

## The End for Stainless Steel?

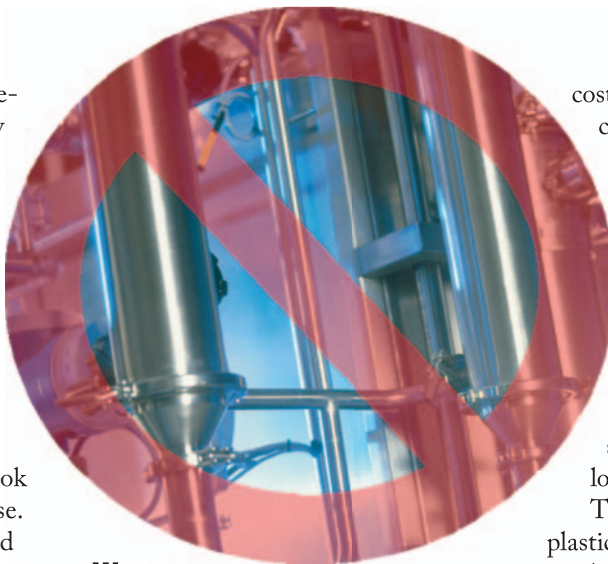
by Pietro Forgione and Mark Van Trier

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**P**rocess integration of single-use technology is a rapidly emerging issue in biopharmaceutical manufacturing. *Single use* is a phrase now commonly associated with the modern approach to manufacturing strategy for both existing therapeutic products and those in development. Considering the multitude of benefits afforded by disposability, you don't have to look too hard to see why this is the case.

In 2006, the biotechnology and pharmaceutical industries are facing a tough challenge of delivering more high-quality products to market within ever-contracting timelines. At the same time, companies must fully comply with exacting standards set by international regulatory authorities that govern their industry. To stay one step ahead of the competition on such an intense and competitive playing field, a company must strive to adopt new methods and tools that enable it to extract the utmost performance from all aspects of manufacturing and scale-up operations.

Here I'm attempting to chart the rise to success of single-use processing. On the way, I examine the benefits offered, some products that are currently available, and advantages of taking a holistic approach to "plastic-factory" implementation. I can then offer a sneak peak into the near future of single-use technology by reviewing a solution that could revolutionize many downstream processing applications in the biotechnology and pharmaceutical industries.



### WHY SINGLE USE?

The shift in manufacturing strategy toward a so-called plastic-factory approach is ostensibly driven by demands for reduced processing times, increased productivities, and reduced costs. On their own, these benefits build a strong case for implementing single-use technology. And its adoption is further encouraged by a regulatory environment that demands product consistency and compliance.

Many users have determined that single-use technology represents the future of production in this industry. By careful implementation of available products, companies are now extracting clear and measurable advantages in certain areas of concern: process economics, image and quality, pipeline management, and speed to market.

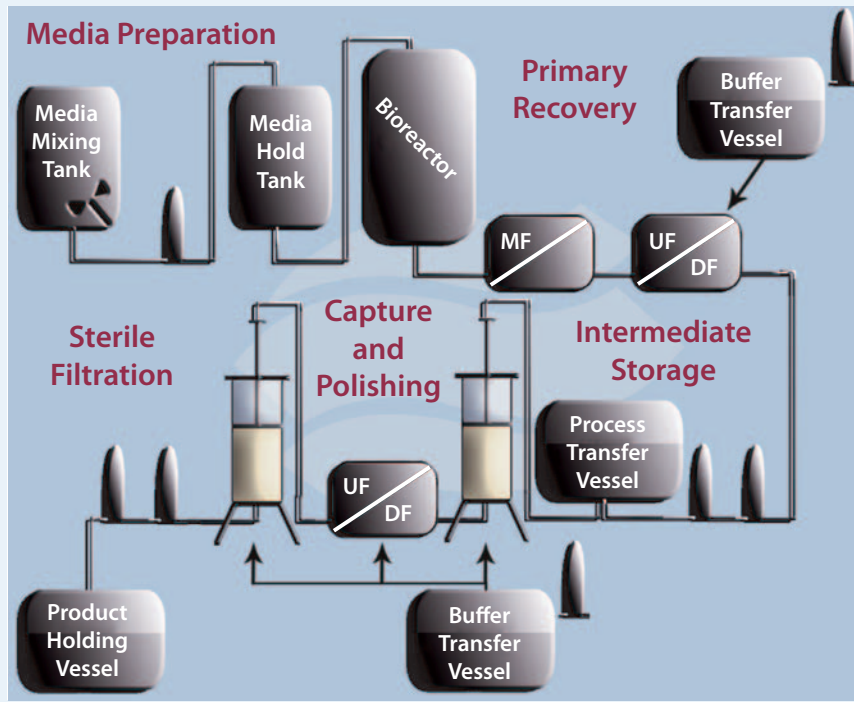
**Process Economics:** Encompassing many aspects of a pharmaceutical process — from facility design to day-to-day operation — process economics is clearly a broad consideration. Manufacturing alone generally equates to more than 20% of total operating

costs for a biopharmaceutical company. Any improvements to that area will have a very real impact on the commercial fitness of a company. Within a controlled manufacturing environment, single-use technologies truly excel. Flexible single-use systems considerably shrink process footprints, in turn allowing for smaller production facilities and lower associated operation costs.

The up-front risk of investing in a plastic factory is considerably reduced on three counts: First, the total sum of investment in designing, building, equipping, validating, and maintaining a facility based on single-use technology is lower than that for a traditional stainless steel process. Second, demand for expensive capital equipment is greatly reduced and deferred in time, which minimizes depreciation of equipment that represents a significant portion of the initial investment. And third, single-use solutions create closed systems, so they provide a significantly higher level of product containment than does traditional stainless steel infrastructure. Importantly, that high level of process containment removes the risks associated with dedicating a facility to producing a single drug. Companies can now manufacture multiple products in the same facility without risk of cross contamination.

Further benefits afforded by a plastic-factory approach become evident when examining a product manufacturing process. Often up to 95% of manufacturing cycle time is taken up by activities that add no real

Figure 1: Generic production process using conventional stainless steel systems (© JM SEPARATIONS)



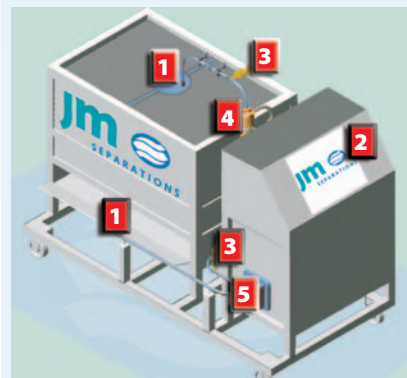
value. Consider the time and manpower required to break down, clean, and maintain a facility filled with stainless steel infrastructure. By careful implementation of single-use technology, most such cleaning and maintenance requirements are eliminated, which lowers labor and utility costs per product unit and improves the efficiency of operator time allocation. By adopting a single-use approach, it is possible for a company to significantly increase its production throughput while maintaining or reducing labor costs.

#### Pipeline Management:

Implementation of a scalable platform using single-use technologies allows more efficient handling of product pipelines. Because of reduced requirements for capital equipment at each stage — never mind the ease of use with disposable systems — a more aggressive approach can be taken to pipeline development. Essentially, that means more products can be developed with the same development budget and within shorter time lines.

Choosing a scalable suite of single-use systems facilitates and expedites process transfer from development to pilot to production-scale manufacture. By maintaining a consistent approach through development to production,

Figure 2: Single-use tangential-flow filtration system from JMS Separations (© JM SEPARATIONS)



- 1 Complete single-use flow path assembly
- 2 Automatic data acquisition
- 3 Single-use pressure and flow meters
- 4 Single-use TFF membrane
- 5 Choice of single-use pump technology

pharmaceutical companies can considerably minimize their validation burden. The nature of single-use systems eliminates requirements for cleaning validation. Development-stage compatibility studies can be considered as worst-case scenarios because of the generally higher surface area-to-volume ratios involved at smaller scales.

**Speed to Market:** When considering time in development, all the benefits of a plastic-factory approach come together to provide companies with a tool so powerful it can help thrust

them into a market-leading position. This is often the single most important consideration to biotechnology and pharmaceutical companies. The time within which a product reaches market very often can be the determining factor of its success.

The importance of speed to market can be difficult to quantify financially. But one global leader in high-technology manufacturing recently reported that getting a new product to market as little as one month early was typically worth more to an organization than the same product's entire research and development cost (1). Furthermore, bringing a therapeutic to market six months early or six months late can lead to a one-third increase or decrease, respectively, in its lifetime profitability.

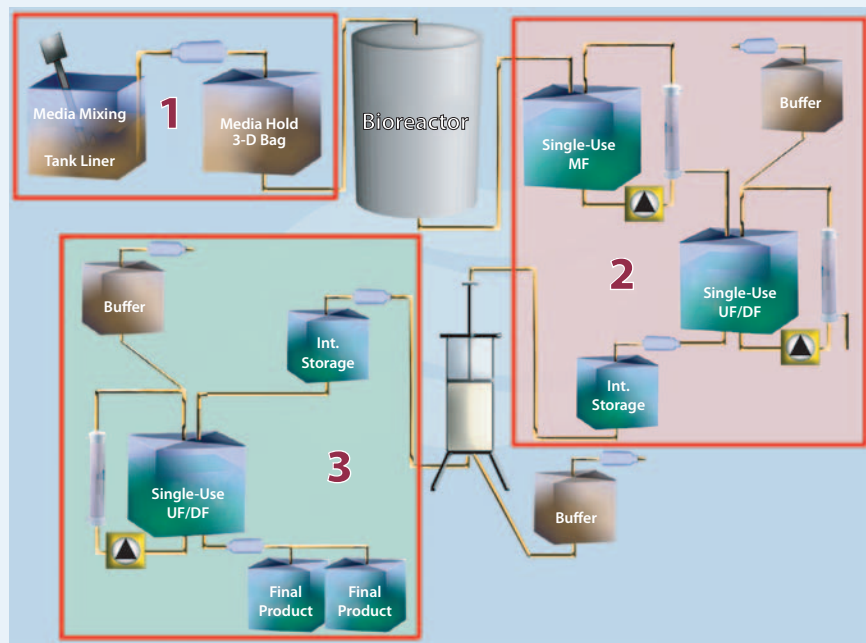
#### THE STORY SO FAR . . .

**Where Are We Now?** Biotech drug companies currently have access to a range of single-use products that can be incorporated into their processes. These include normal-flow capsule filters, single-use tangential-flow filtration (TFF) membranes, sterile liquid containment bags, membrane chromatography capsules, flexible tubing, and connectors. Individual products are often delivered sterile, so they remove some cleaning requirements associated with individual process steps.

Using such products, companies can realize some of the benefits discussed here. But alone, such things fail to live up to the advantages offered by a more holistic approach. By implementing some single-use products, users often end up with hybrid processes that contain a mixture of stainless steel and plastic-factory elements. It rarely delivers the full range of benefits described here.

**Where Are We Going?** The future of single-use technology may lie with holistic solutions that allow whole unit operations to be made completely disposable. The first phase of the plastic-factory revolution focused on individual products; the second phase aims to address whole application needs. At present, the main area of innovation lies with addressing the demands of upstream operations. Solutions such as

**Figure 3:** Full implementation of single-use solutions into a generic mAb process, with three distinct disposable unit operations (© JM SEPARATIONS)



disposable bioreactors, sterile bags with normal-flow filter manifolds, and self-contained fermentor sampling systems are already available. Such innovations allow users to approach some upstream operations with disposables, but there is still much room for development of this concept.

The idea of providing novel single-use solutions to the biopharmaceutical market is relatively new, and it will undoubtedly be an area of further innovation in the near future. In short, the future of single-use technology will focus more on applications than on individual elements. This should allow users to extend the benefits of “single-use” methodology deep into the heart of their processes.

The modern plastic factory approach to production allows small biotechnology companies to add value to their business with in-house pilot and manufacturing capabilities. And large pharmaceutical companies can streamline production, reduce operating costs, and deliver more products to market in less time.

**Is This All Too Good to Be True?** The answer to that question is a resounding *no*. We are on the cusp of a complete revolution in the way modern pharmaceutical processes are designed and conceived. Current “first-phase” single-use products already allow users to reap some of the potential benefits

of disposability. The real revolution lies ahead, however, with a “second phase” in which suppliers will take a more holistic approach to single-use technology and deliver novel solutions that meet the demands of whole process unit operations.

So it is fair to say that a suitable summary of the story of single-use technology so far would be that it is performing well, but that there are much better things to come.

#### THE MISSING LINK?

Right now there is some lack of disposable solutions for downstream processing applications. In a typical monoclonal antibody manufacturing process (Figure 1), the longest cycle times are found in cell culture, chromatography, and TFF units. Two of those three unit operations lie downstream, which should be the main area of focus for innovative single-use solutions. We have already begun to see advances in single-use membrane chromatography, but it has not yet become a viable solution for all such steps in all processes. Single-use TFF has not yet matured past the first “product” phase, with a range of membranes available that still rely on traditional stainless steel systems.

**A Single-Use System:** We at JM Separations (JMS) highlighted downstream TFF as a key area for

innovation where the benefits of single-use solutions could be fully extended into the heart of pharmaceutical/biotechnology processes. For us, this particular unit operation was key to unlocking the potential of downstream single-use technology processing applications. Ours is the first system of its kind available to the pharmaceutical industry (Figure 2). Now whole downstream unit operations can become fully contained and single use.

This modular system is capable of running in microfiltration and ultrafiltration modes. Such versatility allows users to combine filtration steps (Figure 3) without breaking open their closed systems. Experience with single-use solutions allows us to tailor the system to individual requirements. It can add diafiltration or other normal-flow filtration steps without compromising sterility.

#### THE BOTTOM LINE

Membrane area: 5 m<sup>2</sup>  
 Batches per year: 35  
 WFI cost: £1.50/L  
 Volume WFI for CIP and final rinse: 2500 L (£3750)  
 WFI cost per year: £131,250

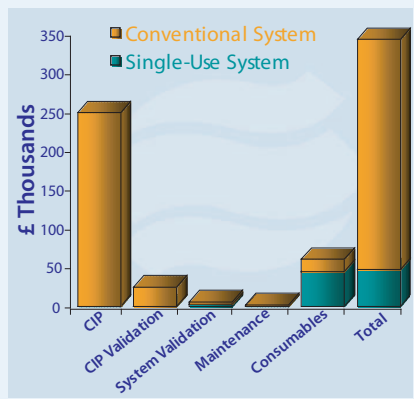
#### Single-Use Assembly

Complete flow path (including bags, tubing, membranes, and pressure transmitters): £1285/assembly  
 Cassette cost: £16,005  
 Labor/operator costs: £30/hour  
 QA sample analysis: £37/sample



**KrosFlow Research II system for process development using 60-mL to 10-L volumes. Single-use flow path assembly and membranes streamline development and allow a smooth transition to pilot production.**

**Figure 4:** Figure 5, graph outlining a summary of cost analysis results obtained when comparing conventional stainless steel tangential flow filtration (TFF) systems with a completely single use TFF solution. © JM SEPARATIONS



Using this single-use TFF method, a range of solutions scale from 60 mL (as pictured in the “Bottom Line” box) to production size. Contact materials are kept constant through scale-up, improving the efficiency of the development process.

#### How Does This System Compare?

The closest that users have been able to get to a single-use TFF operation so far is to incorporate disposable TFF membranes. Although that has removed an element of cleaning and possible cross-contamination, a large part of both still remains (in the system itself). With such stainless steel systems, the demand for utilities, maintenance, and capital expenditure remains high. Downtime and cleaning validation burdens associated with such a hybrid solution remains similar to those for conventional stainless steel systems, so the full benefits of disposability are not delivered.

With a single-use TFF system, capital investment is reduced at each stage of scale-up and manufacture, and cleaning and related validation are eliminated altogether. Because of the completely closed nature of these systems, users can be confident that they are achieving absolute product containment at all times, so multiple products can be manufactured in one facility without compromising their quality or integrity.

All that may sound familiar, and rightly so. By converting the whole TFF application from a hybrid system to one that is fully disposable, users

realize all those benefits discussed above.

The “Bottom Line” box outlines the parameters of a process we used in a cost analysis of conventional TFF versus the completely disposable TFF system. Figure 4 summarizes the results. A “plastic factory” approach can save up to £250,000 (almost half a million US dollars) in annual operating costs. If this approach is adopted early in a product’s life cycle, further savings come in the areas of facility design and build: with smaller HVAC systems (because of built-in product isolation) and downsized water-for-injection installations (because of dramatically reduced peak demand levels).

#### SUMMARY

Single-use technology has successfully navigated the first phase of its own life cycle, serving up a range of products that deliver certain advantages. By taking a holistic, application-centric approach, suppliers are moving single-use innovations into their second phase: to deliver a more complete package of benefits to the bioprocessing industry. By strategically implementing these single-use process solutions, biotech companies can significantly improve their development, production, and delivery of new and existing therapeutics. Solution-based technologies are beginning to revolutionize whole unit operations in the biopharmaceutical industry. With introduction of the single-use TFF platform, it now becomes possible to reshape some of the most resource-dependent applications in downstream processing for more streamlined and efficient operations.

#### REFERENCE

1 Preston JT. Business: Steps to High-Tech Success. *The Industrial Physicist* August–September 2003: 24–26. 🌐

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