles and small product contact change parts; these are tough to track and harder to clean (thus harder to maintain in a state of compliance)."

### **Reduced Operator Training and Oversight**

Disposables may permit lower staffing and training requirements in biopharmaceutical operations. Pall Life Sciences' Pora believes that the risk to expensive production batches due to operator errors can be reduced by decreasing the number of connection points associated with the use of sterile connection technology.

### **Simplified Biopharmaceutical Cleanroom and Facility Design**

As disposable technologies expand, they will have a greater impact on facility planning and design. Cleanroom operations for biopharmaceutical companies and contract manufacturers must manage contamination, yet maximize operations such as fill and finish. This becomes a design issue and the use of disposables must be part of facilities design considerations today. Whether for final product storage, sterile formulation, or mixing, barrier isolator technology that limits personnel interaction with exposed product must be considered.

### **Producing Otherwise Uneconomical Drug Candidates**

The economics of biopharmaceutical drug candidates that appear to be difficult to commercialize may change and disposables may permit the further development and possible commercial-scale production of such drugs. Disposables may permit the development of such "marginal" biologics because disposables work well at smaller batch sizes.

### **Other Areas of Future Opportunity**

Some other effects of using disposables may include:

- Reducing water for injection (WFI) requirements, permitting production in areas where costly WFI usage may impact decisions for building facilities.
- Pasteurization of products at the  $\geq 500$  L scale may be conducted in the future, or potentially outsourced. This is not currently being done.
- Semidisposable products may be used for certain campaigns, reducing costs and providing the benefits of both disposable and fixed systems.

### **STAYING ON TRACK**

To achieve their maximum potential, the work on R&D and developments for disposables continues. Some of the areas that require additional work may include:

- Addressing leachables and extractables from a manufacturing, regulatory, and analytical perspective.
- Identifying ways to reduce costs and enhance the overall value of disposables to increase adoption at the process development stage.
- Improving disposable systems to ensure scalability from process development to large-scale manufacturing for all products, including buffers, bags, reactors, tank liners, etc.

- Creating bag systems with options for easy customization. The cost and time-lag associated with customization is high. Given the infinite variety of configurations at a manufacturing facility, bags need to be easier to customize.
- Establishing standards for bags and connectors and reducing concerns regarding reliance on single-source vendors.
- Increasing product safety by reducing risks of rupture. Fixed tanks can have rupture controllers. Such products are being developed and marketed for disposables. These may be needed to enhance the robustness of existing disposables and broaden market acceptance.
- Creating systems that can help address "zero failure tolerance" situations. Certain applications cannot tolerate failure (e.g., human pathogens, some cytotoxics).
- Moving from a "batch mentality." Many safety concerns in the biopharmaceutical industry stem from a focus on batch production. Several innovations in the pharmaceutical industry came from the food industry, which has moved away from batch production. The pharmaceutical industry may need to move in this direction too.
- Reducing waste solvents in biopharmaceutical manufacturing is a factor in disposable equipment usage. Products should be developed that support these environmental considerations.
- Improving disposable downstream technologies. For example, one technology uses a rotary drum filter for laboratory applications. This uses media that may not suit all applications. Filtration media suppliers will need to expand offerings to meet current and future needs.
- Membrane chromatography, currently in use by many in the upstream analytical phases, has benefits over columns, including good flow rates, high capacities, and newer membranes that have produced sharper resolutions. These need to be further developed.

As single-use components in biopharmaceutical manufacturing processes continue to prove their economic, operational, environmental, and regulatory mettle, we will see greater diversification and increased usage in larger applications. Users and vendors will continue to explore the potential for disposables over the next 10 years. But it seems clear that the products are accepted as effective, useful tools to be considered within each manufacturer's system. They are seen as alternatives, for which economic models and end-user creativity will drive future applications.

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