

Smart Modular Package Units for Single-Use Processing Addressing Cost, Speed, and Flexibility Challenges in Biologics Manufacturing

Burkhard Joksch and Stuart Tindal

With worldwide sales of biologics reaching over \$250 billion in 2017 and the market continuing to grow at a rate of 9.5 % per year (1), biopharmaceutical companies continue to view developing and producing biologics as an attractive proposition. However, the portfolio of biologics is changing. Now many different types of biologics are emerging (e.g., antibody–drug conjugates and cell and gene therapies) with complex manufacturing requirements. And the global market is becoming more competitive as developing countries seek to access and manufacture affordable biologics and biosimilars.

A McKinsey report states that the average costs of drug development (including the cost of product failure in trials) have almost doubled since 2010 from \$1.18 billion to \$2.18 billion in 2018, whereas forecast sales have fallen from \$816 million in 2010 to \$407



million in 2018 (2). To remain competitive in this rapidly changing healthcare landscape, biopharmaceutical companies are continually looking at strategies to reduce their costs. One approach is to increase the flexibility of their biologics' production and improve speed to market, for which facility build times are critical.

The BioPhorum Operations Group (BPOG), a cross-industry organization of biopharmaceutical end users and suppliers, has stated that to respond to these business drivers, the biopharmaceutical industry should aim for a 90% reduction in capital expenditure (CAPEX) and manufacturing costs in the next decade. The industry also should drastically reduce product changeover

times by 90% to improve responses to variability in demand and new biologics classes as well as drive down new facility build times by 70% (3).

MODULARIZATION FOR FLEXIBLE MANUFACTURING

Part of the strategy for achieving these ambitious step changes is to improve process productivity and make more efficient use of manufacturing facilities. Traditionally, biologics have been manufactured primarily in stainless-steel based production plants that have a CAPEX of \$200 to \$500 million to construct (4). These types of facilities have a risk of cross-contamination between batches and require considerable time and resources for steam-in-place (SIP), clean-in-place (CIP), and SIP/CIP

PRODUCT FOCUS: ALL BIOPHARMACEUTICALS

PROCESS FOCUS: MANUFACTURING

WHO SHOULD READ: PROCESS DEVELOPMENT, MANUFACTURING, ANALYTICAL

KEYWORDS: DISPOSABLES, AUTOMATION, FLEXIBILITY, MODULARIZATION

LEVEL: INTERMEDIATE/HIGH

The rise of SU technology has meant that clinical manufacturing as an **END-TO-END** SU process is becoming a possibility.

validation, resulting in high operating expenditures (OPEX). Additionally, stainless steel facilities are dedicated to production of specific biologics, so automation programs are fixed and inflexible in their applications.

This has led to a move away from stainless-steel to an increased application of single-use (SU) technology. By 2009, SU unit operations began to be adopted in biopharmaceutical facilities, leading to the use of more modularization in manufacturing plants (5). SU unit operations have been developed for complex bioprocess steps including media preparation, cell culture, cell clarification/removal, cross/tangential flow, and virus filtration. The use of closed systems in such operations offers greater flexibility and the basis for building more ballroom-style manufacturing facilities with large areas that have no fixed equipment and minimal room separation due.

The advantages of using this type of modular facility compared with a traditional design for monoclonal antibody (MAb) production at 2,000-L scale were reported to be 42% more batch runs per year (6) as well as a reduction in manufacturing footprint of 45% and CAPEX reduction of 67% (5). This provides a 23% (6) and 32% reduction in the cost of goods (CoGs) (5).

The rise of SU technology has meant that clinical manufacturing as an end-to-end SU process is becoming a possibility (7, 8). Many major biopharmaceutical companies such as Amgen (9, 10) and WuXi (11) are moving toward this concept and have set up plants in Singapore and China using multiple 1,000-L and 2,000-L single-use production bioreactors to run perfusion and fed-batch cell culture in

Figure 1: Scope definition of a smart modular package unit in an automation pyramid

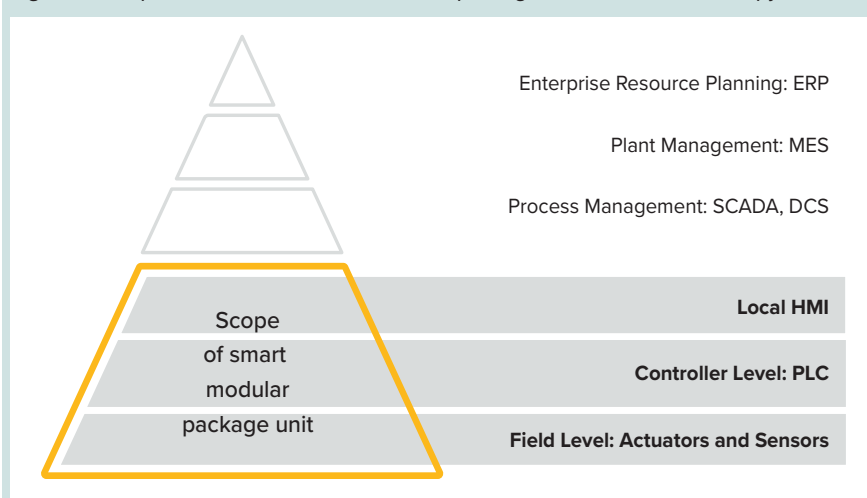


Table 1: Modular package units compared to remote I/O for process integration

| Level | Advantages | Disadvantages |
|--|--|---|
| Smart modular package units (entry points 1 and 2 from Figure 2) | <ul style="list-style-type: none"> Stand-alone capabilities Prequalified and pretested Fast implementation and reduced build-up times Flexibility to change process, move equipment, and use process skids Fewer expensive, skilled bioprocess personnel are required to run processes Easy process capacity extension | <ul style="list-style-type: none"> Requires biopharmaceutical company/CDMO to outsource automation integration to an equipment supplier Needs equipment and SU supplier with industrial automation integration expertise and capabilities |
| Remote I/O (entry point 3 from Figure 2) | <ul style="list-style-type: none"> Standardizes and reduces wiring Increases data availability Allows remote configuration and monitoring | <ul style="list-style-type: none"> No local controller Cannot be used as stand-alone system; Increases engineering effort and testing at the DCS level Requires continuous in-house industrial automation IT expertise (expensive and highly-sought after personnel) for maintenance and lifecycle improvements Requires skilled bioprocess personnel to connect and run unit operations |

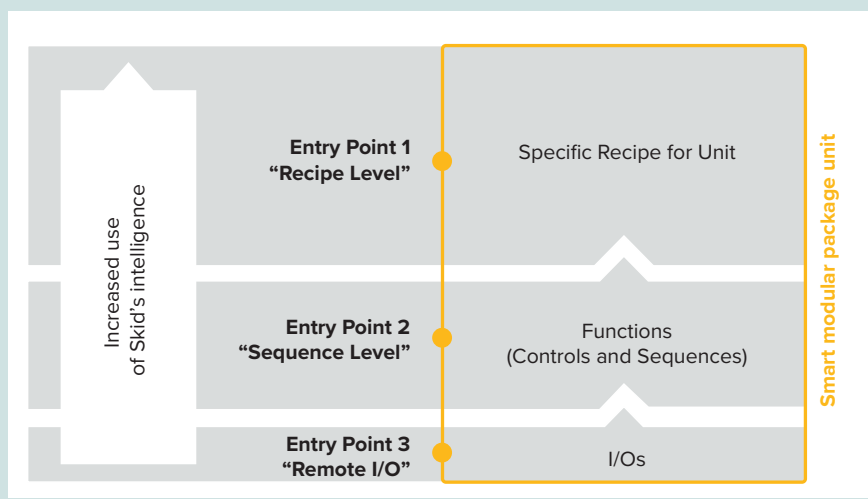
a scale-out model to produce biologics at scale. According to Amgen, using SU technology has meant that its Singapore plant was constructed and operational in 15 months, and WuXi's new facility was ready for current good manufacturing practices (CGMP) manufacturing in two years — both a significantly shorter time frame than the four to five years it takes for a predominantly stainless-steel based plant to begin operation. Also, Amgen states that the Singapore plant can deliver the same quantity of biological

products as a traditional facility with a 75% larger footprint (9).

AUTOMATION IS KEY

SU flexible manufacturing is increasingly becoming a popular choice in biopharmaceutical companies because the benefits of modularization and flexibility, as well as (local) automation in the modular package unit, align with this concept. In early days, modular package units were not controlled by any local automation; thus, sensors and actuators had to be

Figure 2: Overview of entry points for integration of SU smart modular package units into the process management level



Installation of standardized industrial automation platforms into smart modular package units provides a more **FLEXIBLE** method for integration.

where SSB's bioreactor BIOSTAT® STR, is the second. This allows recipe-driven connectivity to a range of bioprocess unit operation skids and SU components (Figure 2, entry point 1 and 2).

Table 1 details advantages and disadvantages of using a smart modular package unit instead of a remote I/O. Execution of process or control phases from an upper recipe system (by contrast with integration of remote I/O), will reduce the automation-related project effort for installing an upstream/downstream bioprocessing facility by 50–75% (13, 14) because some activities are substantially reduced during the integration. One reason is that a smart modular package unit comes with prequalified and pretested functionalities (Table 2).

A further benefit of this approach is a simple process capacity extension by scaling out. If floor space has been reserved for additional modular package units, they can quickly and easily be connected into an existing automation landscape.

User Guidance Reduces Human Errors:

Another benefit of integrating smart modular package units is that they can help overcome manual set-up and running issues. Historically, with the introduction of SU technology, operators were put in charge of process steps for which (e.g.) they had to ensure that a filter did not block or bags and tubing did not leak. The availability of technologies such as SU sensors has enabled creation of control loops to circumvent process deviation and, ultimately, batch losses. However, there remain many manual tasks for operators to perform including setting up SU components as

Table 2: A head-to-head comparison of project activities for remote I/O versus modular integration

| Activity | Remote I/O | Modular Integration |
|--|------------|---------------------|
| Functional Specification | • | • |
| Software Design Specification | • | • |
| Hardware Design Specification | • | • |
| Module Design and Configuration Specifications (CM/EM/EPH) | • | • |
| Construction, Coding, and Configuration | • | • |
| Module Design and Configuration Specifications (CM/EM/EPH) | • | • |
| Software Integration Testing | • | • |
| Hardware Integration Testing | • | • |
| Factory-Acceptance Testing | • | • |
| Site-Acceptance Testing | • | • |

connected to a distributed control system (DCS) by simple hard-wiring.

Automation for biologics manufacturing operates on a number of levels, whereas a modular package unit has a defined scope and has to integrate properly into the process management level and above (Figure 1).

Digital integration of a modular package unit can be performed with different types of interfaces and levels (Figure 2). The Instrument Society of America (ISA) has published ANSI/ISA-88 guidelines for batch control (12). These are industrial engineering standards and recipe definitions, which if implemented by biopharmaceutical companies and equipment suppliers, could ensure seamless integration of automation for SU technology at the

process management level into supervisory control and data acquisition (SCADA) or DCS landscapes.

Flexible Integration: Traditionally, SU technology has been integrated into SCADA or DCS platforms through remote input/output (I/O), thus skipping the control level and the local human machine interface (HMI) (Figure 1, entry point 3). Installation of standardized industrial automation platforms into smart modular package units provides a more flexible method for integration. The first implementation of the Sartorius Stedim Biotech (SSB) automation platform is with the FlexAct® system, which controls specific upstream and downstream unit operations, followed by more SSB units in a series of bioprocessing systems,

well as calibration and recalibration of sensors before, during, and after a process run. If these tasks are put directly into the smart modular package unit and are guided, a supplier can transfer important process knowledge to an operator through recipe phases that will help to significantly reduce human error during set-up and process runs.

Faster Process Changeover: In multiproduct biopharmaceutical facilities, changeover time between products is an important key performance indicator (KPI). SU technologies enhance performance because they reduce changeover time by eliminating CIP and SIP activities. A flexible automation platform will orchestrate the automation, including activation/deactivation of controls, process sequences, and user guidance and finally adapt the HMI for the operator. This is based on the process setup such as the choice of hardware being used (for example, holders, tanks, and pumps) and wetware (SU consumables). This enables a rapid changeover by permitting use of a flexible, smart modular package unit and ensures process safety. Taking this principle further, a smart modular package unit can host several different process steps that are quick and easy to switch between, shown using the FlexAct modules as an example in this article.

SMART MODULAR PACKAGE UNITS

Now in its second generation, SSB's FlexAct is an example of the first in a series of SSB modular bioprocess package units to incorporate an industrial standard automation platform. The unit can be configured for maximum flexibility to control six different upstream and downstream operations using process skids for buffer and media preparation, cell clarification, crossflow filtration, virus inactivation, and virus filtration at processing volumes ranging from 15 L to 2,000 L (Figure 3).

Because the FlexAct can perform multiple unit operations at a range of scales, it does not require as much cleanroom space as a unit that

Figure 3: Flexible multipurpose modular package unit for diverse bioprocess unit operations

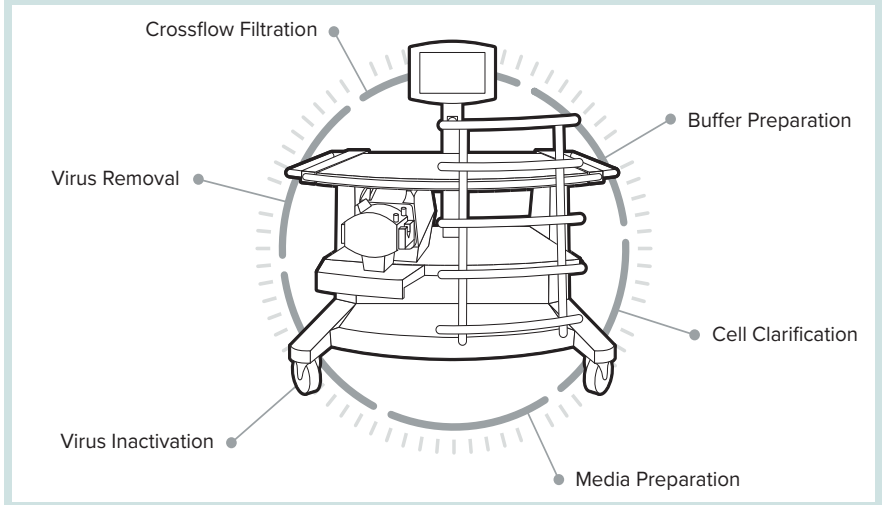
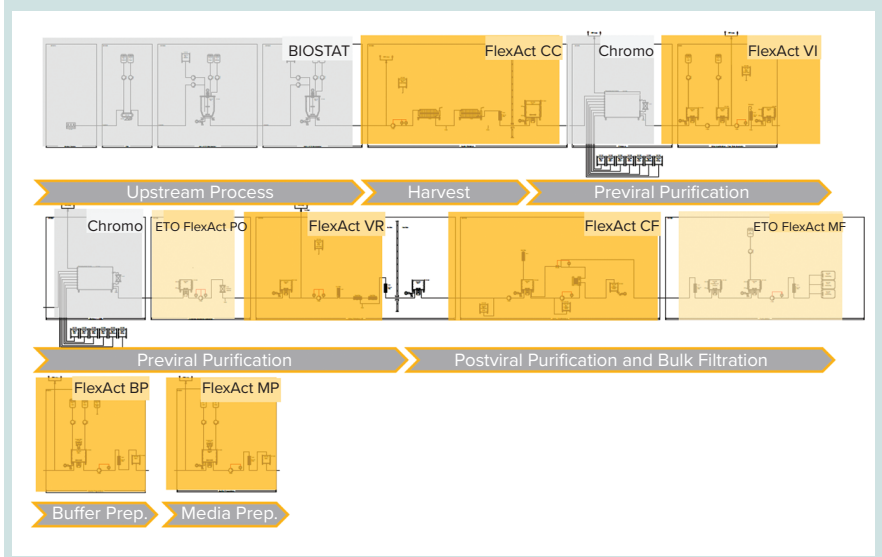


Figure 4: Example process flow diagram showing the application of FlexAct units in an end-to-end CGMP manufacturing process



performs only a single operation. For example, three FlexAct units running two different unit operations will require approximately half the manufacturing space required by six modular package units running a single unit operation. This scenario not only has the potential to reduce cleanroom footprint, but also cleanroom testing and validation costs. The use of SU technology in a typical mAb manufacturing set-up is reported to require approximately 15% fewer manufacturing staff for drug substance production and 12% fewer QA/QC staff, resulting in an estimated 13% lower total headcount than a stainless-steel facility (15). Therefore, reducing the cleanroom footprint even

further could result in less heating, ventilation, air conditioning (HVAC), and CIP/SIP utilities, as well as lower QA/QC testing and staff costs.

SIMPLIFYING THE PROCESS

Digitalization Ready: Incorporating an industrial standard automation platform, as described above, that interfaces with DCSs such as Emerson's Delta-V, Rockwell's Allen Bradley products, and Siemens' SIMATIC PCS7 into the FlexAct, enables direct automation of and communication with different components, including sensor, actuators, pumps, filters, tubing, and connectors. This allows FlexAct to facilitate use of process analytical

Figure 5: Example process layout showing where a FlexAct unit can be used in an end-end CGMP manufacturing process

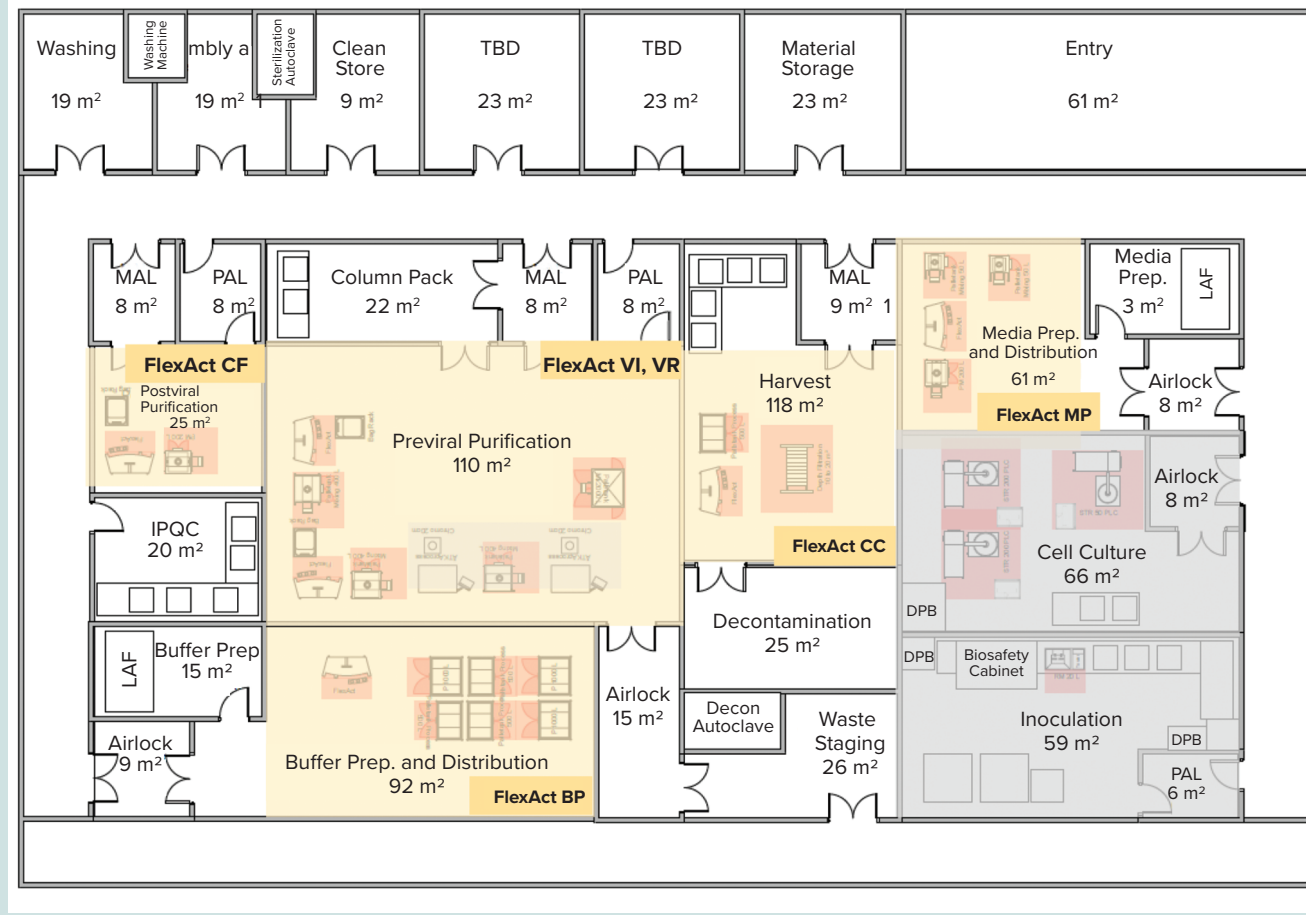


Table 3: Time (minutes) required for SU crossflow filtration

| Wetware Installation | Fill Supplies | Flush/ Equilibrate | First Concentration | Diafiltration | Second Concentration and External Recovery | Teardown |
|----------------------|---------------|--------------------|---------------------|---------------|--|----------|
| 50 | 30 | 20/20 | 120 | 120 | 30 | 30 |

technologies (PAT) and enables a number of data analytics possibilities. The software is prequalified so that operators can connect their skids for SU unit operations and SU components to the FlexAct straight out of the box without having to write additional coding. The software also can be customized, if required.

Easy Set-Up: The FlexAct solution comes out of a configurator to order (CTO) design space, which guides users to identify all the hardware, software, and wetware components they need for their specific unit operation. From that delivered solution, a configurable recipe allows users to perform operations at the desired scale. All steps from wetware installation to postprocess teardown

are guided by recipe operator messages. This reduces set-up time and manual assembly errors because the modular package unit provides clear operational guidance for the correct configuration. Additionally, more than one-unit operation can be installed and overlaid in one system, enabling multifunctional/multiscale capability.

Process Efficiency: FlexAct has the capability for using new types of SU technology such as SSB's MaxiCaps® MR SU filtration unit. This features 90% less tubing than conventional filters and only two connections, which reduces contamination risks and operational connectivity errors. The module also facilitates control of a number of sensors with a left- and

right-sided interface on the FlexAct COM (central operating module). For ensuring operational performance, a range of sensors can be integrated including BioPAT® Flow sensor, which indicates fluid transfer rate and liquid volume measurement, and BioPAT Pressure, which shows line/filter blockage or permits pressure control. The COM also facilitates process performance control with interfaces for SU sensors such as BioPAT SU conductivity and BioPAT SU pH for in-line monitoring.

CASE STUDY

As proof of concept that a modular package unit can maximize efficiency and speed of upstream and downstream unit operations for production of a biologic, FlexAct was used as part of an end-to-end single-use process (Figures 4 and 5) at a cell culture technology company to purify a commercial MAb cultured in a 500-L SU Flexsafe STR bag and BIOSTAT STR bioreactor. Details of operational set-up

All steps from wetware installation to postprocess teardown are guided by recipe operator messages. This reduces set-up time and manual assembly errors because the modular package unit provides **CLEAR operational GUIDANCE** for the correct configuration.

and total process times are described below for upstream and downstream unit operations because they are representative of the five different unit operations used.

Crossflow Filtration: The unit operation set-up included prefilled feed and buffer tanks, three pumps, a 1.4m² SU self-contained Hydrosart® CF filter, and receiving waste and flush tanks. The FlexAct was also connected to load cells, in-line flow meters, and a conductivity sensor for precise first and second feed concentration with a 10× diafiltrate exchange in between. Total crossflow filtration time for 200 L of 5 g/L to 6.2 Kg (approximately 150 g/L) of recovered protein solution was eight hours (Table 3) with a total installation time and teardown time of 80 minutes. This crossflow set-up can be used at 15-L to 200-L recirculation volumes.

Buffer and Media Preparation: The unit operation set-up included a mixing skid, pump, SU Sartopore® 2 filter capsules, and receiving tank(s). For both buffer and media preparation operations, the FlexAct used a flow sensor because that is a more cost-efficient approach than using a load cell. To save time, the modular unit was connected to an automated supply magnetic mixer and a SU pH or conductivity sensor for automatic pH adjustment or homogeneous indication. This buffer and media preparation set-up can be performed at 50-L to 1,000-L scales. Total preparation time for 500 L of media and buffer was six hours and

Table 4: Time (minutes) required for SU 500-L buffer and media preparation performed by a single trained operator

| Application Type | Wetware Installation | Preflush | Prefill | Powder Add | Mix and Adjust | Filter Transfer | Wetware Teardown |
|--------------------|----------------------|----------|---------|------------|----------------|-----------------|------------------|
| Buffer Preparation | 60 | 20 | 30 | 30 | 30 | 30 | 20 |
| Media Preparation | 60 | 20 | 30 | 30 | 180 | 30 | 20 |

Table 5: Time (minutes) required for SU virus removal

| Wetware Installation | Preflush | Equilibration | Filtration | Postflush | Post-IT Offline | Wetware Teardown |
|----------------------|----------|---------------|------------|-----------|-----------------|------------------|
| 60 | 25 | 5 | 60 | 30 | 60 | 30 |

Table 6: Feature and benefits of the FlexAct process platform based on the smart modular package unit approach

| Features | Manufacturing Benefits | Industry Benefits |
|--|--|---|
| Mobile modular, multi-application package unit | Easy to use in ballroom facilities with skids for SU unit operation Cost-effective and saves space as only need one module to run six different upstream and downstream unit operations | Smaller manufacturing footprint and lower CAPEX costs with potential to reduce footprint by estimated 45-75% (5, 9) and CAPEX costs by 67% (5) |
| Intelligent COM design for rapid wetware installation and teardown times (1-1.5 hours average) | Flexibility to changeover scale and unit operation quickly and simply allows multi-product facility use Saves time and costs associated with SIP, CIP and validation tasks | Potential to run 42% more batches per year (6) and respond quickly to fluctuating/ changing market/ product demands Requires fewer staff could reduce headcount by around 13% (15) |
| Automation hardware follows industrial standards (Siemens) and interfaces with Emerson's Delta-V, Rockwell's Allen Bradley products, and Siemens' SIMATIC PCS7 | Easier integration of automated components and devices at the process management level Secure data transfer which facilitates PAT and data analytics | Reduces IT costs and staff headcount. Offers effort savings of potentially 50-75% with SU implementation time (13, 14) |
| Touch screen HMI and software based on industrial engineering principles (ISA/ANSI-88) | Simple to set up recipe driven and standardizes operations to manufacture consistent product | Robust processes reduce costs of operator training and batch failures offers potential for 23 - 32% reduction in the CoGs (6, 5) |
| CTO design space | Supports users in SU unit operation design and set-up to prevent connectivity, filter sizing, and mass balance errors | Standardizing process could reduce training time/costs, staff numbers, material variants and stock housing requirements. Could also improve supply chain network and delivery times |

10 mins and three hours and 40 mins, respectively (Table 4, with a wetware and teardown time of 80 minutes.

Virus Removal: The FlexAct set-up included one supply and a flushing/ equilibration skid, pump, SU Viosart HF filter capsule, and a receiving skid. Total operation time for processing 200 L was four hours and 10 minutes (Table 5) with an installation time of 60 minutes and teardown time of 20 minutes. This virus removal set-up can be used at 50-L to 1,000-L scales.

In summary, using the FlexAct enabled buffer and media preparation operations times for 500 L of between four and six hours, with set-up time of just one hour and teardown of only 20 minutes. In the crossflow filtration and virus removal unit operations at 200 L, total operational time is four to eight hours, with installation times of between 50 minutes to one hour and teardown times of 30 minutes. This is significantly shorter than the time it would take to set up these unit

Using SU technology with a modular package unit incorporating an industrial automation platform is time efficient, offering **FAST, FLEXIBLE** manufacturing and quick changeover between unit operations.

operations with reusable components, for which SIP and CIP activities would take many hours, indicating that using SU technology with a modular package unit incorporating an industrial automation platform is time efficient, offering fast, flexible manufacturing and quick changeover between unit operations.

MANUFACTURING AND INDUSTRY BENEFITS

Because smart modular package units such as the FlexAct units can run prequalified and tested recipes, users can rapidly integrate SSB and other manufacturers' SU technology in bioprocess operations, achieving faster installations with reduced downtime. Table 6 summarizes manufacturing and industry benefits that can be achieved using this modular unit.

ADDRESSING THE NEEDS OF AN EXPANDING GLOBAL MARKET

Integrating automation and single-use technology at the process-management level is enabling biopharmaceutical companies and CDMOs to perform rapid unit operations and changeovers at different scales with a range of different types of biologics, using manufacturing facilities with increasingly smaller footprints. The next step, after automating unit operations, is an integrated SU quality by design (QbD) solution from seed train through to drug substance, with secure open architecture to allow remote preventive maintenance and predictive services to effect repairs or diagnose faults, as well as enable

seamless chemometrics, data analytics, cloud solutions, and machine learning. This intelligent SU facility will offer biopharmaceutical companies the potential to react flexibly and scalably to changing market demands and aligns with the industry's drive to significantly reduce CAPEX and OPEX associated with manufacturing life-saving biopharmaceuticals to an expanding global market.

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Corresponding author **Burkhard Joksch** is Senior Manager Software and Automation, burkhard.joksch@sartorius-stedim.com. **Stuart Tindal** is Product Marketing Manager FlexAct at Sartorius Stedim Biotech, Goettingen, Germany; +49.551.308.0.

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