

Biomanufacturing for the 21st Century

Designing a Concept Facility Based on Single-Use Systems

Andrew Sinclair and Miriam Monge

In its early days, biomanufacturing was driven by science and technology with little regard to costs. Now the focus is on maximizing returns on investment in expensive facilities. Commercially available single-use disposable technologies have the potential to improve manufacturing operations. Reference is made to a typical monoclonal antibody (MAb) process, relating benefits in terms of capital and cost of goods.

The need to challenge the current orthodoxy was discussed at a June 2004 conference in Geneva (1). There was a strong emphasis on changing the mindset in the biotech industry, moving the focus to process optimization and operational excellence. Ways to achieve operational excellence include planning for capacity and reducing time to market by shortening cycles — all while reducing cost of goods. Reducing time to market is affected by shortening not only clinical development time (clone-to-clinic), but also the time it takes to design and build a manufacturing facility.

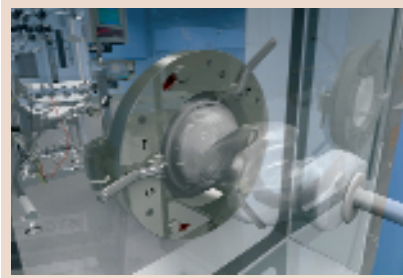
The intention of our study was to develop a leading-edge design for a concept facility that exploits fully the benefits of single-use disposable technologies. By comparing this concept facility with a traditional facility based on reusable equipment

(stainless steel), we sought to identify the benefits of disposable technologies, thereby stimulating industry discussion.

PROJECT HISTORY

Stedim commissioned Biopharm Services (www.biopharmservices.com) to evaluate the impact of available single-use technology on the design of a multiproduct mammalian cell culture facility. The facility design would look afresh at layout, taking into account possible integration of single-use technology. The costs of the concept facility would be compared with an equivalent traditional facility. Biopharm Services worked in partnership with the architects Clean Design (www.clean-design.co.uk). This is the third study that Biopharm Services and Stedim have developed together. It is by far the most radical study in terms of the impact of single-use technologies on facility design and operation.

Photo 1: The RAFT single-use rapid aseptic fluid transfer system (STEDIM)



The study recommends application of single-use disposable systems within the industry as part of the drive for operational excellence.

STUDY DESIGN AND PROCESS SELECTION

Our objective was to design a commercially relevant production facility around the use of single-use disposable technologies and to compare it with a conventional stainless-steel equipped operation. The facility would manufacture mammalian-based therapeutic proteins and be capable of handling multiple products. Material manufactured would be used for a phase 3 clinical trial, building up supplies for product launch and small-scale production. The facility design would simplify operations while maximizing operational flexibility and minimizing capital and operating costs.

Process Selection: Commercially relevant processes were selected for the concept design. The facility was to house a multiproduct, perfusion-based MAb process. The 1000-L scale process would run for 25.5 days, using a standard recovery and purification sequence. The perfusion rate of two volumes (cell culture capacity) per media volume per day would total 2000 L of media/day. Two typical MAb processes were used for the simulation, with a 0.3g/L cell line expression.

The process starting point was inoculum through to the bulk sterile-filtered, purified product — the stage before formulation and filling. The plant capacity is nominally around 90 kg of bulk purified protein per year. The exact capacity depends on the perfusion process itself, the number of products, and changeover times.

THE CHALLENGES

The first challenge was to reduce capital and minimize the project timeline; the second was to increase operational flexibility while minimizing operating costs.

The facility design and build challenges were to design, construct, and validate the facility to reduce the project timeline, thereby allowing the product to get to market faster. This offers the additional benefit of maximizing the project's net present value (NPV), thus using capital more effectively and ensuring a faster return on investment.

The project needed to

- Remain within the given investment budget constraints
- Ensure high flexibility in the facility
- Ensure a smooth and swift validation period
- Meet cGMP demands according to EMEA and FDA for a smooth approval of the drug
- Meet health, safety, and environment (HSE) objectives for the 21st century

The facility operation challenges called for

- Reducing operating costs
- Increasing throughput by reducing turnaround times
- Ensuring high flexibility in the process
- Minimizing operational overheads (labor, materials, waste)
- Developing an appropriate design of the facility to meet lean lifecycle management criteria such as low maintenance and economic use of resources.

SINGLE-USE TECHNOLOGIES

Single-use technologies have gained increasing acceptance by the

industry as a means of achieving safe, compliant, and efficient processes. As the industry awakens to the technology benefits, there is a demand for further integration of disposables into processes. The goal is to develop integrated single-use solutions that offer certain process functionalities (such as mixing, temperature control, aseptic connection and disconnection, and controlled freeze-thaw) within a closed system. Single-use technology innovations that significantly affect the economics and design of the concept facility include the following products and systems (the "Products Mentioned" box lists these products and their manufacturers):

The Flexel 3D Mixing System with Temperature Control: Solutions are made up using an impeller within the Flexel 3D bag and then pumped through a single-use sterilizing disposable filter into a hold bag. The Flexel 3D system with integrated impeller is used within the concept facility to prepare media and buffer solutions.

An alternative method of mixing developed by Stedim but not a feature of the concept facility is mixing by recirculation. This method offers the benefit of being noninvasive, offers process security as a closed system, and is simple to set up.

The Single-Use Rapid Aseptic Fluid Transfer (RAFT) System: This innovative technology brings an integrated solution to a recurrent problem in bioprocessing: how to transfer sterile processing solutions from one process area to another without contaminating progressively cleaner environments.

The RAFT system (Photo 1, opening page) plays a key role in the concept facility by allowing docking of Flexboy or Flexel 3D bag systems from 50 mL to 2500 L with an integrated single-use Beta Biosafe to the Alfa Biosafe door. These systems are stationed in the materials hall. The door is opened, and the bag tubing with integrated Kleenpak connector is transferred through the Biosafe port to make the aseptic

MANUFACTURERS AND PRODUCTS MENTIONED IN THIS ARTICLE

Biopharm Services: Technical consultancy in the biopharmaceutical manufacturing sector; www.biopharmservices.com

Clean Design: Architects; www.clean-design.co.uk

IDC (Isolateur Dénominateur Commun): Biosafe® transfer port system; www.idcbio.com

Integrated Biosystems (a Stedim Company): Celsius FT100 and Cryofin Controlled freeze-thaw systems; www.integratedbio.com

Pall Corporation: Kleenpak™ connector, biopharmaceutical filtration and separations products; www.pall.com

Sebra: Radio frequency (RF) tubing welders; www.sebra.com

Stedim products: The Flexboy® bag system (50 mL–50 L volume) and the Flexel® 3D system (50–3000 L volume); 100- and 2500-L Palletank®; the Single-Use Rapid Aseptic Fluid Transfer (RAFT) System

connection to equipment in the higher classification process area.

The RAFT technology enables segregation of the support operation from the process while increasing productivity, with no more waiting for cleaning, steaming, and cooling.

Kleenpak Single-Use Aseptic Connectors: In collaboration with Pall Corporation (www.pall.com), the Kleenpak connector mounted on Stedim bag systems is a state-of-the-art single-use aseptic connector that eliminates the requirement for capital equipment such as laminar airflow (LAF) cabinets (with their related maintenance), while increasing flexibility regarding placement of connections. Productivity is also increased because those connections can be made in seconds. The Kleenpak connector is used in association with the RAFT system within the concept facility for connecting perfusion bags through the wall to the bioreactor and connecting small volumes of buffers through the wall to downstream processing areas.

Photo 2: The Celsius-Pak (INTEGRATED BIOSYSTEMS INC., IBI, A STEDIM COMPANY)



Flexboy manifolds with integrated disposable filters and tubing collect smaller volume solutions from the purification areas. For easy storage, movement, and space-saving, these manifolds are stored in special racking systems.

Celsius-Pak: In the concept facility, the Celsius controlled freeze-thaw system provides a single-use scalable solution for controlled freeze-thaw. The Celsius-Pak stores bulk product coming out of viral purification to be frozen in the freeze-thaw module for later shipping to final formulation and filling. The single-use Celsius-Paks offer the necessary flexibility for manufacturing in multiproduct facilities (Photo 2).

Other facility features include **2500-L Pallettank or two stacked 1500-L Pallettanks** for holding solutions within the facility and minimizing footprint

Radio frequency tube welding and disconnection devices for removal of samples from the bioreactor and for adding small feeds to the bioreactor

Automated guided vehicles (AGV) for moving solution containers to/from the warehouse and processing areas; for example, to and from buffer and media preparation areas and docking stations adjacent to processing areas.

SINGLE-USE TECHNOLOGIES: IMPACT ON DESIGN

Through the application of the single-use technologies previously described, the facility design can now be based on single use of all support systems and components (disposable filters, bags, sampling arrangements, and so on). This feature, together with the development of methods for making sterile connections, has a major impact on facility design. Facility operations do not reuse materials or

components, thus reducing or removing wash up, cleaning, and sterilization areas; reducing high-quality utility requirements; and reducing liquid effluent. There is, however, an increase in solid waste. Another impact on design is the removal of solutions such as media and buffers from processing areas. This reduces the footprint of high-classification areas, simplifies operational flows, and segregates material preparation and handling from process operations.

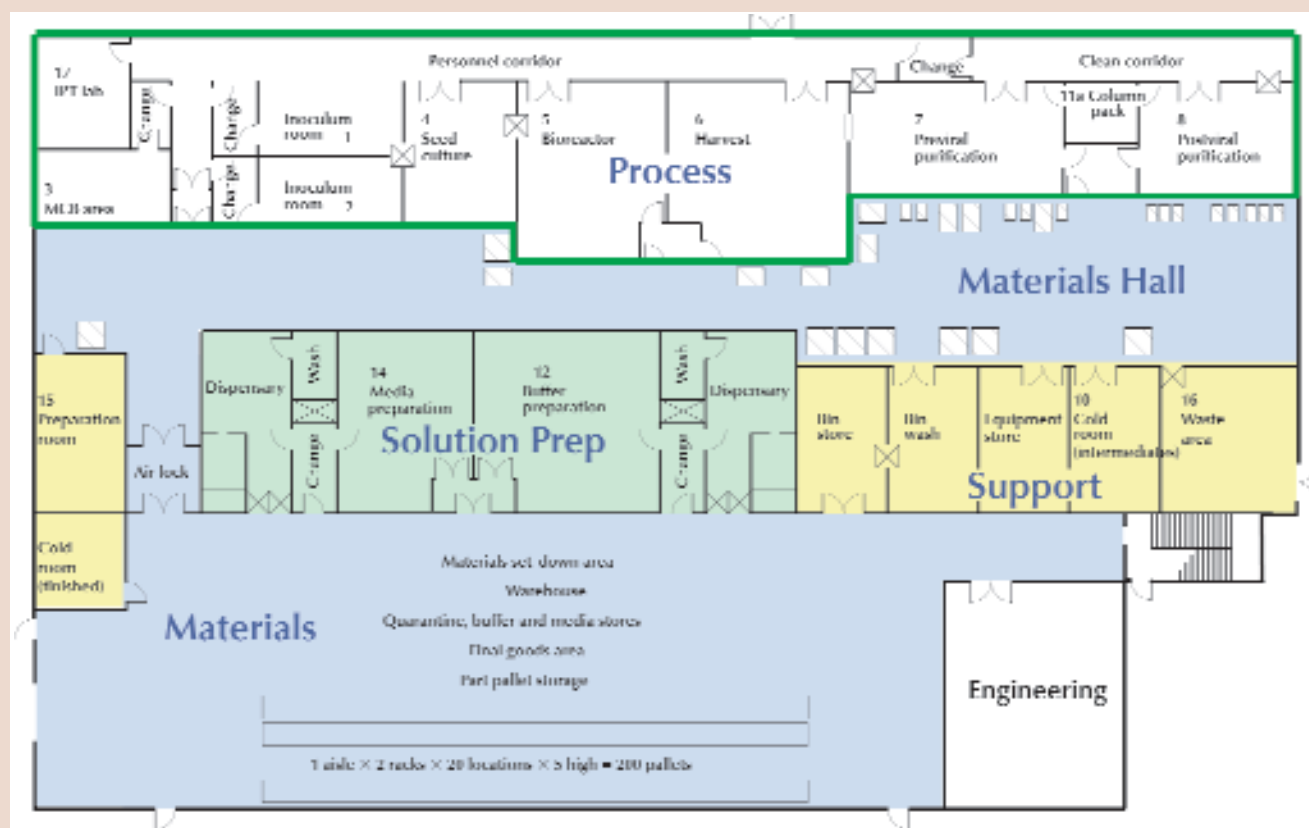
The concept facility fully exploits the potential of single-use systems and challenges the current status quo of traditional facility design.

THE PROCESS

Multiple products were used as the basis of the design. They were based on typical MAb manufacturing processes.

Once inoculum is grown in the inoculum room, it is transferred to the seed culture room through a transfer hatch. The seed is grown in a 250-L bioreactor. The seed culture is used to inoculate the perfusion bioreactor in the

Figure 1: Concept facility layout, showing functional areas



bioreactor room once every 30 days. The 1000-L perfusion bioreactor runs for 25.5 days at a perfusion rate of two volumes of media per volume of cell culture capacity per day (VVD), requiring 2000-L of media every day.

Fresh media are supplied at docking stations in the materials hall. Product is collected into Flexel 3D bag systems (one of two 2000-L systems). The perfusate is clarified and concentrated tenfold. Every 24 hours, 200 L of intermediate product is transferred to the previral purification room where it is purified using protein A chromatography, followed by ultrafiltration, ion-exchange chromatography, and viral inactivation.

The postviral purification room is located adjacent to the previral purification room and is used for gel chromatography, formulation ultrafiltration, and bulk filling. The final bulk product is frozen using the Celsius-Pak system.

THE FACILITY

Footprint: Through the adoption of single-use technologies, the layout of the facility is simplified and certain

Table 1: Comparison of the concept facility to a traditional facility

Changes	Areas Affected
Floor area reductions to all the main process rooms	Bioreactor Harvest Purification suites
Removal of rooms from the facility	Autoclave Wash up Dirty equipment store
Additional step	Palletank container wipe down
Downgrading and simplification	Materials movement into process suites Segregation of people (material handling versus process) Downgrading in materials hall to controlled but not classified

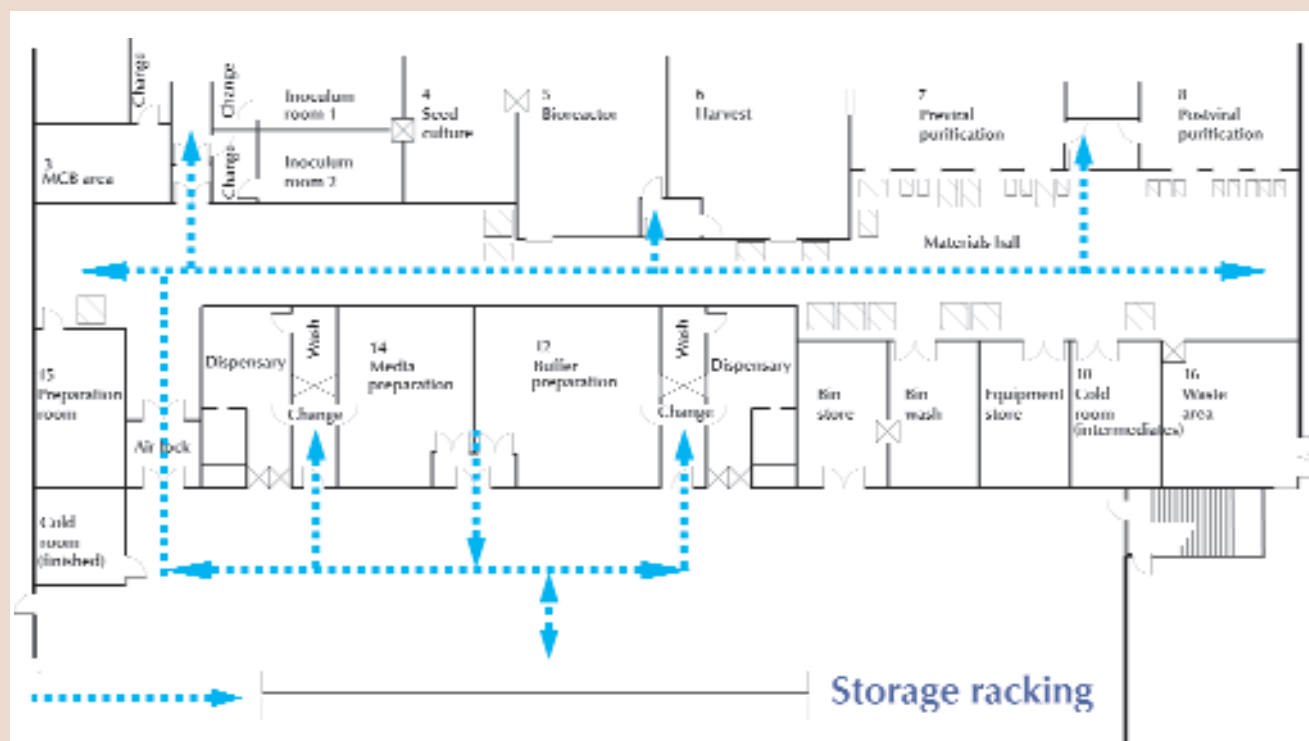
areas are reduced or removed altogether. Table 1 summarizes the changes to the layout.

By this means, the facility layout can be considerably smaller than that of a traditional facility. Figure 1 shows the layout developed for the facility together with illustrations of functional and environmental classifications. Solution holding and product collection are moved into the materials hall. Single-use sterile docking and connection technologies are used to connect the solutions and process containers

through the wall of the materials hall into the process.

Environmental Classification: The removal of the solutions from the processing areas reduces the sizes of expensive cleanrooms. In this facility design, the cell culture and harvest areas are designated as Class D and the purification suites as Class C. The solution preparation areas are designated as Class D, whereas the materials handling areas (the storage area and materials hall) are handling sterile, totally enclosed solutions. Consequently, we can

Figure 2: The flow of materials in the concept facility



designate such areas as controlled rather than classified spaces (CNC).

MATERIALS

All materials enter and leave through the warehouse, where they are stored before use. Figure 2 describes the flow of materials. They include single-use systems (bags, filters, tubing) and raw materials and intermediates (media and buffers). Small components and solutions are moved from the warehouse to production down the materials hall, then enter the production areas through material transfer areas. Large-volume solutions are moved from the warehouse through the materials hall and placed at docking stations outside the production area. Connections to the process are made through the wall using the RAFT aseptic fluid transfer system and Kleenpak connector. That enables sterile docking and connection without compromising system or cleanroom sterility. The facility will use an automated AGV to move the materials from the warehouse into the materials hall to

the point of use stations (Photo 3, Figure 3).

SOLUTION PREPARATION

The concept adopted is similar to buying preformulated solutions in single-use bags: You prepare the solution and hold it in storage before use.

Raw materials are moved from the warehouse to the dispensary, where materials are weighed out in a dispensing booth into a Flexel 3D bag system. Storage is provided in the dispensary area for empty Flexel 3D bags, which are held in racks once the outer packaging is removed. Those preweighed materials are added to WFI or purified water of the required volume in a Flexel 3D bag system with integrated impeller. The

solution is mixed and then transferred to a Flexel 3D bag system through a disposable sterile filter.

Once made-up solutions are held as sterile solutions within their Palletank containers, they are transferred through the material airlock into the warehouse, where the Flexel 3D systems can be stacked up and sterile solutions held in their closed bag systems until required. This approach offers the possibility of manufacturing economic batch sizes that take up minimum floor space. This decouples solution preparation from the process (Photo 4).

PERSONNEL

The advantages gained by using the RAFT system to pass solutions through a wall enable segregation of materials from the main process zones, allowing significant changes in the way the facility can be staffed and operated.

People would not handle materials in the process areas, and they would not be required to manage autoclave and washing

Photo 3: The materials hall (STEDIM)



Figure 3: People and material movements

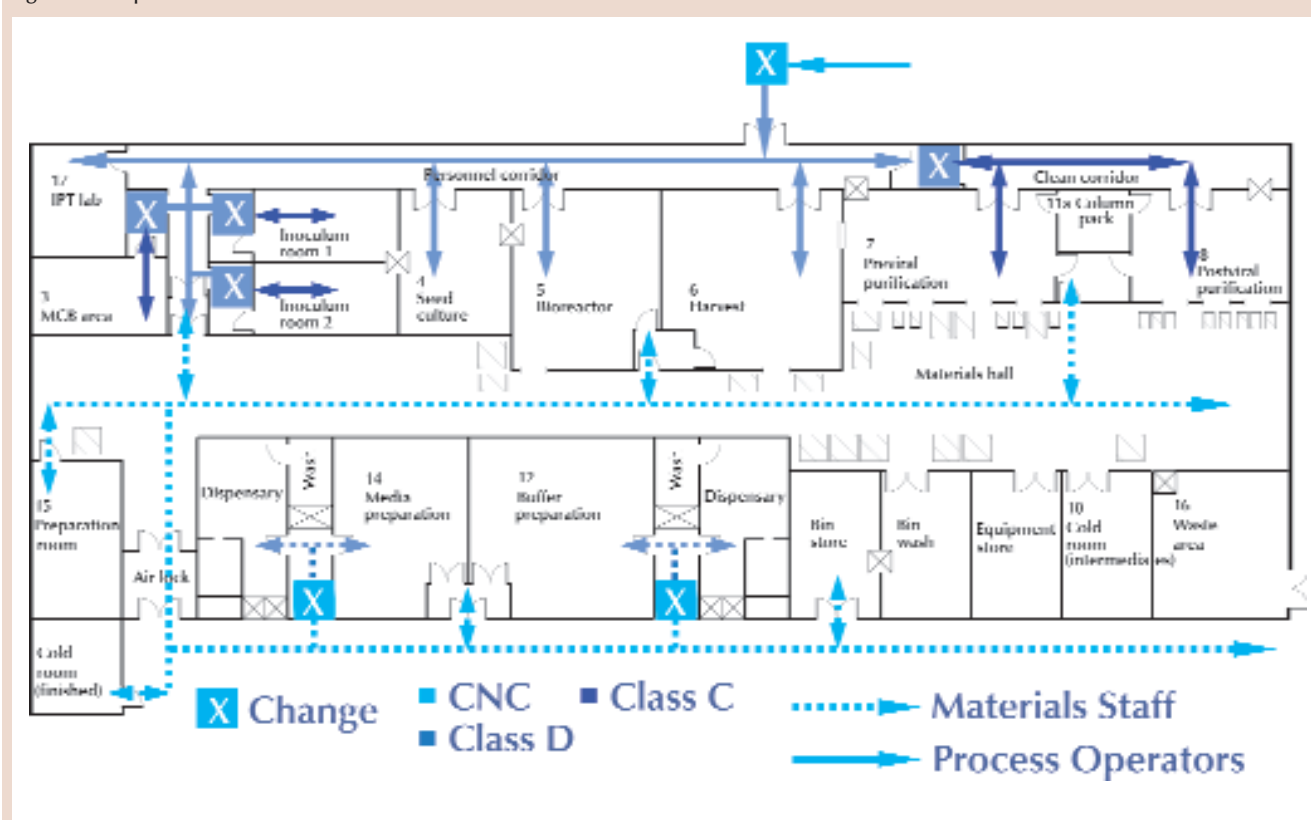
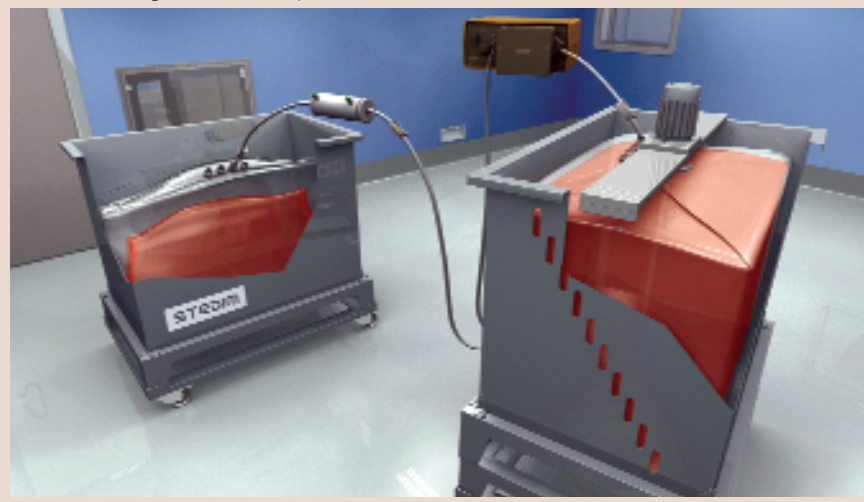


Photo 4: Mixing in Flexel 3D system (STEDIM)



areas. Running the solution preparation as an offline activity and using automation creates more efficient use of the materials-management staff.

A RADICAL REDESIGN

Available single-use technologies can be used to rethink the way we design and operate our facilities. In particular, coupling innovative connection technologies (RAFT and Kleenpak) with single-use bags allows facility designers to remove solutions from processing areas and eliminate the requirement to recycle support equipment through washing and autoclave suites. As a consequence, the facility layout can be radically redesigned by

- Simplifying material flow
- Decoupling the solution preparation from the process
- Simplifying personnel flow
- Reducing the footprint
- Reducing/reorganizing labor
- Reducing the equipment requirements.

These features result in significant benefits in terms of design build and operation of a facility by enabling

- Fast product changeover
- Enhanced product security
- Cost-effective manufacturing
- Reduced labor
- Reduced utilities
- Reduced capital.

In an upcoming issue of *Bioprocess International* (the Facilities supplement scheduled for February

2005) we will look at how these qualitative benefits translate into quantifiable savings in terms of capital, time to build, and cost of goods. We will describe the methods, assumptions, and results. The analysis will take account of operational issues covering maintenance, operations, and validation as well as reductions in capital.

ACKNOWLEDGMENTS

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REFERENCES

1 *BioLOGIC Europe 2004*, 22–24 June 2004 (Geneva). Organizer: Terrapinn, www.lifescienceworld.com. 

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