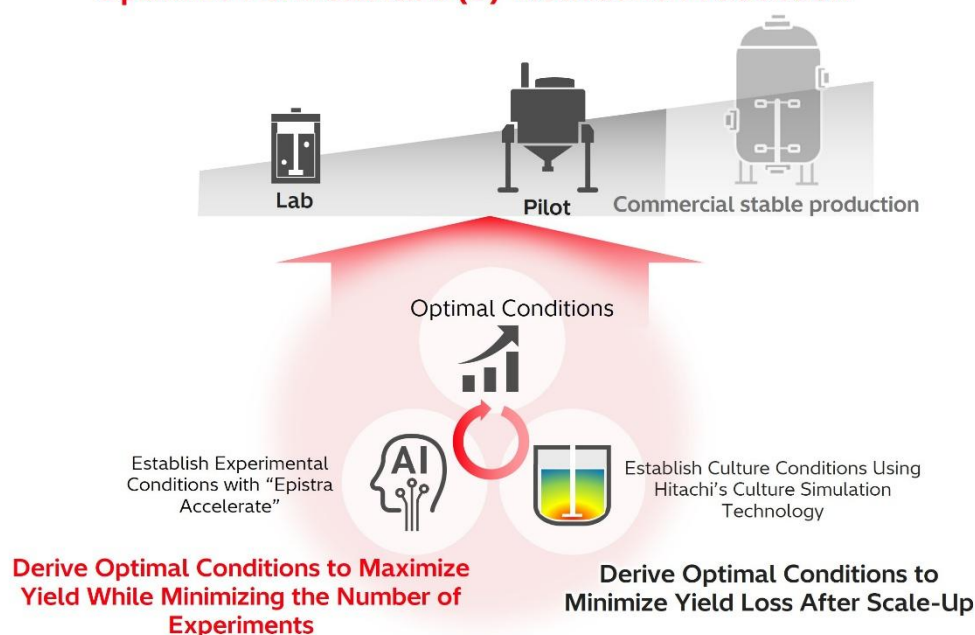




Epistra and Hitachi leverage AI to achieve one of the world's largest yields and up to a 73% reduction in lab experiment iterations in the production of “(S)-Reticuline,” a pharmaceutical intermediate from Fermelanta

By fiscal year 2025, we will conduct pilot-scale demonstrations to suppress yield reduction after scale-up. Looking ahead, Hitachi aims to globally expand HMAX Industry, a solution that supports production process optimization, to regions such as North America, helping customers improve productivity.

Optimize Fermelanta's (S)-Reticuline Production



Overview of initiatives toward commercial production of the (S)-Reticuline

Tokyo, November 27, 2025, Hitachi, Ltd. (TSE:6501, “Hitachi”), Fermelanta Inc. (“Fermelanta”), a synthetic biology startup, and Epistra Inc. (“Epistra”), which provides AI-based R&D support in the field of life sciences, have completed a first phase of lab-scale^{*1} joint proof-of-concept^{*2} in October. This initiative aims to address challenges in establishing microbial culture conditions^{*3} for producing “(S)-Reticuline”^{*4}, a pharmaceutical intermediate used in the production process of anticancer substances and other compounds. Fermelanta, Epistra, and Hitachi plan to carry out pilot-scale^{*5} demonstrations in fiscal year 2025 to minimize yield loss during scale-up. In the future, Hitachi intends to leverage the technologies and insights gained from this initiative to develop production process optimization solutions as HMAX Industry, which embodies Lumada^{*6}3.0, and expand globally to regions such as North America to help customers improve productivity.

In this lab-scale demonstration, Fermelanta and Epistra, Hitachi carried out culture experiments using Fermelanta's proprietary smart cells^{*7}.

Hitachi and Epistra, under conditions designed with scale-up in mind, utilized AI-based parameter optimization technology through “Epistra Accelerate”^{*8} to identify the optimal conditions from an enormous set of approximately 4,300 trillion combinations of 11 variables (such as temperature, pH, aeration rate, and media components) in just 60 experiments. As a result, the yield of (S)-Reticuline increased from 3.2 g/L to 6.0 g/L, and the number of lab experiments was reduced by up to 73% compared to conventional methods^{*9}.

This initiative demonstrates an integrated process combining “AI × Simulation × Smart Cells” and has achieved one of the world’s highest yields^{*10,11} for microbial-based bioproduction. (S)-Reticuline serves as an intermediate for various pharmaceuticals, and the yield achieved here enables cost-effective production of these compounds.

Hitachi’s Connective Industries (CI) Sector has extensive experience in applying culture simulation technology^{*12} to scale-up processes for the mass production of biopharmaceutical antibody-drug conjugates (ADCs)^{*13}. Moving forward, CI Sector focuses on “Integrated Industry Automation,” which aims to expand “HMAX Industry”, which embodies Lumada 3.0, into growth industries horizontally. HMAX Industry provides digital services that combine data from an abundant installed base of digitalized assets, domain knowledge, and advanced AI. By delivering HMAX Industry, CI sector will drive innovation on the frontline workers and contribute to people’s health and enriched lives.

***1 Lab scale:** An experimental scale using culture vessels with volumes ranging from a few milliliters to several liters.

***2** Part of the demonstration experiment is being conducted under the Ministry of Agriculture, Forestry and Fisheries’ Small and Medium Enterprise Innovation Creation Promotion Project (SBIR Phase 3).

***3 Culture conditions:** Refers to the physical, chemical, and operational parameters (such as aeration rate, temperature, pH, dissolved oxygen, nutrients, and culture time) and their set values when culturing microorganisms. These must be quantitatively designed to be reproducible from lab to commercial scale.

***4 (S)- Reticuline:** In the pharmaceutical manufacturing process, which consists of stages from raw materials → intermediates → active pharmaceutical ingredient (API) → pharmaceutical formulation, (S)-Reticuline falls under the “intermediate” category. It is an intermediate product used to synthesize the final active ingredient (API). Intermediates play a critical role in process development to ensure stable quality and yield. In particular, in the synthetic pathways of anticancer drugs and analgesics, passing through (S)-Reticuline enables efficient production.

***5 Pilot-scale:** A test production scale positioned between laboratory scale and full-scale commercial production.

***6 Lumada:** A collective term for Hitachi’s advanced digital technologies, solutions, and services that create value from customer data and accelerate digital innovation.

***7 Smart cell:** A cell engineered with multiple genetic modifications to enhance specific functions.

***8 Epistra Accelerate:** A registered trademark of Epistra in Japan. This is Epistra’s proprietary AI solution specialized in optimizing experimental conditions in the life sciences field. It addresses challenges such as “unmet target performance,” “prolonged R&D timelines,” and “increasing raw material costs,” enabling efficient exploration of optimal conditions. Epistra has improved productivity for customers across a wide range of applications, including drug development, media composition optimization, and bio-manufacturing, and boasts industry-leading results in productivity enhancement within the life sciences sector. For details, visit: <https://epistra.jp/en/epistra-accelerate>.

***9 Basis for 73% reduction:** The reduction rate in the number of experiments is based on a comparison with the required number of trials under a representative classical experimental design method (Box–Behnken design). For 11 factors with one center point, this method requires 221 trials. In this study, optimal conditions were identified in 60 trials, resulting in a reduction of approximately $(221-60)/221 \approx 73\%$.

***10 Basis for “one of the world’s largest”:** According to the latest published academic papers, the yield of (S)-Reticuline using yeast in a 3 L lab-scale culture vessel is reported to be 4.6–4.8 g/L, and no subsequent reports exceeding this yield at lab scale have been confirmed. Therefore, the results achieved here are considered among the world’s largest yields to date.

- Pyne, Michael E., et al. "A yeast platform for high-level synthesis of tetrahydroisoquinoline alkaloids." *Nature Communications* 11.1 (2020): 3337.
- Narcross, Lauren, et al. "Benzylisoquinoline alkaloid production in yeast via norlaudanoline improves selectivity and yield." *bioRxiv* (2023): 2023-05.

***11 Yield:** A numerical value indicating how much of the target substance was obtained during microbial production.

***12 Hitachi’s Culture Simulation technology (CFD):** Based on proprietary know-how cultivated through extensive experience in bioreactor manufacturing, this technology visualizes and quantifies flow, oxygen distribution, and shear

forces inside the bioreactor. It enables optimization of design and operating conditions and supports scale-up, contributing to improved productivity and quality in CHO cell and microbial cultures.

[Website for Hitachi's culture simulation technology](#) (In Japanese)

***13 Antibody-Drug Conjugate (ADC):** A targeted anticancer drug created by chemically conjugating an antibody (Antibody) with a drug (Drug).

Background

Industrial biotechnology, a technology and industry domain that uses biological resources such as microorganisms and enzymes to produce raw materials for chemicals, fuels, and pharmaceuticals, is expected to grow globally as a key enabler for achieving carbon neutrality and a circular economy. This is because it replaces conventional fossil resource-dependent manufacturing processes with bio-based resources and microbial fermentation technologies.

However, material development and commercialization in industrial biotechnology generally proceed through four stages: microorganism development, lab-scale process development, scale-up, and commercial production. Among these, the inreduction in production efficiency of target substances during scale-up has become a major bottleneck. To ensure business viability, it is essential to establish culture conditions that can consistently maintain high yields even at full scale.

Key Points of This Demonstration

This proof-of-concept is characterized by its ability to seamlessly optimize the process from lab-scale development to scale-up by combining Epistra's AI solution "Epistra Accelerate," specialized in life sciences experimental condition optimization, with Hitachi's culture simulation technology.

• Rapid multidimensional condition search with Epistra Accelerate

While taking into account conditions that anticipate scale-up, the AI determines optimal settings by simultaneously optimizing seven operational parameters (such as temperature, pH, aeration rate) and four media components (such as phosphate and magnesium salts). As a result, compared to conventional Design of Experiments (DoE)^{*14}, the number of lab experiments was reduced by approximately 73%, while the yield of (S)-Reticuline improved from 3.2 g/L to 6.0 g/L. This optimization technology has been offered as **Epistra Accelerate** since April 2018 and has a proven track record across various fields, including pharmaceuticals, regenerative medicine, and bio-manufacturing.

• Correcting physical environment changes during scale-up using Hitachi's culture simulation technology

In the pilot-scale demonstration scheduled for fiscal year 2025, Hitachi's culture simulation technology will visualize and quantify flow conditions, oxygen supply, and shear force distribution^{*15} inside the bioreactor. This analysis will identify factors such as changes in flow and oxygen supply that occur during scale-up and lead to yield reduction or quality deterioration. By using these insights to adjust operating conditions and tank design, reproducibility of yield during scale-up will be improved.

Through these efforts, this initiative provides an effective approach to resolving the industry dilemma of "success at lab scale but yield loss during scale-up," thereby improving productivity, shortening development timelines, and reducing costs.

***14 DoE (Design of Experiments):** A statistical method used to efficiently study the effects of multiple factors (parameters) and their combinations on outcomes.

***15 Shear Force Distribution:** A diagram or relationship showing how shear force acting on a structural member varies along its length. Commonly used in structural analysis of beams and girders.

About Hitachi, Ltd.

Through its Social Innovation Business (SIB) that brings together IT, OT(Operational Technology) and products, Hitachi contributes to a harmonized society where the environment, wellbeing, and economic growth are in balance. Hitachi operates globally in four sectors – Digital Systems & Services, Energy, Mobility, and Connective Industries – and the Strategic SIB Business Unit for new growth businesses. With Lumada at its core, Hitachi generates value from integrating data, technology and domain knowledge to solve customer and social challenges. Revenues for FY2024 (ended March 31, 2025) totaled 9,783.3 billion yen, with 618 consolidated subsidiaries and approximately 280,000 employees worldwide. Visit us at www.hitachi.com.

About Fermelanta, Inc.

Fermelanta Inc. is a synthetic biology startup founded in 2022. With approximately 35 R&D members and around 10 business and operations members, the company has built a proprietary technological platform for the fermentation-based production of high-value compounds—such as pharmaceuticals, cosmetic ingredients, and food additives—using engineered *E. coli*. Through this fermentation platform, we design and manufacture a wide range of scalable metabolites, including alkaloids, flavonoids, and carotenoids, enabling an integrated workflow from early research to commercial manufacturing. To date, we have raised and secured over 4 billion yen in combined funding and grants, and under the mission of “delivering effective ingredients to everyone,” we are driving the societal implementation of sustainable bio-based production.

About Epistra Inc.

Epistra is an AI solutions company that supports research and development in the life sciences, including pharmaceutical process optimization and biological manufacturing. Leveraging proprietary technologies such as the experimental-design optimization AI “Epistra Accelerate” and the image-analysis AI “Epistra Vision,” Epistra provides hands-on, collaborative support services to accelerate experimental workflows and data-driven research. With more than 60 successful projects across the life sciences industry, Epistra has demonstrated its ability to enhance R&D efficiency and reproducibility. In collaboration with RIKEN, Epistra achieved over an 80% improvement in the differentiation efficiency of retinal pigment epithelial cells—results that were published in the international scientific journal *eLife*. Visit us at <https://epistra.jp/en>.

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