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SUPPLIER Side

Single-Use Technology Enables Flexible Factories

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The biosimilars market is rapidly evolving, with more than 450 biosimilar molecules in development worldwide, and many anticipated transfers of molecules in process around the globe. With US$85 billion of biopharmaceutical products coming off patent by 2020 (**1**), the driving force to develop biosimilars is strong. The market will be highly saturated, with dozens of biosimilars currently in development for each current blockbuster molecule. We know of 46 trastuzumab biosimilars and 39 rituximab biosimilars in development. Because the biosimilars market is projected to be a commoditized one (with multiple entrants in most regions), it will be very cost competitive.

Current Biosimilars Market

Costs and Pricing: Deep discounting already has been part of the market. Norway's price regulator has been offered a 72% discount on biosimilar Remsima infliximab (produced by Celltrion and licensed by Orion Pharma) for 2015–2016. Previously, Hospira had offered a price discount of 51% off Remicade infliximab pricing for the biosimilar Inflectra infliximab (**2**). In Japan, the reimbursement price of Remicade infliximab is US$750.32, compared with $513.95 for the biosimilar Remsima infliximab, representing a 32% discount. The reimbursement price of Neupogen filgrastim is $197.28, compared with $129.69 for the biosimilar filgrastim in Japan, representing a 35% discount (**3**). For certain gastroenterology indications in Norway, Remsima infliximab has gained 48% market share as opposed to Remicade infliximab's 13% market share, because of cost savings to payers (**4**).

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Process Focus: Product development, manufacturing

Who Should Read: Process engineers, facility design, manufacturing

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Level: Introduction

Although biosimilars are expected to offer price discounts over originator molecules, they still incur hefty investment for development and manufacturing. Biosimilar drug development is estimated to cost US$100–150 million, by contrast with generics that cost only US$2–3 million and originator biological drugs with a very high cost of $800 million (**5**). A significant savings in development costs for biosimilars has come from a reduction of R&D for drug development (because the drug target is known). Clinical trial costs for biosimilars also are lower than for innovator drugs, especially at phase 3 because patient numbers can be reduced for biosimilar clinical trials. However, biosimilars will not have the large profit margins enjoyed by originator drug products. So cost is a critical factor in biosimilar manufacturing. The industry is targeting cost of goods (CoGs) at <$100/g for the 2,000-L disposable scale. That is aggressive costing using single-use systems and thus requires careful process design.

Manufacturing: Many biosimilar molecules will be manufactured at the 2,000-L scale or smaller because these products are expected to have smaller market demands than originator drugs (several biosimilars are expected to share each market). Given the anticipated scale of biosimilar processes and the accelerated speed to market and need for flexibility with technology transfers, biosimilar molecules are a good fit for the "flexible factory" concept.

The trend for single-use and flexible factories is increasing (**6**). A flexible factory is a single-use facility designed for ease of use, reduced risk of contamination, and flexibility of processing. A flexible factory enables rapid suite configuration for different processes and rapid changeover between batches. Minimized need for water for injection (WFI) and clean-in- place (CIP) solutions enables less cost investment in a facility and capital equipment.

"Pharmerging" markets are the highest growth areas in the pharmaceutical industry. Many countries, including Korea, Brazil, and Turkey have government programs to establish local biologics manufacturing. The need for rapid and flexible installation with reduced utility requirements is rising. Korea, Singapore, Malaysia, and China are predicted to expand their manufacturing capacity by 180% by 2018 (7). India leads the world with 85 biosimilars development projects, followed by 51 projects by multinational companies, and 48 projects in North America (7).

Leveraging Single-Use Systems for Flexibility

The flexible factory concept includes a number of factors such as single-use equipment implementation, facility design, modular or classical engineering, and enhanced flexibility. It allows reduced capital expenditures while increasing facility modularity and adaptability to meet local market demands.

Benefits: Smart implementation of single-use technologies allows drug manufacturers to get the best possible outcomes from those technologies, including easy and fast modification of set-ups for different processes, increased capacity with rapid changeovers between batches, fewer sterilize-in-place (SIP)/CIP steps with associated time and costs savings, ease of use, lowered contamination risk, and an ability to run some process steps closed and continuously with potentially lower cleanroom classifications.

Despite introduction of new single-use technologies, the majority of bioprocesses and facilities still contain some stainless steel and multiuse equipment. Using available equipment, all steps from upstream to downstream and fill–finish can be completed with single-use systems. That is true not only for bench and pilot scale, but also large-scale processing. Routine good

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manufacturing practice (GMP) processing can be conducted with disposables as well. Today, implementation of single-use technologies is possible from development scale to GMP manufacturing at the 2,000-L scale.

With single-use systems, risk of contamination is reduced at all steps because disposable systems arrive sterile without a need to clean or sanitize them, and they are set up for manufacturing runs without opening. For example, bioreactor bags are connected to media bags through sterile connectors, so there is no open phase. Harvesting can be completed in the same way. Sterile welds can be used as well, depending on scale.

Single-use systems are easier to use than traditional equipment. Operators require less training with single-use systems than with stainless steel equipment because disposable equipment is much simpler in design (e.g., less piping and no spare parts). Single-use assemblies (e.g., Flexware by MilliporeSigma) are usually preconfigured for quick and easy installation. Finally, operations are mostly automatic, and recipes are well known.

Efficiency: In terms of enhanced flexibility, single-use equipment implementation can provide a number of advantages. Bioreactors are no longer fixed; they can be moved from one suite to another depending on need. Downtime is reduced to a few hours rather than several days (as is the case with stainless steel equipment). Moving equipment from one suite to another in less than a day provides flexibility and allows quick changes in production plans. Similarly, buffers can be prepared in single-use mixers and then rolled into a suite for use. Because no equipment is fixed, there is no need for hard piping. A new buffer can be brought in or taken out without affecting a suite and other areas of a process.

New generations of equipment (e.g., the Smart Flexware system from EMD Millipore) allows the use of one piece of equipment for several operations. These systems enable either chromatography or tangential-flow filtration (TFF) with a single piece of equipment, for example. The additional cart contains pumps for chromatography or a tank for TFF. That concept not only reduces the footprint, but also investment and operator training. Flexibility is embedded in the equipment design. Cart mobility enables optimal placement in the suite when carts are in use and then rapid storage in a corner when they are not, enabling more effective use of suite space.

Costs: We have compared the savings associated with the single-use systems with that of glass or stainless steel in a development laboratory and in production suites. Our evaluation was based upon a "standard" process development, including three consecutive runs and associated analytics followed by technology transfer to production, with cell expansion and manufacturing of one preclinical and three GMP runs. We observed a 15% time saving for monoclonal antibodies (MAbs) projects with single-use technologies.

Focusing only on production areas, we found that moving to single-use technologies enabled us to double per year at medium scale (50–200 L) and make an additional 42% runs at large scale (1,000–2,000 L). These changes were mainly due to the "non-value added" work that doesn't exist with single-use technologies such as CIP/SIP and associated preparation of the suite. Whereas a stainless steel suite is cleaned and prepared in three to five days, a similar suite equipped with single-use equipment is ready in half a day.

Leveraging single-use systems not only saves time, but also CoGs. For a 3,000-g clinical-scale MAb campaign at 200 L or 2,000 L, the CoGs are significantly lower with single-use systems. We observed a 42% cost savings at the 200-L scale and a 23% cost savings at the 2,000-L scale. Significant savings such as for electricity and water can be achieved with single-use technologies, and fewer technicians are needed to operate a disposable process than a stainless-steel system.

Facility Design

Equipment is a key component of a flexible factory, but it is only one piece. The design of a facility itself is essential. Our company uses a templated process to design the facility needed for a specific process or program. To accomplish that, we first need to understand exactly how many molecules and how many runs of each molecule will be needed every year for the next 10 years. That ensures that we do not design a facility for only today, but rather one that meets requirements of the next 10 years. This approach is important for both modular concepts and classical buildings.

Based on the processes and number of runs, we define an equipment list that indicates a footprint for each suite. The sum of all suites with their associated "support" areas (e.g., washing and storage) defines the footprint of the facility. Finally, that footprint is translated in a number of layouts that represent different operating options for a facility. At that stage, decisions need to be made regarding facility design. Options include corridors for dispatch of buffers to different suites with carts and mixers or central buffer and media preparation areas for dispatch through "mouse holes" based on numbers of run, scales, number of suites, and so on.

Related decisions dictate future facility expansions. A corridor is an interesting option for duplication of a facility by mirroring existing suites on the other side of a corridor. A central buffer and media preparation area is a good option for an extension of a facility by just extending the area further and adding more suites around the newly created space. Other options include pure duplication of capacity (if the land allows it) and extension into new suites in a wider facility.

One important decision is selecting between modules and classical engineering. Modules are definitely the choice for 2,000-L scale facilities. Constructing a typical project at such a scale requires 10 months less time with single-use systems than with than classical engineering. The savings comes primarily from reduced engineering (6–7 months) and site installation (4–5 months). Modules also allow equipment integration at a modular facility provider for shipment of a "turnkey" facility, which is preconfigured and ready to run the first batches for staff training at a receiving site.

Modules enable faster installation, but they are not always the best choice for processes at very large scale. At such capacities, classical engineering may be favorable. Some construction requires multiple floors, for example, and the complexity of designing this feature with modules can eliminate the benefits of a modular design.

A third option is a hybrid design using modules and traditional (stainless-steel) equipment. Our company has recently designed a large facility in which modules were used for manufacturing suites, but all larger areas (such as fill–finish and warehouses) used traditional construction. The manufacturing area could be shipped preconfigured with equipment integrated. And because some space was kept for future expansion, such expansion would have a modular design as well.

Choosing the Right Partner

Timelines and costs are important drivers in biosimilar production, and the aspects of a flexible factory described here are key to a company's biosimilar strategy. The benefits of a flexible facility and a holistic approach of implementing single-use or modular facilities can maximize savings and ensure success. Selecting partners for your strategy definition can be a difficult decision because engineering is not manufacturing (and vice versa). Today, only a few companies have knowledge about all aspects of what a biosimilar company needs regarding facility design, process development support, manufacturing equipment, regulatory support, and GMP training.

An accelerated timeline for biosimilar process development mandates that productivity and scalability be carefully considered during bench-scale development. Biosimilar molecules will undergo technology transfer, often to new facilities in emerging markets that can have limited experience in biomanufacturing. This requires processes to be robust and scalable to minimize risk of failure during technology transfer.

New technologies in single-use processing increase robustness of MAb processes and allow for rapid process development with proven scalability. Careful advance planning and consideration of long-term needs are required for selecting an ideal installation that meets manufacturing needs and delivers process robustness, flexibility, and optimal CoGs. Choosing an appropriate industry partner to assist in those manufacturing design decisions can lead to significant savings in both time and money and result in a flexible and robust facility design.

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