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Application Note

October 8, 2024

Keywords or phrases:
StreamLink® CC 15, mAb, monoclonal antibody, cell line development, CLD, Ambr® 15, Ambr® 250, Sample preparation, Sample prep, Cost reduction, Time saving, Cost saving, Purification, Clarification, Automation, Automated sample preparation, ROI, Return on investment, Downstream processing, Process automation, High throughput, Screening, Workflow optimization, Sartobind® Rapid A, Sartoclear® disc filter

Optimizing Time and Cost Efficiency in Cell Line Development With StreamLink® CC 15

Hannes Korndörfer[1]*, Heiko Dinter[2], Magnus Warnke[1], Alexandra Stützer[1], James Edwards[3]

[1]Sartorius Stedim Biotech GmbH, August-Spindler-Straße 11, 37079 Göttingen, Germany
[2]Sartorius Stedim Cellca GmbH, Marie-Goeppert-Mayer-Straße 9, 89081 Ulm
[3]Sartorius Royston, The Automation Partnership (Cambridge) Ltd., Grantham Close, York Way, Royston, Hertfordshire, UK, SG8 5WY

*Correspondence
Email: hannes.korndoerfer@sartorius.com

Abstract

The high demand for monoclonal antibodies in the medical field requires time- and resource-efficient development processes in the biopharmaceutical industry to keep costs and time to market as low as possible.

The upstream process of cell line development is significantly accelerated by using the Ambr® 15 microbioreactor. However, an easy-to-use solution to speed up downstream processes has been missing until now. The new StreamLink® CC 15 closes this gap by enabling seamless processing of cell culture samples from the Ambr® 15, Ambr® 250 or any other mammalian cell culture in a time- and resource-efficient downstream process.

This application note describes the downstream process of cell culture clarification and chromatographic monoclonal antibody purification with the fully automated StreamLink® CC 15 compared to the conventional process of manual clarification and purification with a standard chromatographic system in terms of time and cost savings.

Introduction

In recent years, monoclonal antibodies (mAbs) have established themselves as one of the key products in the biopharmaceutical industry. The increasing use of mAbs for therapeutic applications makes the development pipeline of new mAbs a central element of the research and development activities of biopharmaceutical companies. Consequently, there is a high demand for fast and efficient development of mAb-producing cell lines.

The Ambr® 15 microbioreactor system has set a new standard in the upstream process of cell line development. This success story now continues seamlessly with the StreamLink® CC 15 in downstream product processing.

The StreamLink® CC 15 (Figure 1) is a fully automated high throughput system for clarification and | or subsequent purification of mAbs for critical quality attribute (CQA) analysis. It processes cell culture samples from 5 to 30 mL derived from the Ambr® 15, Ambr® 250 or any other culture.
The system can be used inside a biological safety cabinet or on the bench and processes up to 48 cell culture samples in one run (48 samples with a volume of 10 mL ± 5 mL, 24 samples with a volume > 15 mL).

A robotic liquid handler provides the samples to two independent filter stations for clarification and | or purification. Clarification is performed with the Sartoclear® Disc, a single-use multilayer filter with a final layer of 0.2 µm that clarifies cell culture samples without the need for centrifugation.

Subsequent product purification is carried out with the multi-use Sartobind® Rapid A Nano membrane adsorber, which can process up to 72 samples when used with the StreamLink® CC 15 System. Its Protein-A-based convecdiff membrane is characterized by high-binding capacities and short residence times, allowing rapid cycling between membrane loading and elution. A UV sensor downstream of the Sartobind® Rapid A Nano device gives an estimation of the eluted mAb in terms of concentration and purity. UV peak cutting allows the user to concentrate the eluate in the case of a low mAb titer. The intuitive software allows quick familiarization and efficient use from the start.

With its high degree of automation and rapid mAb purification, the StreamLink® CC 15 significantly accelerates downstream processes in cell line development and reduces costs. In addition, the purchase price is significantly lower compared to other automated options with similar functions.

This application note describes the downstream process of cell culture clarification and mAb purification for subsequent CQA analysis with the StreamLink® CC 15 compared to the conventional process of manual clarification and mAb purification with a standard chromatography system. The processing of 48 cell culture samples was compared in terms of overall process times, hands-on times, and costs (full-time equivalent [FTE] and consumables). The comparison was carried out in a cell line development service unit in Ulm, Germany.

Materials and Methods

Cell culture samples were cultivated with the Ambr® 15 microbioreactor, an automated workstation that controls up to 48 cell cultures in parallel. Downstream processing of these 48 samples, each with a processed volume of 10 mL of cell culture, was either carried out with the StreamLink® CC 15 (Figure 1) or a conventional process.

The StreamLink® CC 15 uses the Sartoclear® Disc single-use filters for cell culture clarification and the Sartobind® Rapid A Nano multi-use membrane adsorber for subsequent mAb purification. Figure 2 shows the StreamLink® CC 15 consumables with their product characteristics.
The conventional process uses a chromatography system without an autosampler, equipped with a prepacked 1 mL column with Protein A affinity resin. The system can process up to 7 samples without pausing, cleaning the inlet lines, or adding new samples. During the conventional process, the cell broth is clarified manually using a syringe filtration kit (Sartoclear Dynamics® Lab P15 mL, 0.2 µm).

To effectively compare the overall process and hands-on times, the workflows were divided into six distinct steps from documentation and preparation of buffer solutions, through clarification of the cell culture, mAb purification (affinity capture), to final cleaning of the system (Figure 3).

The cost comparison takes into account the expenses for one full-time employee (FTE) per hour, as well as the costs for consumables, including system-specific items like the Sartoclear® Discs (one per sample) and the Sartobind® Rapid A Nano (one per 48 samples) for the StreamLink® CC 15, and the pre-packed column containing 1 mL Protein A affinity resin for the conventional system. Additionally, buffer stock solutions, single-use plastic labware (e.g., pipette tips, tubes, and bottle top filters), and other items required for both are included in these costs.

Figure 1: *StreamLink® CC 15 System*

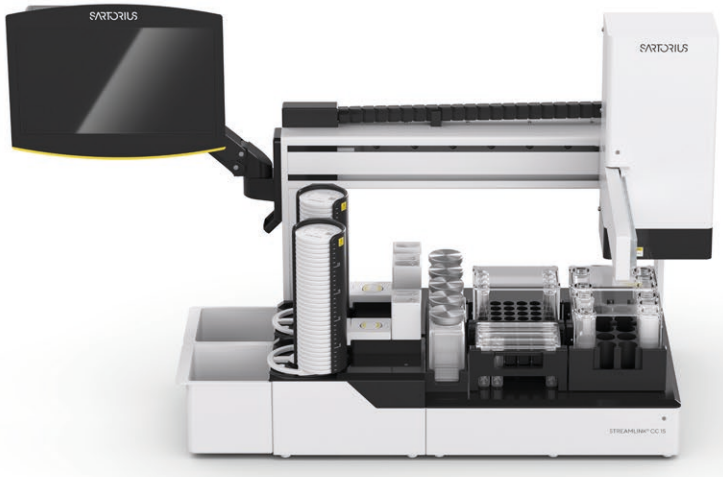


Figure 2: *StreamLink® CC 15 Consumables*

Clarification

Sartoclear® Disc

- Multi-layer synthetic filter (5 layers)
- Final 0.2 µm membrane – purification pre-filtration
- Single-use
- Specifically developed for automated use in StreamLink® CC 15
- 20 cm² filter surface area
- Sized for 5 – 15 mL culture
- ~90% Product Recovery

Purification

Sartobind® Rapid A Nano

- Protein A membrane adsorber
- High flow rates
- Low fouling
- >95% product recovery
- 1.2 mL membrane volume
- ~35 mg binding capacity
- Part of a scalable portfolio

Results

Clarification and purification of mAbs for CQA analysis with the StreamLink® CC 15 showed a high potential for time, resource, and cost savings compared to the conventional process. Cost savings are mainly due to the reduction in FTEs.

Table 1 shows the chromatographic recipes used for the conventional chromatography system and the StreamLink® CC 15. The StreamLink® CC 15 requires higher volumes of buffer solutions. However, due to the faster flow rate, purification of one sample takes only 10 to 15 minutes* (including cell culture clarification with the Sartoclear® Disc) compared to 120 minutes with the conventional chromatography system.

Figure 3 outlines the individual steps of the entire workflow, beginning with the documentation and preparation of buffer solutions and culminating in the cleaning of both systems following sample purification and neutralization. The figure shows the time required for each step and per sample when samples are processed with the conventional setup or with the StreamLink® CC 15. Icons indicate whether an individual step must be carried out manually (✋) or whether it is automated (⚙). Using the StreamLink® CC 15, most steps of the entire workflow are processed automatically compared to the conventional process where only the chromatographic mAb purification is automated.

In addition, the processing time—except for neutralization—is significantly shorter than with the conventional method; in particular, the time for mAb purification per sample differs considerably at 10 minutes compared to 2 hours. It should also be mentioned that the time required to clean the sample inlets when processing more than 7 samples in the conventional process was not considered.

The time required for the entire workflow (process time) and the pure hands-on time are shown in Figures 4A and 4B. The high degree of automation and the reduced time required for most of the process steps lead to a significant reduction of process and hands-on times with the StreamLink® CC 15 compared to the conventional method.

Using the StreamLink® CC 15 for system setup saves three hours of hands-on time compared to a conventional process. Additionally, the final cleaning of the system is not only automated but also takes only a quarter of the time, saving 1.5 hours compared to the standard process.

Most importantly, the StreamLink® CC 15 enables remarkably faster mAbs purification, reducing the process from 120 minutes to just 10 minutes per sample. These significant time savings become increasingly beneficial as the number of samples increases.

Table 1: *Chromatographic Recipes Used for the Conventional Process and the StreamLink® CC 15*

	Conventional Process		Streamlink® CC 15	
Step	**Volume [mL]**	**Flowrate [mL/min]**	**Volume [mL]**	**Flowrate [mL/min]**
Binding | loading	-	0.16	-	12
Filter rinse	-	-	5	12
Wash	8	0.5	12	12
Elution	6	0.5	12	12
H_2O	3	0.5	-	-
CiP	3	0.5	6	6
H_2O	3	0.5	-	-
Equilibration	6	0.5	18	12
Time/sample	**120 minutes (Purification only)**		**10 – 15 minutes (Clarification + Purification)**	

Note. CiP = Cleaning in place

Figure 3: *Steps of the mAb Downstream Processing With the StreamLink® CC 15 or a Standard Chromatography System*

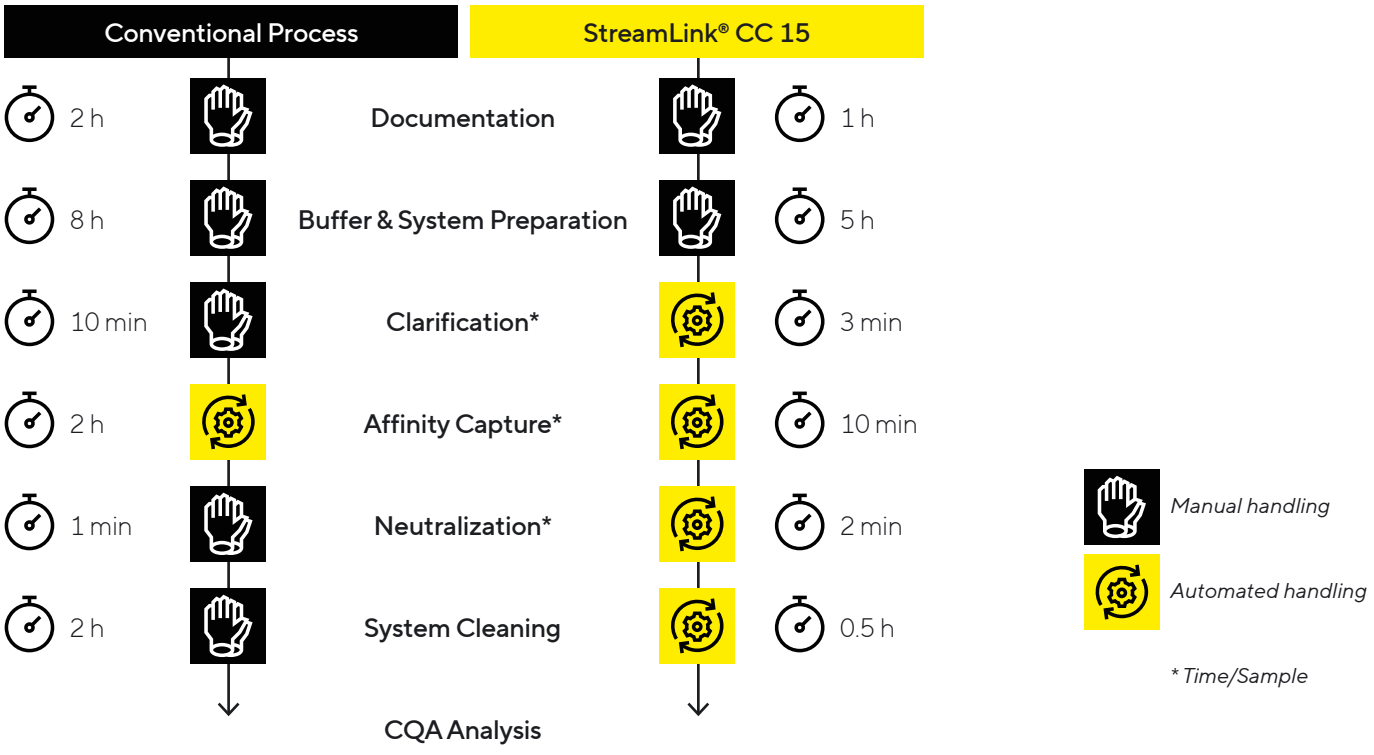
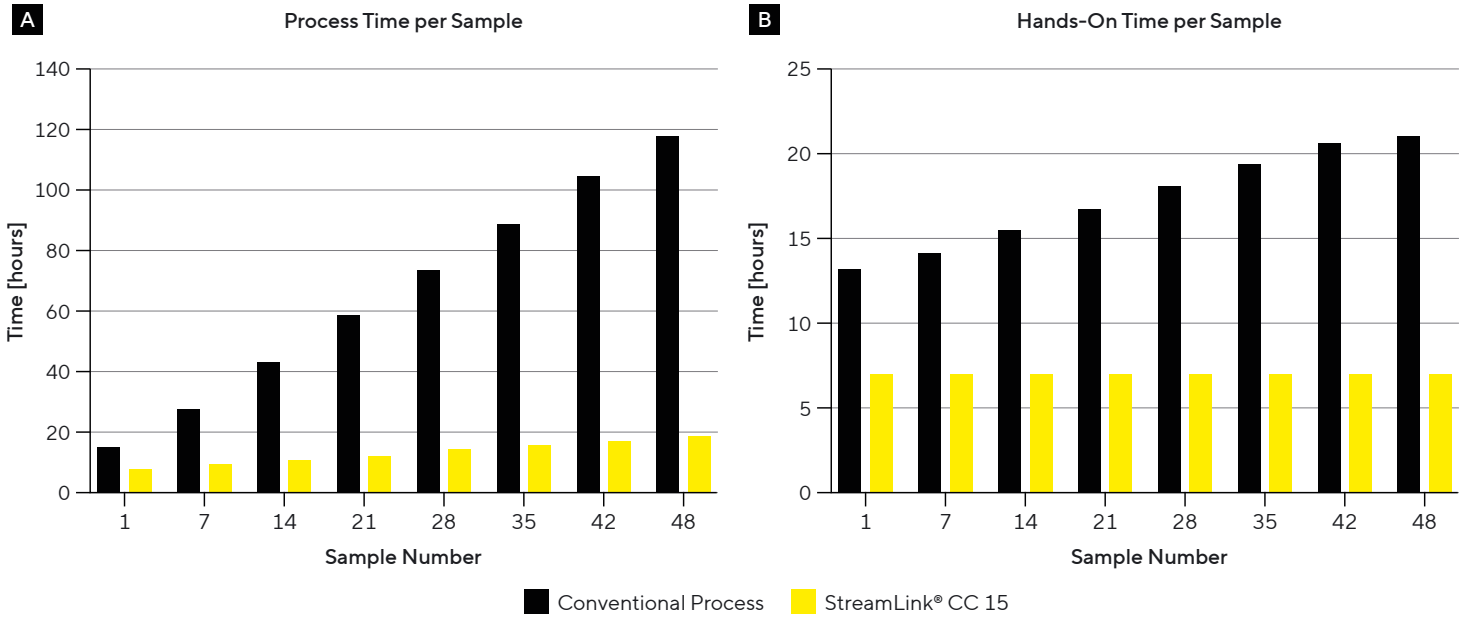


Figure 4: *Comparison of* ***(A)*** *Overall Process Times and* ***(B)*** *and Pure Hands-On Times*



Note. Downstream process time from cell culture clarification to preparation of purified mAbs.

A visual comparison of the time required for the individual steps when processing 48 samples is shown in Figure 5.

Figure 5: *Time Required for the Individual Steps of Sample Processing With the StreamLink® CC 15 Compared to the Conventional Procedure (48 Samples).*

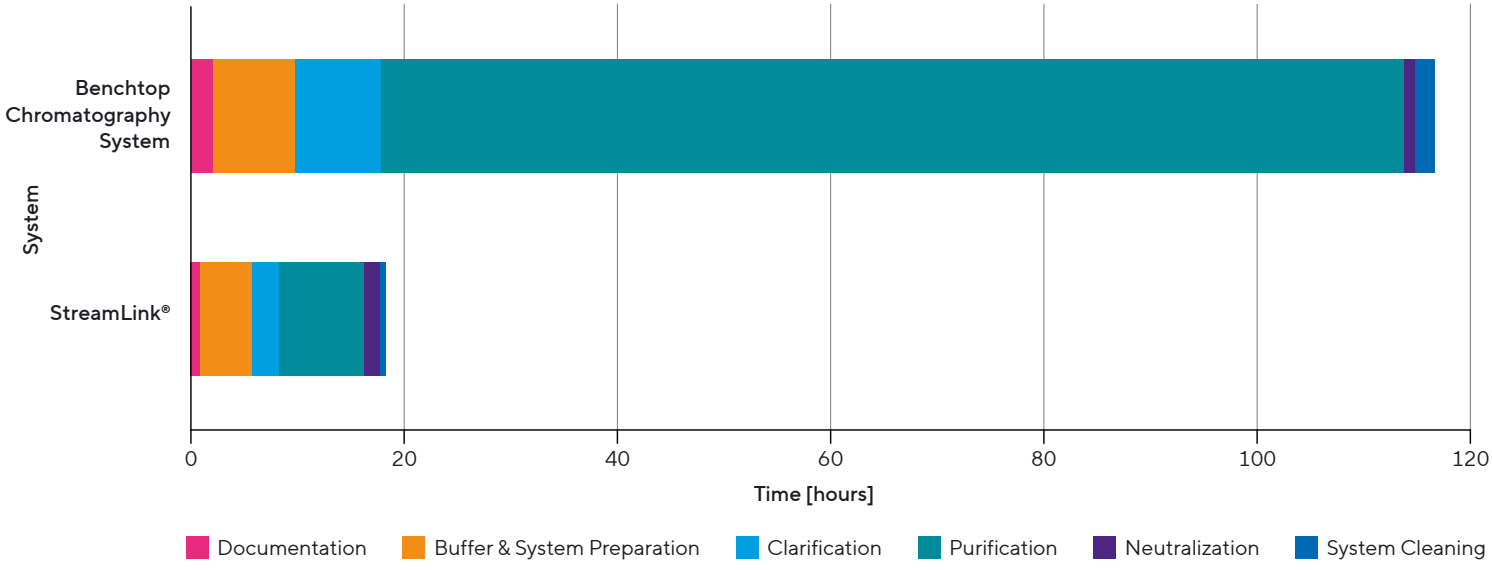
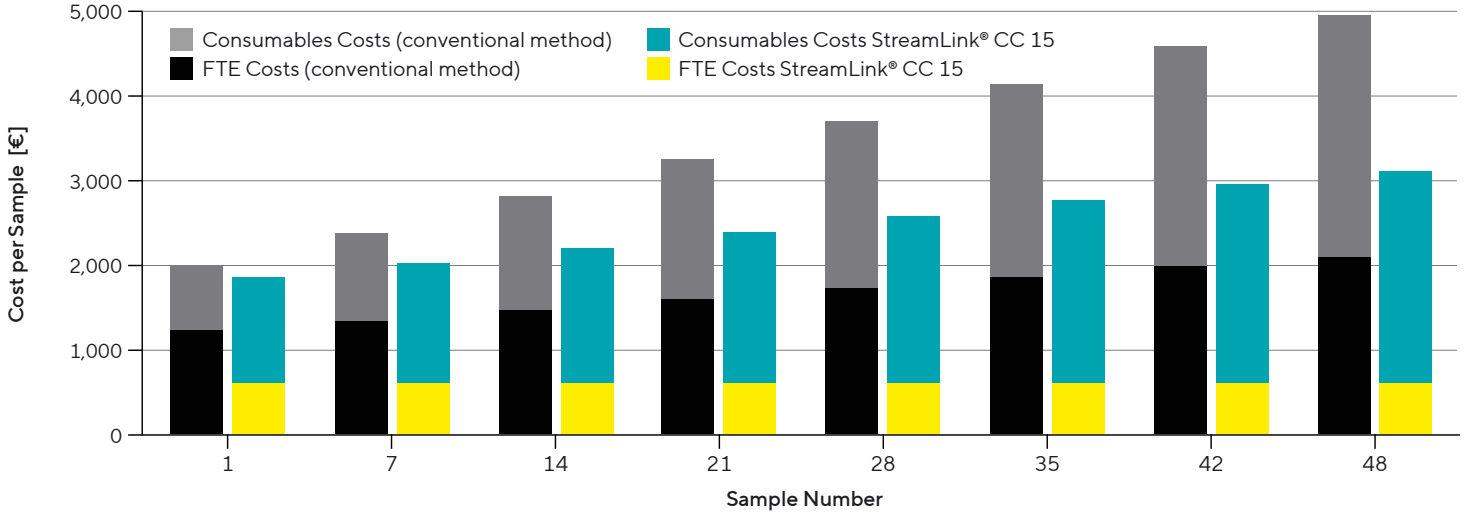


Figure 6 shows the comparison of costs, considering costs for FTE per hour and costs for the consumables. FTE costs, accounting for the largest share of costs, were assumed at €100.00 per hour. The costs for the consumables were calculated per sample. As the number of samples increases, the workflow using the conventional method takes considerably longer, significantly raising costs compared to the StreamLink® CC 15.

Figure 6: *Cost Comparison*



Note. Costs of cell culture clarification and mAb purification using the StreamLink® CC 15 compared to the conventional process.

Discussion

Time to market and costs are critical aspects of biopharmaceutical research and development activities. The StreamLink® CC 15 optimizes both parameters by mitigating the downstream bottleneck of clarification and mAb purification in cell line development. Compared to the conventional process, the workflow is significantly accelerated and requires considerably less hands-on time using the StreamLink® CC 15. Moreover, the Streamlink® CC 15's automation improves the reproducibility of mAb purification.

Processing 48 samples with the StreamLink® CC 15 requires a process time of only ~20 hours, in stark contrast to the ~120 hours needed with the conventional method. Automated cell culture clarification and mAb purification with the StreamLink® CC 15 reduces hands-on time by ~16 hours, minimizes handling errors, and enables robust reproducibility of the results. Using the Sartobind® Rapid A Nano membrane adsorber, product purification is considerably accelerated due to high volumetric flow rates and short residence times. Product purification takes only 10 minutes per sample compared to 120 minutes using a conventional resin column-based chromatographic system. Additionally, the Sartobind® Rapid A membrane adsorber can process up to 72 samples, enabling uninterrupted operation without the need for replacement while handling 48 samples.

Due to the long process times, the conventional chromatographic method limits purification to a maximum of three samples per working day. When additional samples are processed, they must be frozen post-clarification. Freezing and thawing can have a negative impact on product quality, which can be avoided with the StreamLink® CC 15. Sample neutralization and mixing allows the StreamLink® CC 15 to process samples with true walk-away operation overnight.

Conclusion

With its high degree of automation and significantly faster chromatographic purification, the StreamLink® CC 15 ensures the downstream processing of up to 48 samples from one day to the other with high reproducibility and considerable cost savings, mainly in terms of FTE costs.

Following the groundbreaking advancements introduced by Ambr® 15 in the upstream process, the StreamLink® CC 15 is now setting new standards in the downstream process of cell line development.

Want to find out more about the StreamLink® CC 15 and how it can save you time?
sartorius.com/streamlink-cc-15

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Germany
Sartorius Stedim Biotech GmbH
August-Spindler-Strasse 11
37079 Goettingen
Phone +49 551 308 0

USA
Sartorius Stedim North America Inc.
565 Johnson Avenue
Bohemia, NY 11716
Toll-Free +1 800 368 7178

For more information, visit
sartorius.com

Status: 10 | 2024