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Pionic® Spin: An Innovative Solution for Continuous Low pH Flow-Through Virus Inactivation

Karolina Meyer-Heinrichs[1], Tobias Steinwedel[1], Johannes Wortmeyer[1], Lisa Lipski[1], Oliver Stark[1], Franziska Krumbein[1], Stuart Tindal[1], Chad Varner[2], Akshat Mullerpatan[2], Michael Coolbaugh[2], Kevin Brower[2]
[1] Sartorius Stedim Biotech GmbH, August-Spindler-Strasse 11, 37079 Goettingen, Germany
[2] Global CMC Development Sanofi, USA

Correspondence
Email: karolina.meyer-heinrichs@sartorius.com, kevin.brower@sanofi.com

Abstract

The rising use of biopharmaceuticals in medical applications necessitates a shift toward more efficient and cost-effective biomanufacturing of active pharmaceutical ingredients. Integrated continuous biomanufacturing (ICB) plays a crucial role in this transition by replacing traditional batch processing with continuous processing. Pionic® Spin represents a pioneering solution that drives this transition with its compact design, aseptic processing capabilities, and substantial cost savings. It is a modular platform for automated continuous virus inactivation and is part of Pionic® Platform, which is designed for up to Level 3 ICB in the downstream processing of active pharmaceutical ingredients.[1]

This application note highlights the transformative potential of Pionic® Spin in advancing biopharmaceutical production processes, paving the way for future innovations in ICB.

This work is the result of a Collaboration & License Agreement between Sanofi and Sartorius.

Introduction

The Role of Process Intensification in Biopharmaceutical Production Processes

Biopharmaceuticals are in high demand as these innovative therapies target severe illnesses—such as certain cancers, genetic disorders, and degenerative diseases—with high efficacy and good tolerability. With the number of approvals and clinical trials continuing to grow, efficient and cost-effective production is becoming increasingly important. In this context, process intensification (PI) will be crucial for long-term success.

A key goal of PI is to enhance efficiency and productivity through continuous processing. Traditionally, biopharmaceutical manufacturing relies on periodic batch processing (Level 0), which involves distinct unit operations in both upstream and downstream processing. The transition from batch processing to integrated continuous processing—also called integrated continuous biomanufacturing (ICB)—brings numerous advantages, including shorter production times, reduced facility space requirements, lower cost of goods sold (COGs), and a reduced carbon and water footprint.

The transition to ICB usually takes place in stages, starting with the intensification of individual unit operations (Level 1) and progressing to the connection of at least two downstream processing units for simultaneous, integrated operation (Level 2). The greatest benefit can be achieved with a fully automated ICB process (Level 3), which encompasses all steps of the downstream process and operates in a steady-state flow. However, the benefits of ICB become increasingly significant as more process steps are handled continuously. The degree of ICB needed varies depending on the specific biopharmaceutical production process, and will typically fall between Level 1 and full ICB (Level 3).[1,2,3]

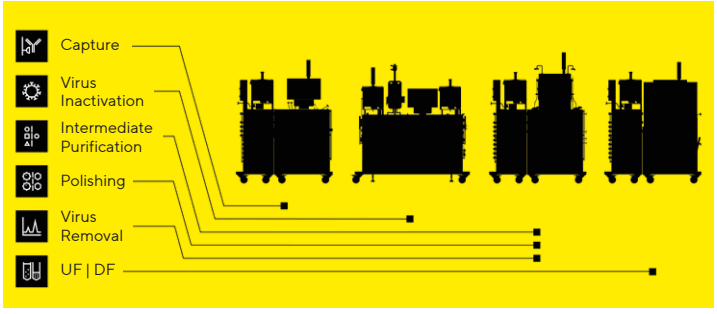
The Sartorius Solution for Continuous Virus Inactivation

Pionic® Spin is an innovative operational unit designed for continuous virus inactivation (cVI) through a fully closed, irradiated, ready-for-use flow path. Pionic® Spin is part of the Pionic® Platform, a modular PI platform that includes ready-for-use units designed to support operations up to Level 3 of ICB.

Virus inactivation (VI) is an essential step in the downstream processing of active pharmaceutical ingredients (API's). Typically located between the capture and polishing steps, this process significantly reduces the risk of viral contamination, thereby enhancing the safety of the final product. Furthermore, VI is required by regulatory authorities such as the Food and Drug Administration (FDA) and the European Medicines Agency (EMA).

Pionic® Spin intensifies VI by enabling automated, robust virus inactivation at low pH under continuous operation. It is specifically designed for long-term perfusion-based processing, supporting continuous operation for up to 28 days without the need to exchange ready-for-use components or process analytical technologies (PATs). Automated inflow pH titration of the incoming feed is carried out in a single step, achieving a control accuracy within ±0.1 pH units of the target value. The modular Pionic® Spin Incubator features a serpentine design that ensures a uniform minimum residence time of 30 minutes for low pH incubation. It reduces active viruses by ≥5 log reduction values (LRV; 99.999%), meeting regulatory requirements for VI. Integrated surge vessels at the inlet and outlet balance the flow, further supporting consistent processing conditions for effective cVI.

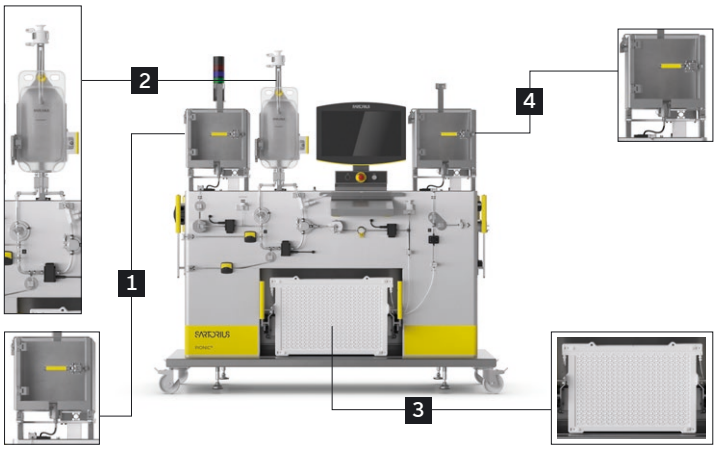
Figure 1: *Pionic® Platform Facilitates up to Level 3 ICB by Encompassing all Downstream Processing Steps, From Capture to Ultra- and Diafiltration*



Note. Individual units from Pionic® Platform can be seamlessly integrated into existing downstream processes, enabling a transition from batch processing to the desired level of ICB.

Pionic® facilitates the implementation of a downstream processing line for up to Level 3 ICB. The platform is shown in Figure 1, and Pionic® Spin module is shown in Figure 2. The orchestrated operation of Pionic® Spin with the integrated upstream and downstream units for capture and intermediate purification requires close communication between the individual operational units. This is achieved using open platform communication (OPC), an industry-standard solution that allows the integration of Pionic® Spin into supervisory control and data acquisition (SCADA) and distributed control system (DCS) platforms. Additionally, the system is compatible with both cyclic and continuous capture outputs from the preceding chromatographic capture step.

Figure 2: *Pionic® Spin With its Four Functional Zones*



Note. **(1)** homogenization of the feed, **(2)** acidification of the homogenized solution, **(3)** flow-through virus inactivation, and **(4)** neutralization.

Scalable Continuous Virus Inactivation for Flexibility From Clinical to Commercial Scale

Pionic® Spin offers scalability from clinical- to small and medium commercial-scale operations with bioreactor volumes of ~100 to 2,000 L, and average incoming elution flow rates of 1–20 L/h (Figure 3). The appropriate average elution flow rate depends on individual process conditions, such as the perfusion bioreactor volume, product characteristics in the withdrawn medium, and the upstream chromatographic approach, including consumables, recipes, and performance.

Pionic® Spin Incubator offers one dedicated ready-for-use consumable, available in different formats. These options support a scalable, uniform, and optimized cVI that ensures an LRV compliant with regulatory requirements, while minimizing the API's exposure to acidic conditions.

The Four Functional Zones of Pionic® Spin

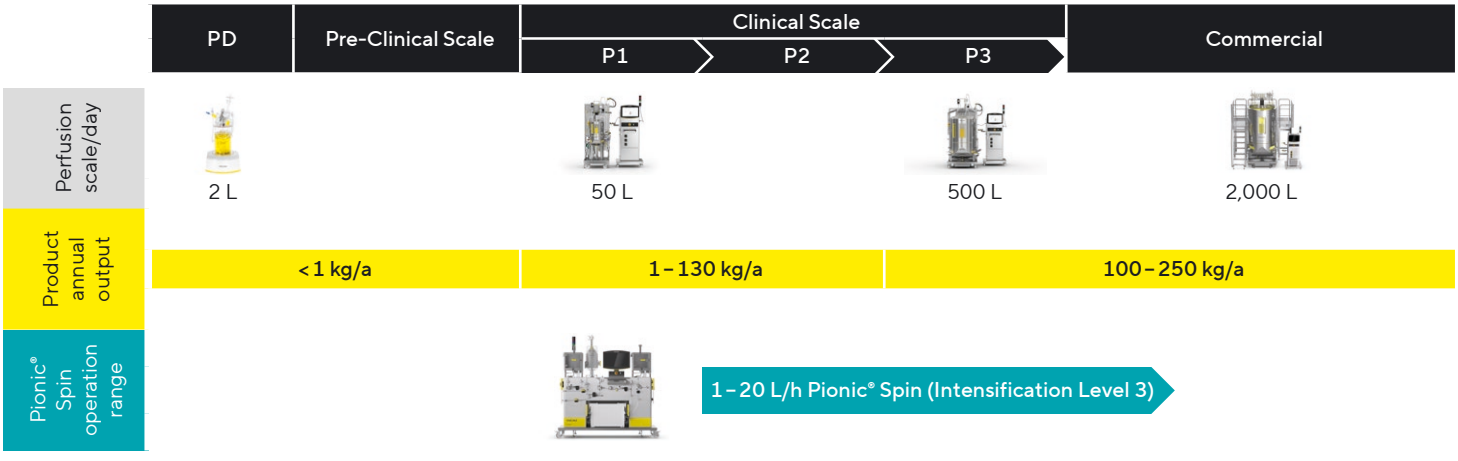
Figure 2 depicts Pionic® Spin and outlines its four main functional zones. Homogenization and balancing of incoming elution fractions are performed in the 20 L integrated homogenization bag. The solution then flows into the 3 L recirculation bag, which is integrated into a unique low-volume recirculation mixing loop where the acidification of the homogenized solution takes place. The recirculation mixing loop enables precise and uniform acidification through fast and robust pH titration to the selected pH setpoint, using a novel pH control system for optimal performance.

The acidified solution flows into the innovative Pionic® Spin Incubator, which ensures consistent incubation time and narrow residence time distribution (RTD). Different variants allow customization to individual process requirements, considering factors such as the flow rate, feed viscosity, and the required incubation time.

Finally, the solution is neutralized in the 20 L integrated neutralization bag, with the pH control system precisely titrating to the specified pH setpoint. Once neutralization is complete, the solution is transferred either to the subsequent processing unit or to a collection vessel.

Ready-for-use components and the modular Pionic® Spin Incubator provide operational flexibility, enabling switching between different production operating scales and | or API's. A suitable configuration can be selected from our Pionic® Spin Incubator portfolio to match the process requirements.

Figure 3: *Operating Range of Pionic® Spin for Continuous Virus Inactivation*



Note. Scale-up trajectory of perfusion-based biopharmaceutical manufacturing processes, illustrating the transition from process development (PD) and pre-clinical scales to Phase 1 (P1; 5 – 50 L), Phase 2 (P2), and Phase 3 (P3; 200 – 500 L) clinical scales, and up to commercial scale (≥ 1,000 L). The diagram also highlights PI strategies, including an elution flow rate of 1 – 20 L/h for Pionic® Spin operation (classified as Intensification Level 3), implemented during the Clinical-to-Commercial transition to enhance volumetric productivity and maintain product quality.

Materials

Precise pH Control Ensured by Classical Feedback and Disturbance Control

Precise and rapid pH titration to the acidic pH setpoint is essential for process effectiveness. Pionic® Spin features a pH control system that combines established feedback control with advanced disturbance control. In addition to pH measurement in the respective adjustment volume, the control system also considers the titration characteristics of the specific feed material to achieve the pH setpoints required for acidification and neutralization.

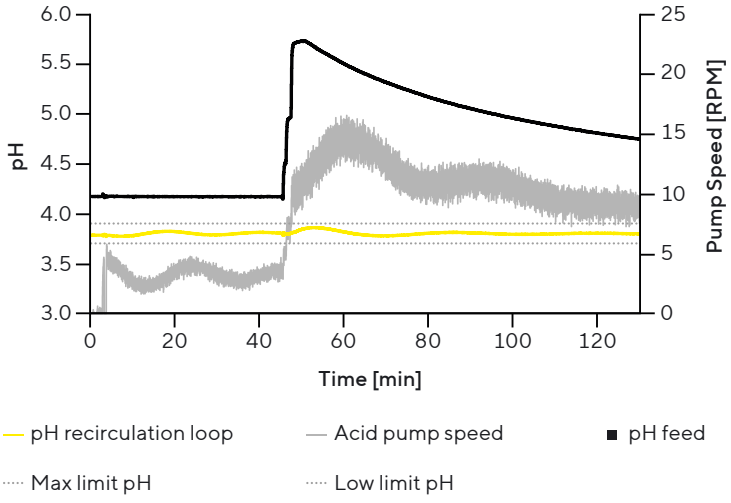
Three pH sensors, positioned in the homogenization bag, the recirculation loop, and the neutralization bag, continuously monitor the pH values. For acidification, the disturbance control continuously calculates the difference between the pH of the incoming eluates in the homogenization bag and the pH target setpoint. Considering the titration characteristics of the eluates, the system determines the appropriate amount of acid to adjust the incoming feed material to the acidic target pH setpoint. The residual pH difference is eliminated using the feedback PID controller, which relies on the pH measurement within the recirculation loop. The system compares both values to generate a control signal for adjusting the acid pump speed. This enables precise one-step titration of the product before it enters Pionic® Spin Incubator.

For neutralization, the same disturbance control calculation is conducted using the pH measurement within the recirculation loop and the target neutralization setpoint. The disturbance control and the feedback PID controller work together, similar to their operation during acidification. If the pH value falls outside the acceptable working range for VI, the system will close a valve at the outlet of the recirculation loop. This valve is designed with a minimum dead volume to prevent unadjusted product from entering Pionic® Spin Incubator. To regain steady-state conditions, the system will titrate acid or additional feed material into the recirculation loop until the pH returns to the specified range.

Figure 4 illustrates the ability of the pH control system to maintain a constant pH in the recirculation loop during a disturbance test involving the introduction of base into the homogenization bag (black line). In response to the increased pH difference between the feed and the target pH, the acid pump increases its speed (grey line) to counteract the change. The control system maintains the pH target of 3.8 (yellow line) within a tolerance of ±0.1 pH (dotted lines), ensuring stable operation.

This regulation occurs before any change in pH within the recirculation loop is detected, enabling faster response times compared to conventional feedback control.

Figure 4: *Rapid and Reliable pH Control in the Recirculation Loop of Pionic® Spin Using a Novel pH Control System Combining an Established Feedback Controller With Disturbance Control*



Note. Stable and robust pH-adjustment performance due to combined feedback and disturbance control.

Methods

Minimum 30-Minute Incubation Time With Pionic® Spin's Incubator

Ensuring a reliable incubation time of at least 30 minutes for all molecules is a challenge in a continuous process characterized by laminar flow. Normally, a laminar flow path leads to a wide range of residence times, mainly because friction decelerates the fluid near the wall, leading to a parabolic flow profile (Figure 5A).[4] Differences in RTD caused by different flow path geometries are depicted in Figure 5B. A narrower peak indicates a more consistent RTD of molecules flowing through the flow path; the narrowest of the three peaks corresponds to the innovative Pionic® Spin Incubator. Its serpentine design (Figure 6) facilitates secondary flows (Dean vortices), resulting in a narrow RTD, which is essential for a reliable VI while minimizing the API's exposure to acidic conditions.

Figure 5: (A) *Varying Residence Times of Two Molecules (Pink Dots) Flowing Through a Laminar Straight Flow Path;* **(B)** *RTD Resulting From Various Flow Path Shapes, Including the Serpentine Shape of Pionic® Spin Incubator*

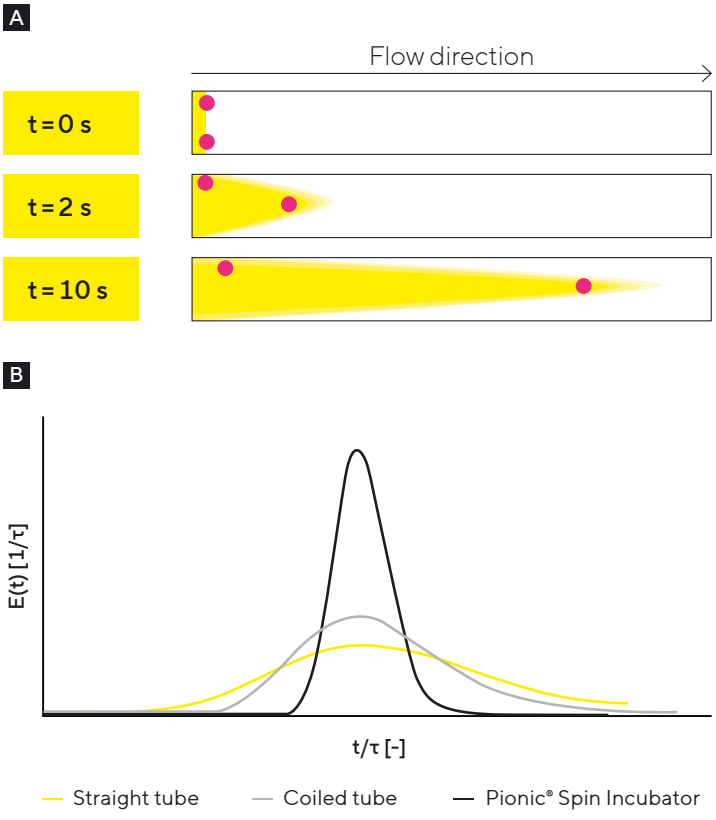


Figure 6: *The Pionic® Spin Incubator Features a Serpentine Flow Path Design That Ensures a Uniform Residence Time at Acidic pH for All Molecules Flowing Through It*

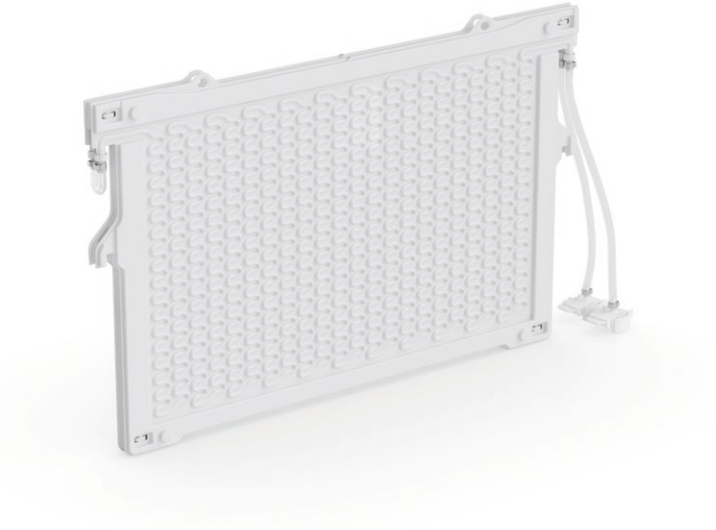
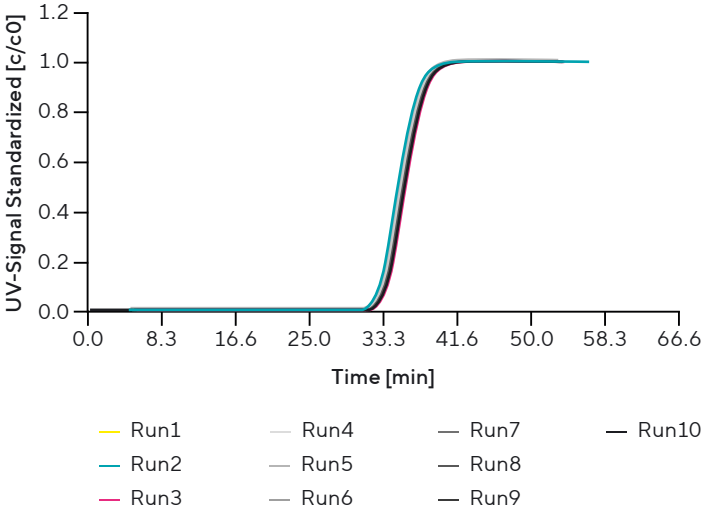


Figure 7 demonstrates the maintenance of a residence time of ≥ 30 minutes for acidic incubation, with a narrow RTD for all molecules of a batch. Several breakthrough curves were measured with a UV-tracer to characterize Pionic® Spin Incubator 1.4 device. The UV-tracer solution had an incubation flow rate of 40 mL/min and a viscosity of 1 mPas.

A maximum pressure drop of 13.5 mbar at the same incubation flow rate indicates the flow resistance. The congruence between the 10 replicates highlights the reproducibility of the independent runs. The sharp rise of the breakthrough curves at ~30 minutes indicates a narrow RTD with the UV tracer particles remaining in Pionic® Spin Incubator for a minimum of 31.3 min (t(0.01)) and a maximum of 40.9 min (t(0.99)). A quotient of t(0.99) and t(0.01) close to 1 is favorable, indicating that the tracer particles are only slightly distributed; the closer this value is to 1, the more uniform the distribution of the tracer particles.[5]

Pionic® Spin ensures reliable and consistent narrow RTD during cVI, achieving results that meet regulatory requirements, while keeping the API's exposure to the acidic conditions as short as possible.

Figure 7: *Determination of RTD and Pressure Drop of Ten Acetone Samples Used as UV Tracers Flowing Through Pionic® Spin Incubator*

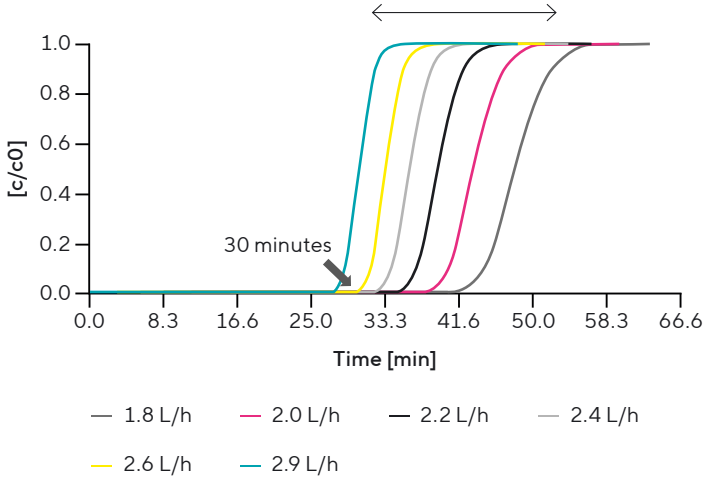


Note. All measurements were conducted using different Pionic® Spin Incubator 1.4.

Results

Figure 8 illustrates the RTD of the UV tracer at different incubation flow rates using the Pionic® Spin Incubator 1.4. A high incubation flow rate results in a narrow RTD (turquoise line), while a lower one leads to a broader RTD (dark grey line). The average incubation flow rates highlighted by the black arrow, specifically from 2 L/h to 2.4 L/h (pink, black, and light grey lines), are considered appropriate for Pionic® Spin Incubator used in this setup. Faster average incubation flow rates result in minimal residence times (t(0.01)) below 30 min, which may not meet the regulatory requirement of achieving a 5 LRV for active viruses (turquoise and yellow lines). The lowest average incubation flow rate of 1.8 L/h (dark grey line) results in a broad RTD, with a t(0.99) of 55 minutes, which could impact the API's stability in practical applications.

Figure 8: *Residence Time Distributions of Acetone Samples Used as UV-Tracers at Different Average Incubation Flow Rates, Flowing Through Pionic® Spin Incubator 1.4*



Note. Highlighted area depicts recommended flow rates for the operation of this specific incubator configuration to guarantee a sufficient residence time distribution.

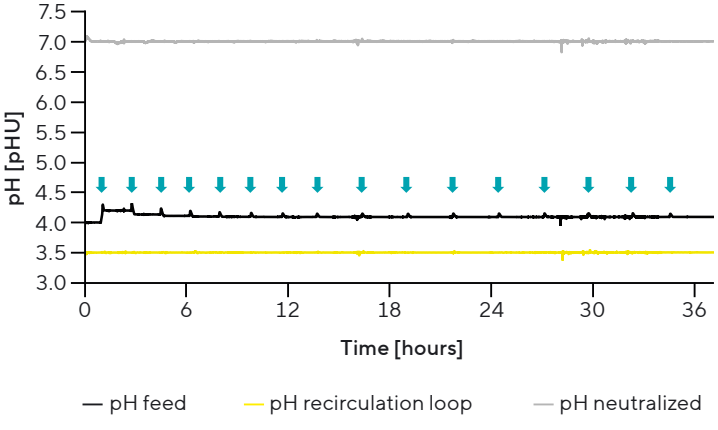
Performance of Pionic® Spin in pH Adjustment During Practical Application

The effectiveness and functionality of Pionic® Spin in cVI were assessed in a 28-day long-term run using a Pionic® Spin Incubator suitable for a 2.4 L/h operation mode. The results presented focus on the first 36 operational hours during which the output of 16 chromatography cycles was processed.

Figure 9 illustrates the capability of Pionic® Spin to maintain constant pH values in the recirculation loop and the neutralization bag throughout this initial operational period. Fluctuations in the pH value of the incoming feed (black line) from each chromatography cycle (blue arrows) were effectively controlled, and the pH setpoint of 3.5 (±0.1) was consistently maintained in the recirculation loop (yellow line) and subsequently in Pionic® Spin Incubator. Additionally, the pH setpoint of 7 (±0.1) was maintained in the neutralization bag (grey line).

These results demonstrate the pH adjustment performance of Pionic® Spin during mid-term operation. However, they only show the beginning of the long-term operation. The full long-term results will be covered in more detail in a future application note.

Figure 9: *Maintenance of pH Values in the Recirculation Loop (Yellow Line), Neutralization Bag (Grey Line), With Feed Influx (Black Line) From 16 Chromatography Cycles (Blue Arrows) During cVI With Pionic® Spin Over 36 Hours*



Discussion

Pionic® Spin enables autonomous cVI in long-term perfusion-based biopharmaceutical production processes. It overcomes major challenges associated with continuous in-flow processing and achieves both adequate incubation time and effective acidification, complying with regulatory requirements.

The curved design of Pionic® Spin Incubator ensures precise in-flow incubation for a minimum of 30 minutes, achieving a ≥5 log reduction value that effectively reduces the risk of active virus particles contaminating the final product. Various modular configurations of Pionic® Spin Incubator enable customization to specific process requirements, optimizing the RTD and minimizing the time the API is exposed to acidic conditions. The pH setpoints in the recirculation loop and the neutralization bag are quickly achieved and maintained by the pH control system that combines well-known feedback and disturbance control. Any in-flow pH fluctuations from the incoming feed are reliably balanced, ensuring a stable acidic pH (± 0.1 pH) in the recirculation loop and subsequently in Pionic® Spin Incubator.

Initial insights from a long-term practical application demonstrate the ability of Pionic® Spin to maintain constant pH values. Whenever feed from the integrated chromatography system was sent to Pionic® Spin, it immediately balanced pH peaks and maintained constant pH levels in the recirculation loop and the neutralization bag. Notably, this stability was achieved from the first hour of operation, confirming the robustness of the system.

Conclusion

The growing demand for biopharmaceuticals raises the need for streamlined production processes with higher productivity and reduced overall production costs. This development is driving the transition from traditional batch processing to integrated continuous biomanufacturing. The reliable automation of Pionic® Spin reduces hands-on time, while its continuous processing enhances productivity, reduces overall production time, and results in substantial cost savings.[6] The system has a small footprint while being suitable for clinical- to medium commercial-scale operations. Closed-loop, ready-to-use components ensure aseptic processing and provide flexibility when changing the processed API and | or the scale, while further lowering operational costs and streamlining production times. Consequently, Pionic® Spin, as one operational unit of Pionic® Platform, represents an innovative solution for cVI, supporting the critical shift to integrated continuous biomanufacturing.

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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

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