

TECHNOLOGY HORIZONS

A publication by Zetron, the pilot plant specialists

FALL 2024

IN THIS ISSUE

Pioneering: Takeda's Leap into Next-Gen Pharmaceutical Development

The Implementation of Continuous Manufacturing at AstraZeneca

Advanced Bioreactor Delivered to Circe

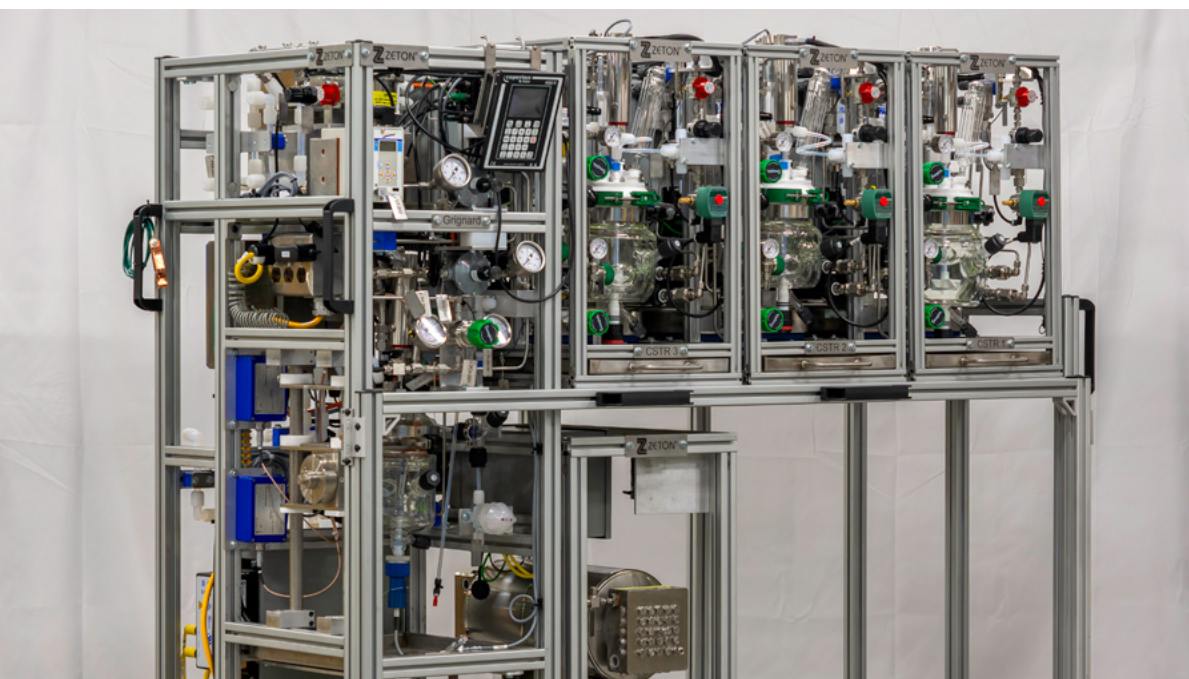
Zetron Supports Be-Come Foundation

In Brief

AND MORE!



Horizons is also available on our website at zetron.com



PIONEERING: TAKEDA'S LEAP INTO NEXT-GEN PHARMACEUTICAL DEVELOPMENT

The drive for efficiency and innovation propels the scientists and engineers at companies like Takeda Pharmaceuticals to challenge conventional processes.

Led by the synthetic molecule R&D team based in Cambridge, MA, the project was born from a visionary ambition: to establish a library of lab-scale unit operations, freeing the team to concentrate on chemistry rather than the logistical intricacies of module construction and to be able to quickly pivot to new target molecules without requiring additional hardware. This vision materialized in compact modular subframes housing continuous stirred tank reactors (CSTRs) ranging from 250 mL to 1 L, complemented by a custom-made ultra low-rate solids feeder, and a high temperature adjustable volume plug flow reactor (PFR).

However, turning this vision into reality presented formidable challenges. Accommodating all components within limited space necessitated meticulous planning and extensive collaboration among the team, engineers, and shop personnel. Overcoming spatial constraints while

ensuring ergonomic efficiency demanded innovative solutions. Aluminum framing, offering both flexibility and structural integrity, was employed, while 3D scanning technology ensured precise fitting within the designated space.

Electrical panel design posed another challenge, requiring extensive upfront work to minimize size and ensure compatibility with each sub-module.

Nevertheless, the project yielded remarkable success. A standout feature of the plant is its modular control system, allowing for seamless addition or removal of instrumentation and direct configuration via a web-based interface. This allows scientists, rather than controls engineers, to add sensors relevant to their specific reaction and collect real time data for analysis.

Collaboration between Takeda and Zetron was integral to the project's success. Takeda's openness to sharing insights and techniques, coupled with Zetron's manufacturing and engineering experience proved invaluable in overcoming obstacles.

Looking forward, the project serves as a benchmark for the industry, aligning with the growing trend towards continuous manufacturing in pharmaceuticals. Plans for expansion include incorporating additional sub-modules for solvent exchanges and continuous distillation at a lab scale.

Working alongside Takeda Pharmaceuticals' Laboratory group underscored the importance of effective collaboration and innovation. Their commitment to pushing boundaries and embracing new technologies highlights their position as pioneers in the pharmaceutical R&D landscape.

"Partnering with Zetron has been outstanding. Their innovative modular approach helped us revolutionize lab-scale unit operations. Zetron's expertise and collaboration were key to overcoming challenges associated with compact designs while maintaining functionality and aesthetics. This project sets the foundation for our modularized process development in continuous manufacturing."

- Takeda Pharmaceuticals ■

THE IMPLEMENTATION OF CONTINUOUS MANUFACTURING AT ASTRAZENECA: GREENER AND SMARTER WITH GREATER SPEED, AGILITY, AND ROBUSTNESS



At a time when efficiency, sustainability and safety are crucial, AstraZeneca, a major player in the pharmaceutical industry, looked to transform its manufacturing processes. They have adopted continuous production, a novel approach that guarantees to bring about not just small enhancements but to truly make a significant impact.

AstraZeneca approached Zeton with a request to install a new system at their existing site. The goal was to improve the speed to the patient by having a flexible system that could run continuously and adapt to changing needs. AstraZeneca wanted an innovative solution, which led Zeton to introduce a new concept, which was still under development at the time. This system uses a "backbone" approach that improves efficiency and flexibility by using shared supply lines and standard connections. This solution, now known as ContiUnity, was further developed with valuable input and collaboration from AstraZeneca, as well as other involved leading pharmaceutical companies. Together with these partners we continuously improve and expand our ContiUnity® portfolio.

ContiUnity® is a comprehensive platform comprising three modular and extensible components, namely the Backbone,

Bookcase, and Process modules. ContiUnity® provides you with the ability to design and configure GMP- and GAMP-compliant processes quickly and efficiently. The modules of ContiUnity® are designed as standard building blocks with a wide operating range, making them easily configurable to meet the unique process requirements of customers. ContiUnity®'s flexibility covers the entire process lifecycle without the need to redesign, validate, or decommission equipment, providing a value-based solution and minimizing time to market.

AstraZeneca faced a number of challenges but found a solution in the ContiUnity® system. It provided them with several benefits such as speed, sustainability (less energy consumption, waste and raw material use), quality (improved consistency), scalability, and safety (small volumes and near-instantaneous reactions made dangerous reactions more accessible). By processing smaller volumes and enabling faster reactions, they were able to operate more efficiently and safely.

The benefits were clear: faster heating and cooling, improved mixing, higher operating pressure, and more control over the process. This translated into a production line that was more compact, leading to a more sustainable factory for the future.

The project was completed to time and within budget and gave AstraZeneca the ability to test and expand various processes for clinical and commercial production.

Some interesting project facts:

- From initial contact to delivery, the overall project was completed within 16 months
- Plant design and build within schedule ~12 months faster than greenfield
- Facility capable of allowing flow chemistry steps to be developed, GMP clinical trial and launch scale capacity
- ~20 kg/day active manufacture
- Reconfiguration time to change from one process to another is in hours now, not months

In short, AstraZeneca's move towards continuous manufacturing is an example of innovation and perseverance. It shows that the future of manufacturing is moving towards continuous, and that companies that embrace this change are paving the way for more sustainable and efficient delivery of medicines to patients. ■

"Through this project and our partnership with Zeton, we have provided an integrated continuous platform technology, which will allow a faster delivery of molecules to medicines to meet an ever greater patient need in a sustainable manner."

- Roger Shillitoe, AstraZeneca

ZETON DELIVERS ADVANCED GAS FERMENTATION PILOT PLANT TO CIRCE BIOSCIENCE

Circe, a Boston, MA-based spin-off from The Wyss Institute for Biologically Inspired Engineering at Harvard University, first contacted Zeton in the summer of 2021 for the design and build of an advanced gas fermentation system. Tests at the laboratory scale had proven promising, and it was time to scale the technology to pilot scale as an important step towards commercialization.

Progressing through (Phase 1) Basic Engineering into (Phase 2) Detailed Design, Procurement, Fabrication and Factory Testing, a major challenge the Zeton and Circe engineering teams faced was how to precisely control the gas feeds into the fermentation vessel. The project teams, together with Dr. Mike Schultz, Managing Director of PTI Global Solutions, and safety consultants Baker Engineering and Risk Consultants, created the requisite engineering controls, process design changes, additional safety interlocks, and automated processes to drive the system in a safe and controlled manner.

The project, which was partly funded by a US DOE award through the ECOSynBio program, continued through 2022 and 2023, with final delivery in December 2023. Currently the project is undergoing start-up and



commissioning at Circe's state-of-the-art facility in Massachusetts, with ongoing support from Zeton.

"Navigating this project through several complex engineering challenges and then delivering the pilot plant to our customer's new facility was a rewarding experience for the entire Zeton team. We would like to thank Circe for trusting Zeton to design and build their first gas fermentation pilot plant, and we are proud of what the project teams, working collaboratively, were able to accomplish."

- Nelson Carvalho,
Senior Project Manager, Zeton Inc.

"Working with Zeton on this advanced gas fermentation pilot system has been a truly rewarding experience. Their expertise and collaborative spirit were instrumental in overcoming the technical challenges we faced as we've scaled up from lab to pilot scale. Zeton's commitment to delivering a high-quality system and their continuous support throughout the process have made them an outstanding partner. We are excited to see this project come to life and look forward to demonstrating a revolutionary step forward in biomanufacturing."

- Ciaran Dunn,
Vice President of Engineering, Circe ■

TEAM SPIRIT HIGHLIGHTING THE ACCOMPLISHMENTS OF OUR STAFF IN THE DUTCH AND CANADIAN OPERATIONS

ZETON BV SUPPORTS BE-COME FOUNDATION

Zeton BV is excited to share our support for the Be-Come Foundation, an organization that helps an orphanage in Busia, Kenya, near the Ugandan border. One of our colleagues, Bram Aversch, is secretary of the foundation. The Be-Come Foundation provides help from the Netherlands by funding various projects that contribute to the self-sufficiency of the orphanage and the local community.

The project to which Zeton has contributed is the establishment of a duck breeding farm. This initiative not only provides a new source of food for the orphanage, but also creates opportunities for economic growth and education in the region. Through a market,

a collection, a generous donation from Zeton and a fun race with rubber ducks, a total of €2,395 was raised. This amount will pay for needed facilities such as a duck shelter, pond, ducks and the necessary feed.

We are pleased to be able to contribute to this worthwhile project and wish the Be-Come Foundation and the orphanage in Busia every success in setting up the duck farm. We hope this project will have a lasting positive impact on the community and look forward to seeing how it progresses.

For more information, please go to
<https://www.be-come.nl/> ■



IN BRIEF

HIGHLIGHTING RECENT AND COMPLETED PROJECTS AND ENGINEERING STUDIES

- A continuous manufacturing pilot plant for APIs
- An R&D testing unit for hydrogenation catalysts
- An alternative feedstocks screening unit
- Several electrolyzer test plants
- An engineering study for a battery-grade manganese pilot plant
- An engineering study for a ContiUnity® recirculation module



A 1 kg/h plastic recycling pilot plant



A 150 bbl/day biomass to liquids demonstration plant



Factory testing of a ContiUnity® module in Zeton's shop



A ContiUnity® bookcase with several process modules

SPECIAL ANNOUNCEMENT

Zeton B.V. is organizing a symposium on March 6, 2025 titled "**Innovative Horizons: Mastering Continuous Manufacturing and Modular Plant Solutions.**" Industry leaders will showcase modular plant solutions and automation approaches, demonstrating the integration of continuous manufacturing and flow chemistry. The event includes a manufacturing shop tour and provides an opportunity to understand cutting-edge modularization solutions. Please contact Esther Schröder at marketing@zeton.nl for the symposium program and registration.



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OR ITEMS IN THIS ISSUE OF HORIZONS, PLEASE CONTACT:

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