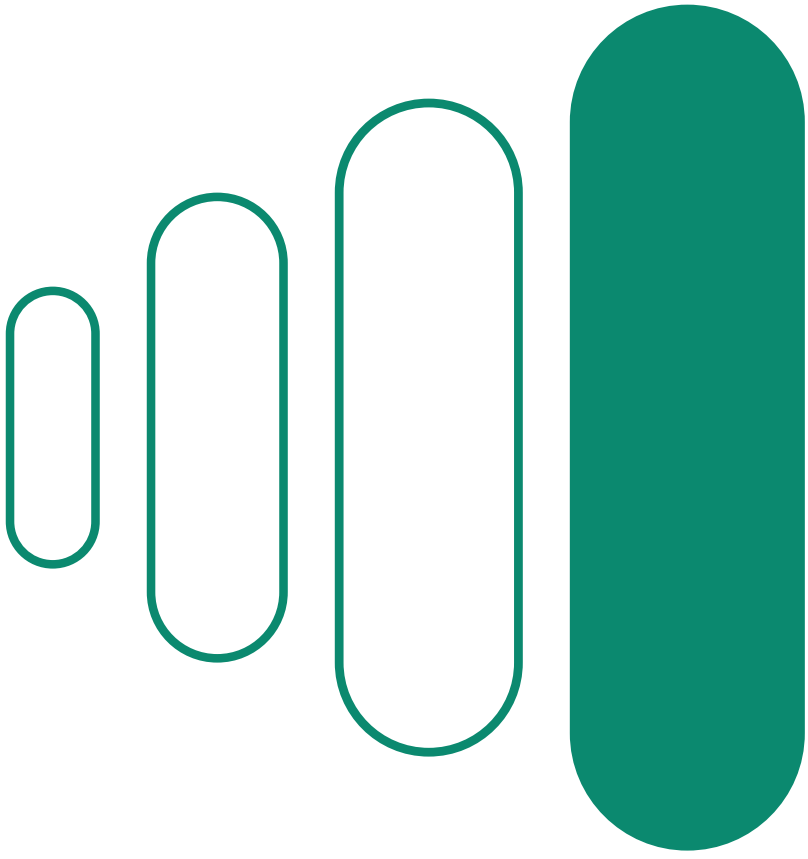
cytiva

Case study

Improve process economy by cycling of prepacked chromatography columns

The use of disposable technologies in downstream processing has increased significantly over the last years, as they reduce the need for time-consuming cleaning and cleaning validation operations as well as eliminate start-up procedures such as column packing. The challenge, however, of using disposable technologies relates to the often higher consumables and operating cost as compared with stainless steel solutions. As projects are scaling up to manufacturing scale, it becomes attractive to cycle equipment for specific campaigns for full capture of process economy gains. This customer case study evaluates process performance and economy when reusing a prepacked ReadyToProcess™ 32 L (450/200) chromatography column over several cycles in a multiproduct facility. The results indicate that cycling and reusing ReadyToProcess 32 L columns give consistent performance and enables significant process economic benefits.



Introduction

Ready-to-use technologies are gaining increased interest in the bioprocessing industry. For downstream processing, prepacked and prevalidated chromatography columns enable substantial reductions in labor related to elimination of cleaning-in-place (CIP) and sanitization-in-place (SIP) operations as well as associated validation procedures. Prepacked columns also eliminate the need for column packing and performance testing. When changing between production campaigns, prepacked, disposable columns require a changeover period of hours, as opposed to the days or weeks required for stainless steel columns, enabling significantly higher facility throughput.

Starting off as primarily addressing clinical manufacturing scales (column volume < 20 L), prepacked columns are now increasingly being used for regular commercial manufacturing in scales to meet the feed volumes from single-use bioreactors of up to 2000 L (column volume > 30 L). In regular commercial manufacturing, however, process economic aspects of using large-scale prepacked columns come in focus, and the possibility of reusing these columns over several cycles and across multiple production campaigns becomes important.

In upstream operations, disposables, constituting a format or carrier unit such as a bag or bioreactor, offer significant cost and time-savings as compared with stainless steel equipment (1). In downstream operations, on the other hand, units are more than just a format or carrier unit. A disposable column consists, not only, of the disposable column, it also contains the chromatography resin, to which the larger part of the prepacked column cost can be attributed. However, chromatography resins are designed for up to several hundreds of cycles, justifying their cost per volume. When addressing process economy, the time-saving benefits of prepacked columns, while reducing operating cost by the possibility of reusing the column multiple times, should be evaluated.

Here, we present a customer case study in which both process economy and the technical performance of a ReadyToProcess MabSelect SuRe™ 32 L (450 mm i.d., 200 mm bed height) column, when used in 19 cycles (12 cycles with mAb feed load and 7 wash cycles with buffer and 0.1 M NaOH), were evaluated. The column was used in a multiproduct facility, running several non-GMP projects annually. The facility is a hybrid, using both stainless steel and single-use equipment, like many facilities throughout the industry. The study was conducted to evaluate the column for use in clinical and GMP manufacturing.

Column performance was characterized by monitoring column integrity as well as process performance attributes such as mAb recovery and impurity clearance. The values were compared with values obtained by using a BPG glass column (450 mm i.d., 200 mm bed height). In the analysis of process economy, the benefits that prepacked columns can provide to a hybrid clinical manufacturing facility were evaluated. Factors such as run rate, labor cost, and consumables were considered in the analysis.

Technical performance

In the evaluation of the technical performance of the prepacked ReadyToProcess MabSelect SuRe 32 L column, durability and robustness of the column as well as comparability of the column to the existing solution (BPG column) were considered. As process material, 500 L cell culture feed was used. Process material from five different mAb productions (Feed A, B, C, D, and E) were used. The mAb titers ranged from 3 to 7 mg/mL. Altogether, data from 19 cycles (12 cycles with mAb feed load and 7 wash cycles with buffer and 0.1 M NaOH) was recorded.

Height equivalent to a theoretical plate (HETP) and asymmetry factor (A_s) were used to monitor integrity of the bed. As shown in Figure 1, the results demonstrate a stable bed performance.

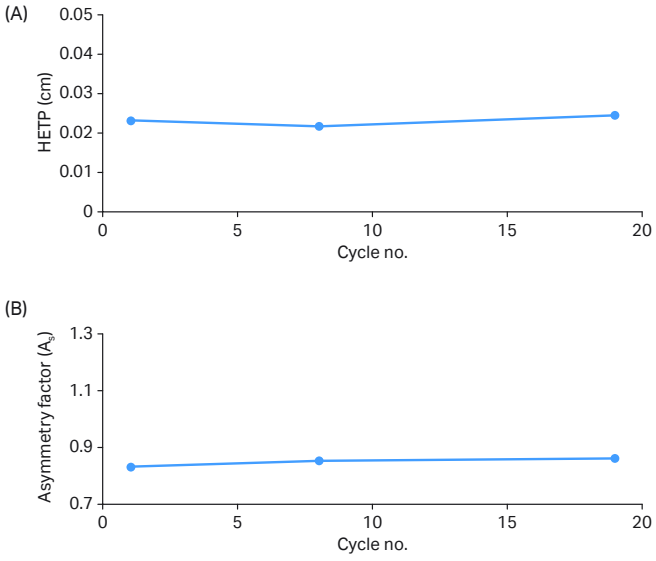


Fig 1. (A) HETP and (B) A_s for ReadyToProcess MabSelect SuRe 32 L column, determined after cycle no. 1, 8, and 19.

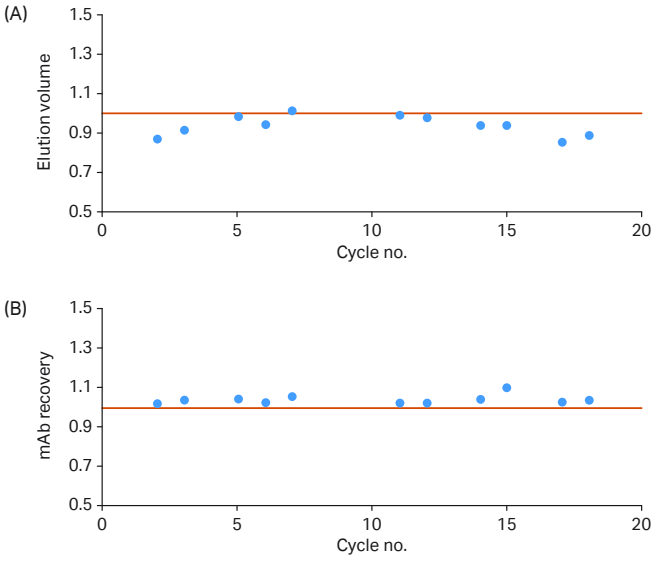


Fig 2. (A) Elution volume and (B) mAb recovery of process run on ReadyToProcess MabSelect SuRe 32 L column. Data normalized against data obtained from reference process (BPG column).

Elution volume and mAb recovery over the process cycles are shown in Figure 2. Data normalized against data obtained from process run on BPG column (reference process) indicates consistent performance of the prepacked column as compared with the conventional column. Removal of mAb aggregates, host cell protein (HCP), host cell DNA (hcDNA), and endotoxin were also comparable between the column formats and within set acceptance criteria. Monomer content between the column formats were within ± 1%. Table 1 summarizes functional performance for Feed A for Cycle 2, 3, 17, and 18, enabling attributes to be compared between cycles.

Table 1. Functional performance (Feed A)

Parameter	Cycle 2	Cycle 3	Cycle 17	Cycle 18
ΔP at 300 cm/h (PSI)	17.8	18	NA	NA
mAb recovery (%)	92.3	94.3	93.2	94.1
mAb monomer (%)	99.8	99.8	99.8	99.8
HCP (ng/mL)	996	1121	1081	1023
hcDNA (ng/mL)	0.76	0.92	0.73	0.81
Leached protein A (ng/mL)	21	14	23	17

Process economy calculations

In the evaluation of process economy of using the prepacked ReadyToProcess MabSelect SuRe 32 L column, the financial justification of column cost was considered. The following assumptions were made:

- Facility: existing production area
- Resin: MabSelect SuRe, list price 2016
- Labor:
  - Packing and unpacking: 48 man hours
  - Cleaning and changeover: 28 man hours
  - Buffer preparation: 12 man hours
  - Quality control: 16 man hours
- Buffer
  - Cost of water and chemicals
- Other
  - Column maintenance and changeover
  - Depreciation of BPG column: 10 years, 4 projects/year

The process economy calculation was focused on the gains of eliminating column packing/unpacking procedures in a multiproduct facility. Usage of production area was not factored in the cost analysis. Initial cleaning validation cost for the BPG column was not included in the analysis.

The total column costs were comparable between the formats, while for the prepacked column, the larger part of the column cost can be attributed to the resin.

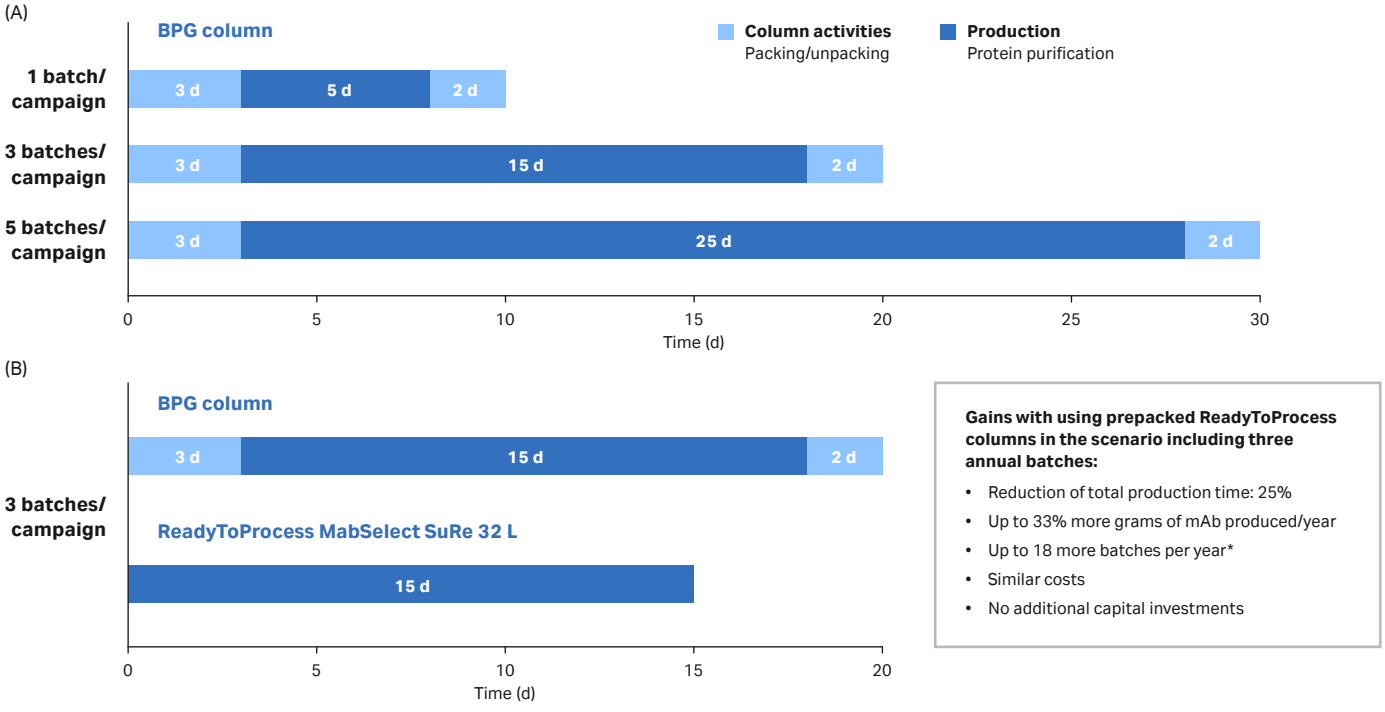


Fig 3. (A) Utilization of the production suit outlined for the conventional reference process (BPG column) for three different production scenarios. (B) Productivity improvement achieved by using ReadyToProcess MabSelect SuRe 32 L column the scenario including three annual batches.
*Facility runs year round.

Figure 3A outlines facility utilization for 1, 3, and 5 batches using the reference process (BPG column). As shown in Figure 3B for 3 batches, productivity can be significantly improved by using the prepacked column. Compared with the 20 days required for production of three batches using the manually packed column, the same amount of product can be produced in only 15 days with the prepacked column. For a facility running all year, up to 18 more batches can be produced using the prepacked column, generating 33% more product.

One way of reducing the resin cost can be by using a smaller prepacked column, however, in additional cycles. By using the time required for column activities related to a manually packed column for the additional cycles, the same amount of product can be produced in the same process time, that is, 20 days, with a smaller prepacked column.

In reoccurring campaigns, procedures such as column unpacking, resin storage, and column repacking can be eliminated by using prepacked columns. The prepacked column can just be wheeled into storage until next use. In addition, prepacked columns are particularly advantageous for multi-column systems, such as periodic counter-current chromatography (PCC), as they omit the need for column packing and performance testing of the many columns included. Purification of target molecules in continuous downstream processes using PCC can be used to increase utilization of the chromatography resin capacity, allowing sample load to much higher levels compared with what is possible in traditional batch chromatography (2).

Conclusion

This case study evaluates the technical performance of the prepacked ReadyToProcess MabSelect SuRe 32 L column when used over several cycles in a multiproduct facility. Compared with results obtained from the process run on a conventional manually packed column, the prepacked column exhibited a similar bed integrity, performance, and product purity and recovery. The performance of the prepacked column was shown to be consistent over 19 cycles, including 12 mAb feed load cycles and 7 wash cycles and comprising 5 different mAb projects. No technical concerns were observed with repeated cycling of the prepacked column.

In addition, a process economy analysis of the use of the ReadyToProcess MabSelect SuRe 32 L column was conducted. The results show that the total cost for the prepacked column was comparable with total cost for the manually packed column (within 5% of total cost). However, the prepacked column can eliminate 25% of the time required in production suite, while keeping costs at a similar level. If cost and not time is the concern, the cost of the prepacked column format can be reduced by using a smaller column in additional cycles. Smaller columns, however, need to fit into the proposed process and the number of cycles needs to be verified.

Disclaimer

The results and conclusions presented in this case study are valid for this specific study only. Other study conditions and assumptions could have significant impact on the outcome. The number of cycles that can be run on the ReadyToProcess MabSelect SuRe 32 L column is dependent of application and operating conditions, that is, feed composition, efficiency of CIP procedure, properties of applied liquids, pressure drop over the column, storage conditions, and similar. The bed integrity over time will, to large part, depend on above mentioned conditions.

The overall finding is that productivity can be significantly improved by using prepacked columns versus the use of manually packed columns. Prepacked columns enable quick startup and changeover between productions, contributing to that more batches can be produced per year compared with using manually packed columns.

When producing in a hybrid GMP facility, containing both stainless steel and single-use equipment, cleaning and cleaning validation operations cannot be eliminated entirely. In such a facility, equipment exists that will still need to be subjected to CIP and SIP procedures. The time-savings shown here can only be attributed to the prepacked column included in this study. Many bottlenecks that can still occur in a production facility may relate to, for example, bioreactor turnover, product and buffer tank availability, and support functions such as buffer preparation and cleaning operations.

Reference

1. Application note: Process economy and production capacity using single-use versus stainless steel fermentation equipment. Cytiva, 29143348, Edition AB (2015).
2. Application note: The use of dynamic control in periodic counter-current chromatography. Cytiva, 29169950, Edition AA (2016).

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