Unlocking the potential for efficiency in downstream bioprocesses

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CY13795-25May20-WP

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In today's bioprocessing industry, there is a demand to cut manufacturing costs while maintaining product safety and quality. Additionally, flexibility needs to be increased and time to market reduced. Upstream processes are more efficient and produce higher titers than before. With these improvements, new challenges arise. Downstream processes have to handle higher amounts of both target protein and impurities. So, in order to make full use of upstream advances in an efficient manner, it is essential that downstream processes are intensified.

This white paper covers methods of improving downstream operations through process intensification. It describes techniques like continuous processing and in-line conditioning buffer preparation, system automation, and more. It also shows how implementation of efficient process designs can overcome traditional downstream bottlenecks, such as time-consuming column packing, cleaning of equipment, and laborious buffer tank farms.

Introduction

The biopharmaceutical market is evolving and manufacturing facilities and processes are changing with it. Instead of focusing on a few blockbuster drugs in large quantities, facilities need to be flexible to handle multiple products in smaller batches. They also have to be built in a manner so they can be easily scaled up to meet increasing product demand.

Improvements in productivity and efficiency is ranked as the single most important area on which the biomanufacturing industry should focus its efforts (1). As a result, modern solutions like single-use systems and connected processing are evaluated as options when setting up new manufacturing facilities or replacing individual units. These techniques can help improve overall process economy, while still ensuring end product quality.

In upstream bioprocessing, improvements in manufacturing processes have resulted in routine titer levels of three to five grams per liter (2). Downstream processing needs to match these advances in a cost-efficient way. There are already various process intensification solutions available that can help make this possible (Fig 1). These technologies can increase facility use and increase productivity and throughput.

A process intensification toolbox

Process intensification can be thought of as a toolbox comprising a set of practical tools that include solutions such as single-use technologies and connected processing. When these tools are applied independently, or in conjunction with each other, they can significantly improve the efficiency and economics of existing or new facilities.

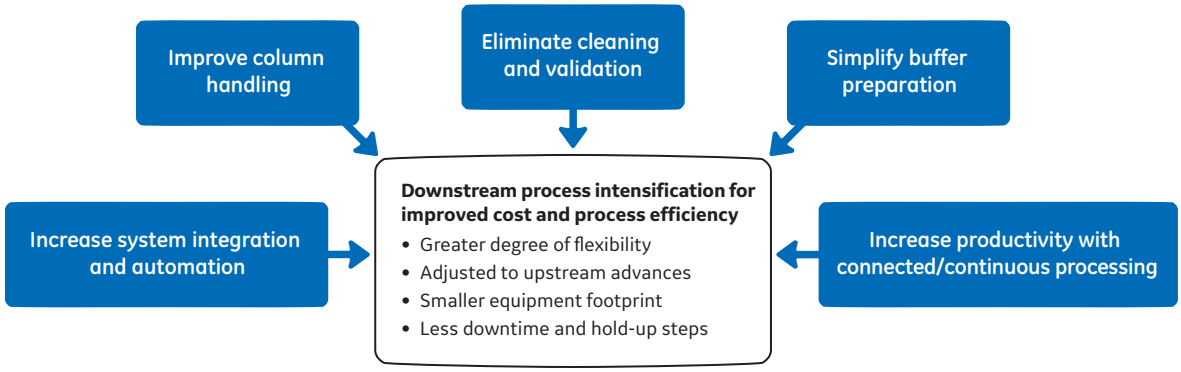


Fig 1. Solutions that can help achieve process intensification by overcoming traditional downstream bottlenecks.

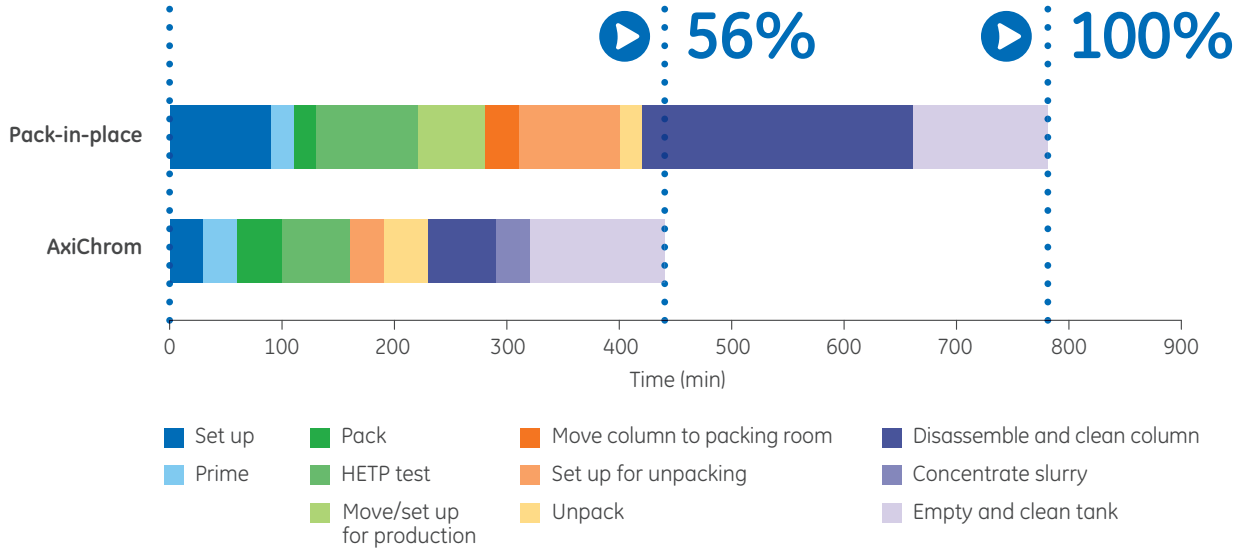


Fig 2. Packing, unpacking, and maintenance of an AxiChrom column only takes 56% of the time required for a traditional column. Data compiled from GE Healthcare assessment studies.

GE Healthcare is working closely with biomanufacturers to find different solutions for process intensification. We offer individual tools, like Inline Conditioning systems, as well as start-to-finish solutions, such as KUBio™ mAb manufacturing facilities. By analyzing each bottleneck in a specific process and examining available downstream solutions, increased productivity and cost efficiency can be unlocked.

Improve column handling

Traditionally, column packing has been an art rather than a science. The process can consume essential time and resources. Risking poor performance with a suboptimally packed bed is not an option. Packing success is therefore key to ensure an efficient purification process with high yield and throughput.

Packing success from the start

Today it is possible to get packing right at first try. Automated columns can help save both time and labor costs (Fig 2). AxiChrom™ columns have been designed for easy and reliable packing (3,4,5). Preprogrammed, verified, and automated packing methods together with a purposeful column design enables one operator to quickly achieve packing success, independent of previous experience. AxiChrom columns also demonstrate real scalability throughout the platform, which adds flexibility to the entire process (6). AxiChrom columns have a proven performance, and as a result they are already part of many FDA-approved manufacturing processes globally.

Intensifying the downstream process, an example*

With the advances in upstream bioprocessing, the same amount of protein can be produced in a 1000 or 2000 L bioreactor, at higher titer, as in a 10 000 L bioreactor. Up to six of these bioreactors can feed one intensified downstream process enabling a yield of a ton of mAb each year, at a titer of around 6 grams per liter.

In order to achieve these results, the intensified downstream process would include modern high capacity chromatography resins. It would also require an automated column for fast preparation and maintenance time. In-line buffer preparation and smart automation, allowing connecting steps without hold time, would significantly reduce the tank footprint. The described set-up also provides a more flexible solution as the number of bioreactors can be adjusted to a gradually increasing demand or new products.

*Based on a facility setup at a GE customer site.

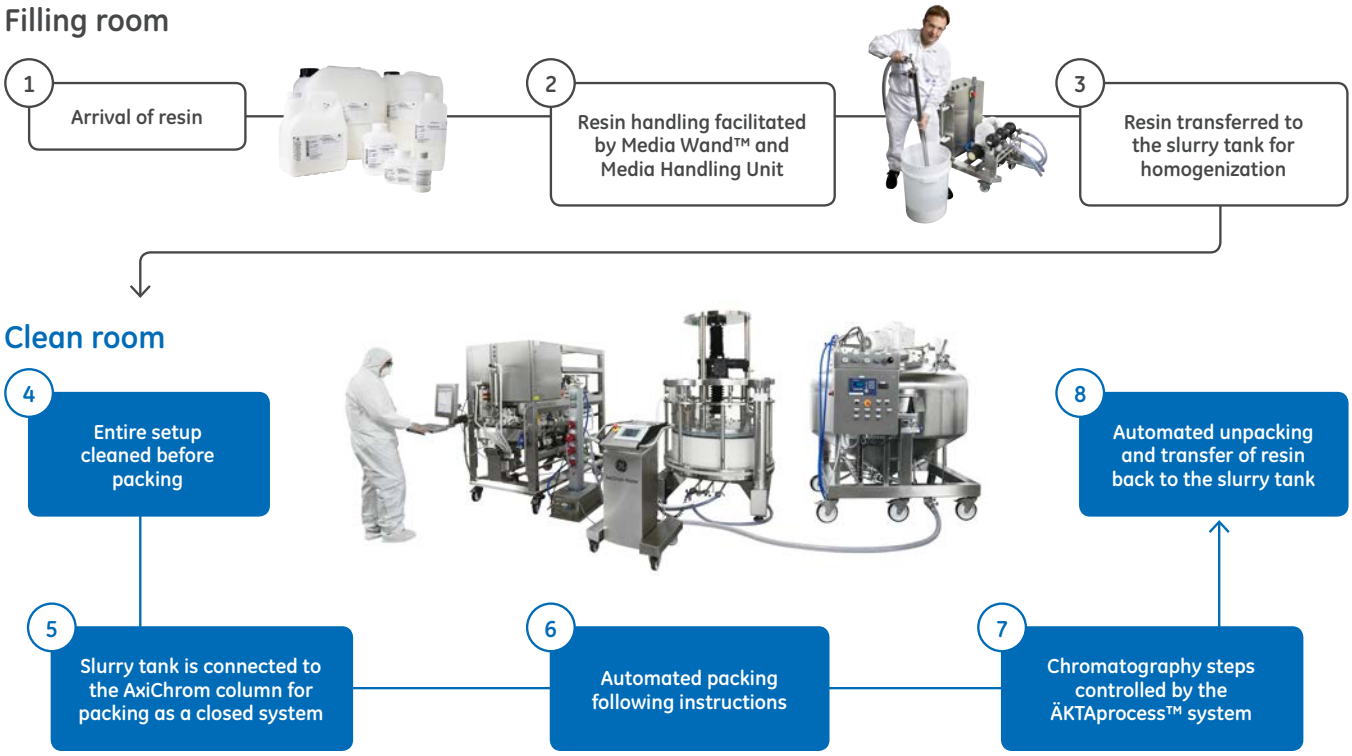


Fig 3. Contamination risks can be kept to a minimum by decreasing any manual handling of chromatography resin and buffers. This can be achieved by connecting the column, slurry tank and chromatography system in a closed system (blue boxes).

Minimized bioburden

Both column handling and design can affect the risk of bioburden contamination, which can be extremely costly. Contamination can result in product loss or, in a worst-case scenario, a shutdown of the facility. Several AxiChrom features contribute to minimized bioburden, like the planar distribution system and the priming groove (7). By connecting the column, slurry tank, and chromatography system in a closed system, manual handling is kept to a minimum and the contamination risk is further decreased (Fig 3). This setup also minimizes resin loss, enabling more efficient use of the resin.

Eliminate cleaning and validation

In bioprocessing, thorough cleaning is critical in order to take full benefit of the resin by removing impurities. When using conventional chromatography solutions, cleaning and cleaning validation consumes a considerable amount of time and facility resources. Cleaning-in-place protocols are performed before, during, and after a campaign.
A major bottleneck is the time it takes to get the results from the cleaning verification process. This problem can be addressed by using single-use technologies, which eliminate the need for cleaning and cleaning validation.

Fast turnaround with single-use technologies

Single-use solutions, such as chromatography systems with single-use flow paths, plug-and-play chromatography columns and membranes, as well as presterilized filters and tubing offer an option to eliminate cleaning and validation activities (Fig 4). Flexibility to handle several products in a facility is also increased by using single-use technologies. Fast turnaround time between batches or products results in a quicker product release.

Chromatography systems using single-use flow paths

ÄKTA ready is a chromatography system built for process scale-up and manufacturing. The system operates with ready-to-use, disposable flow paths eliminating cleaning and validation between products and batches (Fig 5). Replacing flow paths is fast, and when used together with ReadyToProcess columns, the risk for cross-contamination is removed. The ÄKTA ready system has a sanitary design and is well-suited for use in a cGMP-regulated environment. The simple procedures and low downtime between products and batches of ÄKTA ready enables improved economy and productivity.

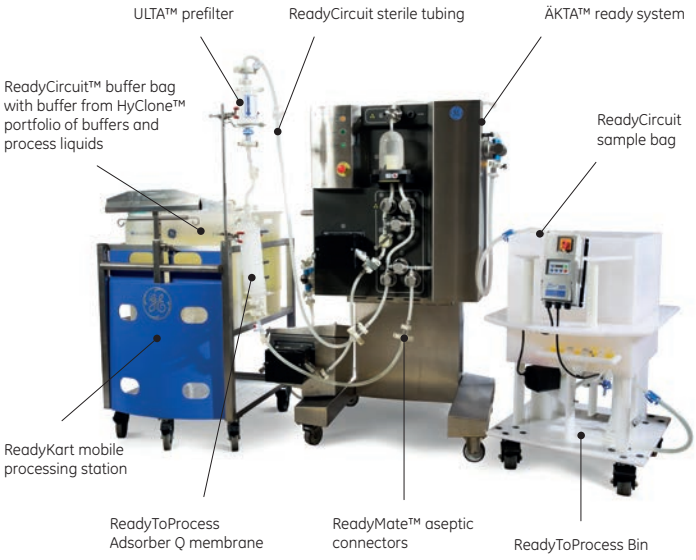


Fig 4. Example of single-use hardware and assembly setup for a 150 L mAb process where ReadyToProcess™ Adsorber Q is used as third purification step.

Prepacked chromatography columns and single-use membranes

Our ReadyToProcess product line includes several solutions that can eliminate the need for cleaning. The ReadyToProcess columns are prepacked, prevalidated, and prequalified. The columns enable extremely fast preparation times for the chromatographic purification step from preclinical to manufacturing scale.

Depending on both scale and batch frequency, adsorber membranes can be a suitable alternative to packed bed chromatography. Our portfolio includes ReadyToProcess Adsorber single-use membranes. They can be easily switched in and out of manufacturing processes and are of high value in low- to mid-frequency manufacturing setups and in multi-product facilities. The choice between packed bed and membrane chromatography, however, is always case-dependent and requires careful analysis.

Rapid access to single-use cGMP manufacturing capacity

Our single-use technology is also available as an integrated FlexFactory™ biomanufacturing platform. This platform gives rapid access to cGMP manufacturing capacity for key biologics, such as mAbs and vaccines. It can be tailored to fit both new and existing facilities. The sample will go from start to finish without manual handling, eliminating cleaning and validation in each step. Furthermore, the platform provides flexibility to modify individual processes as production needs to change.

Taking it one step further, we also offer KUBio prefabricated cGMP-compliant facilities. A KUBio facility is designed for scalable and cost-efficient production of mAbs. The facility consists of prevalidated modules that are assembled on site. The resulting facility is ready to run within 14 to 18 months. KUBio facilities include the integrated FlexFactory biomanufacturing platform.

Ensure a robust supply chain and include extractables and leachables considerations

Switching any element of a validated process requires significant additional work. Therefore, it is important to ensure the supply chain is robust when selecting single-use consumables. It is also essential to evaluate the vendor's capabilities around extractables and leachables testing. At GE, we are actively strengthening our services and capabilities around extractables and leachables. For example, we offer subscriptions to the latest validation guides and change notifications. We are also aligning with Biophorum Operations Group's (BPOG) proposal of a standard approach to doing extractables and leachables testing on single-use manufacturing components and systems (8).

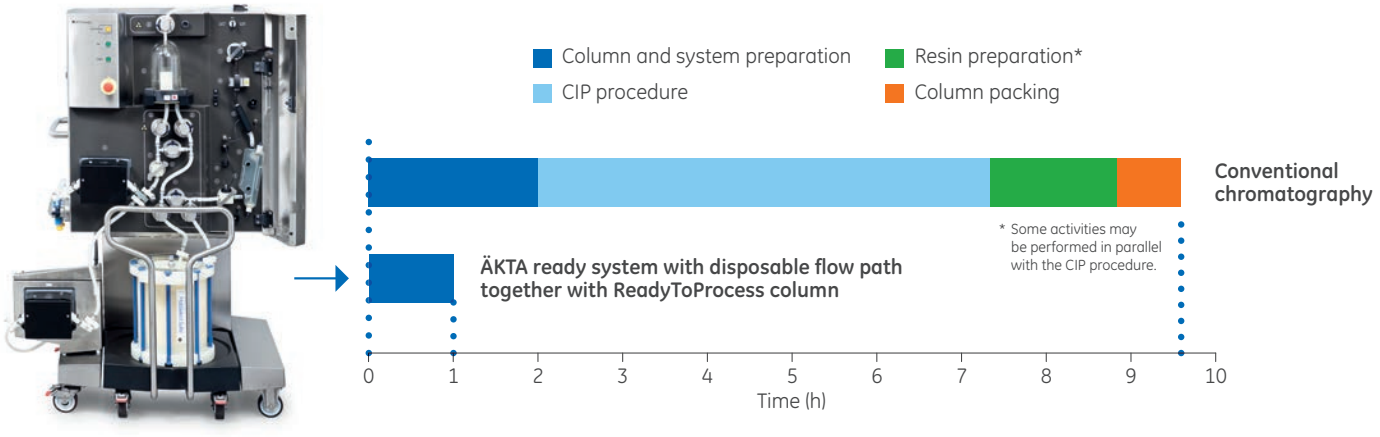


Fig 5. ÄKTA ready system together with ReadyToProcess chromatography columns enable a nearly ten-fold reduction in set-up time compared with a conventional setup. Data compiled from GE Healthcare assessment studies.

Simplify buffer preparation

The volume and number of buffers for a typical downstream process can be considerable. Preparation of these buffers is a challenge that in-line conditioning can overcome. In-line conditioning simplifies buffer preparation and offers significant reduction in number of tanks, buffer solutions, and floor space needed. The technology also limits manual preparation time.

With in-line conditioning, buffers are prepared from concentrated stock solutions of salt and water for injection (WFI) plus an acidic and a basic component (e.g., NaH_2PO_4 and Na_2HPO_4, respectively). Our extensive HyClone buffer and process liquids portfolio includes stock solutions suitable for in-line conditioning. Both standard and customized formulations are available.

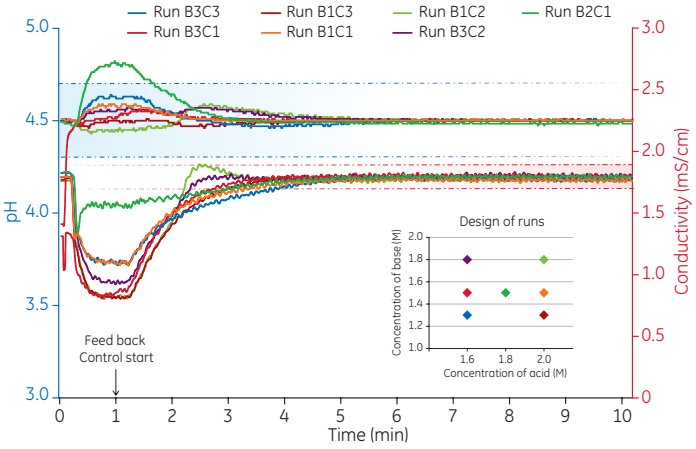


Fig 6. Demonstration of the robustness of the dynamic control function. The graph shows conductivity and pH curves from seven runs using dynamic control. Significant stock solution variations were used to challenge the system. The details of these solutions are shown in the insert. The dotted lines indicate the specification range for pH and conductivity. (9)

In comparison to in-line dilution, in-line conditioning also addresses the complexity and inherent variability in buffer preparation. Common salt effects are avoided in in-line conditioning, enabling higher concentrations and smaller volumes. The Inline Conditioning systems from GE use a dynamic control of pH, flow, and conductivity for this purpose (Fig 6). These customized, large-scale manufacturing systems can either be used as a buffer preparation station, or be integrated as part of a chromatography or filtration system.

Process economy gains from in-line conditioning

Figure 7 shows results from process economy calculations done on four chromatography steps in an albumin purification process. The results show that the footprint was reduced by about 50% for in-line conditioning, in combination with single-use stock solution bags, compared with prepared buffers and in-line dilution.

Furthermore, in-line conditioning decreased the volume of solutions to prepare by about 95% and 60% compared with prepared buffers and in-line dilution, respectively. (10)

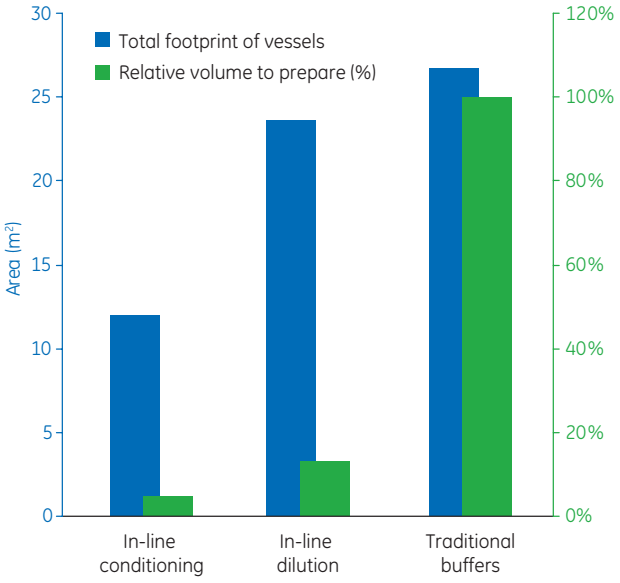
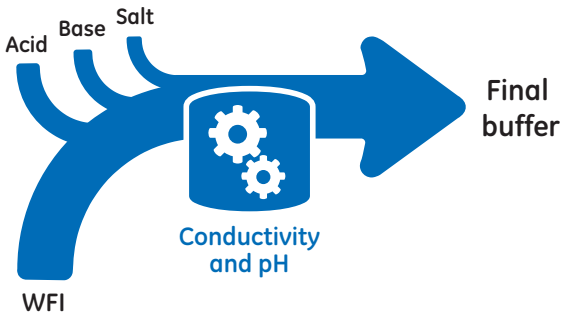


Fig 7. Comparison of in-line conditioning, in-line dilution, and prepared buffers, looking at footprint and relative volume of buffer to prepare. The comparison between in-line conditioning and in-line dilution is based on single-use equipment, apart from WFI hold tank and acid stock solution. Costs of stainless steel vessels were taken from BioSolve Enterprise V5.0 process economic simulation tool (BioPharm Services).

In-line conditioning vs in-line dilution

In-line dilution means diluting concentrated buffers with water. pH needs to be preadjusted, or adjusted after dilution. In-line conditioning means buffers are formulated using concentrated stock solutions of the required acid, base, WFI, and salt. A wide range of buffer concentration and pH solutions can be created. Conductivity and pH adjustments are automatically done throughout the process.

Common ion effect can limit the max achievable dilution factor for a buffer. This limitation is avoided in in-line conditioning as single-component stock solutions are used. Compared to in-line dilution solutions, the stock solutions have higher concentrations and smaller volumes.



Increase system integration and automation

In the biopharmaceutical industry, data is used in multiple ways throughout the process. However, the equipment used are often not integrated with each other. Using comprehensive automation solutions to connect process data can facilitate technology transfer and scaling throughout process development and to final manufacturing scale (11). Consolidation of process data under a single automation platform allows operators to spend time on more productive tasks, like process analysis, exception handling, and compliance support.

Taking one step further, the benefits can be even greater when process data from different suppliers can be consolidated. Manufacturing efficiency and facility utilization can be improved by extending the breadth of the data sources and making the automation platform an integral part of a business' information management structure. For this to be possible, the automation solutions must interface with manufacturing execution systems (MES) and enterprise resource planning (ERP) systems.

Automation solutions throughout scales

In highly regulated industries such as the biopharmaceutical industry, data creates the foundation upon which quality and compliance are based. Automation is an essential element in the acquisition, management, and use of data at each phase from the supply chain to the boardroom. GE offers several automation solutions to help improve data management, increase unit operation integration, and provide comprehensive control.

Our downstream process hardware is automated using UNICORN™ software. Features such as a design of experiments (DoE) tool and the ability to make quick evaluation of results make UNICORN software a suitable solution for process development needs. A common interface and data management approach extends connectivity throughout our ÄKTA chromatography systems, including large-scale systems used in manufacturing.

An efficient manufacturing operation requires coordination among business functional groups, the flow of raw and waste materials, procedures, and the unit operations that make up the bioprocess train. GE offers a variety of products suited to today's manufacturing environments. For example, the FlexFactory platform is available based on either Wonderware™, together with Allen-Bradley™, or DeltaV™ automation platforms. Each platform is capable of integrating our bioreactors, purification systems, and mixers as well as third party unit operations. The use of Wonderware and DeltaV with FlexFactory helps ensure broad compatibility with the leading MES and ERP systems. Our automation solutions and the breadth of our bioprocess portfolio can be combined in a multitude of ways, to address process and operational requirements of customers worldwide.

Increase productivity with connected or continuous processing

Continuous processing has proved a very successful model in many industries. As such, there has been a growing interest in using continuous concepts also in biomanufacturing. The benefits include productivity gains, reduced equipment and facility size, as well as improved product quality. One area where continuous processes are particularly useful is in manufacturing unstable products.

Implementing an end-to-end continuous process in biomanufacturing might still be years away for most companies. However, there are some real advantages in using continuous or connected processes in certain areas. An example is process intensification in mAb production by implementing continuous or semi-continuous downstream processes. This solution can contribute to cost-savings and improved productivity (12). Emerging technologies such as straight-through processing (STP) and periodic counter-current chromatography (PCC) can be used as alternatives to traditional batch processing.

STP for increased efficiency

In STP, two or more chromatography steps are connected in series, with in-line adjustment of process conditions between columns to ensure optimized loading conditions during the next step (Fig 8 and 9). This setup will eliminate the need for intermediate conditioning steps required in traditional batch processes. Removing these steps results in minimal need of hold-up tanks and an increase in process throughput.

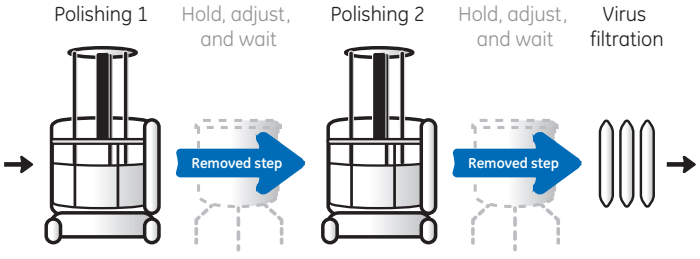


Fig 8. The total equipment footprint can be reduced by connecting the purification and filtration systems in a series and moving adjustments in line.

Fig 9. Example of a STP setup using a custom-built ÄKTAprocess chromatography system integrated with an Inline Conditioning system.

PCC for minimized process time

PCC is a multi-step approach to maximize the chromatography resin capacity utilization and minimize process time. The technology employs three or more chromatography columns to create a continuous purification step. In a PCC setup, columns are switched between the loading and nonloading steps, such as wash and elution. PCC increases the use of available resin and enables smaller equipment footprint and shorter processing times compared with batch processing.

PCC system with dynamic control

ÄKTA pcc 75 system from GE supports continuous chromatography in a three- or four-column (3C or 4C) PCC setup. Loading can be controlled either statically, based on time, or dynamically, based on UV absorbance. Dynamic control enables system operation under process conditions where either feed concentration or chromatography resin capacity varies. There are several advantages with this, for example, eluate consistency can be ensured when the capture step is connected to a perfusion culture with varying titers (13).

Summary

With fewer blockbuster drugs in sight, biomanufacturing facilities need to be flexible and highly efficient. Downstream processes also need to be intensified to match advances in upstream productivity. With a toolbox for downstream process intensification, GE can help meet these demands.

Equipment footprint can be reduced through, for example, in-line conditioning buffer preparation and connected or continuous processing. Automated column packing can be completed in half the time it takes to pack a traditional column. Cleaning and validation steps can be eliminated by introducing single-use technologies. Together with facility automation, these tools also create more flexible solutions for multi-purpose facilities.

Process intensification tools can be used independently or in conjunction with each other, depending on the specific process needs. More importantly, they can significantly improve the overall efficiency and economics of both existing or new facilities.

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29195721 AB 12/2016