

PRAXIS

A publication by Bioengineering AG

Celltrion's mission in biotechnology is to improve the quality of human health on a global scale: through state-of-the-art manufacturing, drug development, and marketing in the global biopharmaceutical industry, with a core competency in large-scale mammalian cell culture technology.

BIOENGINEERING

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Celltrion Inc., 23-acre manufacturing facility, Icheon, Korea, 7:45 p. m.



Celltrion, the facility in close proximity to Incheon International Airport and downtown Seoul. 5:56 p. m.

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Celltrion profile



Corporation

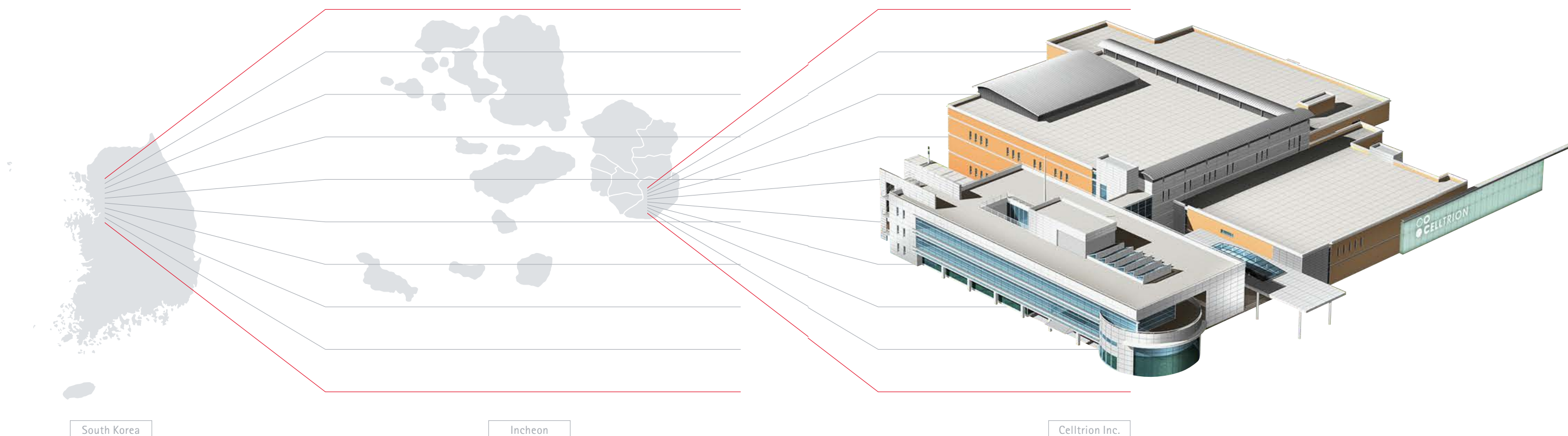
Celltrion is a biopharmaceutical manufacturing company dedicated to supplying the next generation of biopharmaceutical products to the global community. Celltrion's experienced management team, favorable cost structure and strategic location in the rapidly growing North-East Asian pharmaceutical markets makes it an ideal choice for clients seeking world-class contract manufacturing services.

Location

Celltrion's 23-acre manufacturing operation is located at the center of the high-technology park in Songdo New City, a new high-technology complex in the Incheon Metropolitan City, South Korea. The Celltrion facility is in close proximity to both the Incheon International Airport and downtown Seoul. Construction of Celltrion's 50,000-liter fermentation capacity biopharmaceutical manufacturing facility is designed to comply with the cGMP (current Good Manufacturing Practices) Standards of the U. S. Food and Drug Administration and EMEA. It is planned to expand the capacity within this decade to several hundred thousand liters based on client demand.

Facility

The facility layout wraps the process and critical process support areas in a highly automated, clean, safe, cGMP and regulatory compliant environment. It has been optimized to facilitate all logical flows.



Departments and teams

Celltrion's integrated departments and teams, including research and development (R&D), engineering, QA/QC, and manufacturing, as well as business services and marketing, work closely together to understand and address the business and technical needs of Celltrion's partners and therefore meet their demands in the best possible way.

The role of Bioengineering AG

Behind all production installations and clean utilities lies the specialized experience of Bioengineering AG. Detailed engineering, construction, commissioning and qualification have been performed by Bioengineering AG together with its local subcontractor Daewoo Engineering and Construction Co. of Korea.

Celltrion today

Celltrion is now evolving into a fully integrated biopharmaceutical company through the development of biologics via in-licensing and co-development relationships.

Celltrion's mission

Celltrion's mission is to improve the quality of human health on a global scale. Its goal is to be at the forefront of biotechnology, through state-of-the-art manufacturing, drug development, and marketing in the global biopharmaceutical industry, with a core competency in large-scale mammalian cell culture technology.

Development

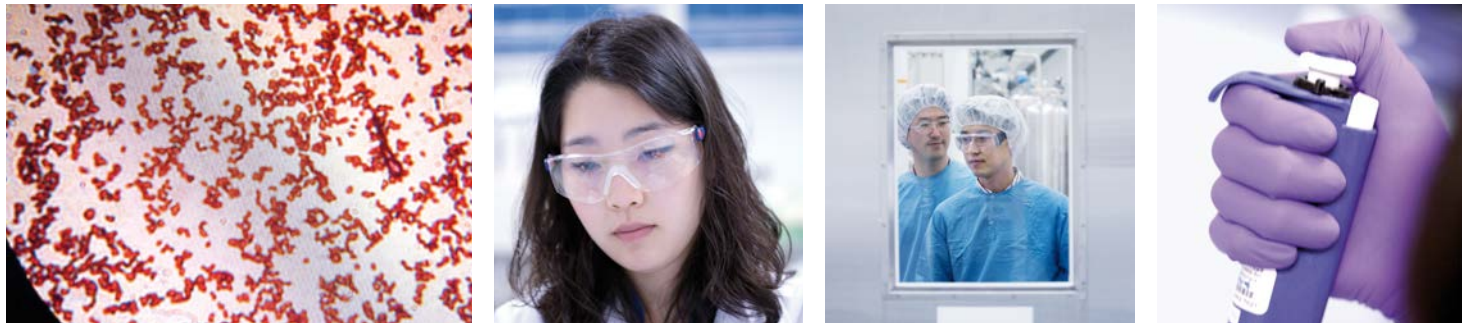
In a three year period, beginning in 2002, Celltrion was able to complete the construction of a large-scale 50,000-liter manufacturing facility in Incheon, South Korea. Celltrion is scheduled to manufacture its first commercial product in 2007. Celltrion's success is setting a new standard in the biopharmaceutical industry.

Geopolitical advantage

Celltrion is located in the Incheon Free Economic Zone (IFEZ), which is situated in the hub of Asia – the crossing points of China, Japan, India, and Russia – with a potential market of 4 billion people. It has geopolitical advantages with a new international airport, seaports, and railroads.



Head area of 16 m³ bioreactors.



February	2002	Establishment of Celltrion
March	2003	Ground breaking ceremony for large-scale manufacturing facility
July	2003	Establishment of R&D center
June	2005	Long-term supply contract with first client
July	2005	Mechanical completion of manufacturing facility
July	2005	Co-development contract with a European company
November	2005	Initiate full scale development runs after successful sterile hold tests for all equipment
February	2006	Enter into land purchase agreement for expansion of facility
July	2006	Signing ceremony for expanded long-term product supply agreement with a major international pharmaceutical company
July	2006	Groundbreaking ceremony for first expansion project

In February of 2002, Celltrion was established as a joint-venture between Korean investors and VaxGen, Inc., which contributed CHO cell based monoclonal antibody and recombinant protein manufacturing technology. Celltrion started construction of its facility in the Incheon Free Economic Zone (IFEZ) with support from the Korean government, which has strategically chosen the biotechnology industry as an engine for future growth in Korea.

In 2004, towards the end of Celltrion's facility construction, a large global pharmaceutical company approached Celltrion regarding a potential business collaboration. The initial discussions were followed by a year of due diligence by the client. In June of 2005, Celltrion and the client entered into a long-term supply agreement to manufacture the client's lead product, a therapeutic biologic for the treatment of rheumatoid arthritis. This lead product for Celltrion was in Phase 3 clinical trials at the time of executing the supply agreement. The client's product received BLA approval from the U. S. FDA in December of 2005. Celltrion is presently undertaking process validation runs after a phenomenally successful series of development and engineering runs. After validation of the manufacturing facility, Celltrion expects to receive sBLA approval from the U. S. FDA and will manufacture and supply bulk commercial product in 2007.



Harvest area: depth filtration skid.

Celltrion's engineers of success



Jung-Jin Seo, Co-Chief Executive Officer. His energy and dedication has put Celltrion on the track to become a future world leader in the biopharmaceutical industry.

Jung-Jin Seo, Co-Chief Executive Officer

Mr. Seo holds a bachelor's and master's degree in industrial engineering, Konkuk University, Korea. Mr. Seo is presently the Co-CEO of Celltrion and the CEO of the Nexol Group in Korea. Mr. Seo joined Celltrion after a ten-year tenure at Daewoo Group, where he was the Executive Managing Director. Prior to joining Daewoo Group, he had a 20-year tenure at the Korea Productivity Centre, where he provided strategic consulting to various leading Korean corporations, including Samsung Aerospace, Kia Motors, Ssangyong Motors, Anam, and Samyang Company.

Mr. Seo is one of the founding members of Celltrion. Under the visionary leadership of Mr. Seo Celltrion overcame all initial hurdles and is now experiencing an unparalleled success. Mr. Seo's energy and dedication has put Celltrion on the track to become a future world leader in the biopharmaceutical industry.

Jim Panek, Co-Chief Executive Officer

Mr. Panek has more than 20 years of experience in the biotechnology and pharmaceutical industries. Prior to joining Celltrion and VaxGen, Mr. Panek was the Senior Vice President of Product Operations at Genentech, where he led the development of the world's largest biotechnology manufacturing facility and was responsible for all operations involved in supplying products for pre-clinical, clinical, and commercial use. Mr. Panek holds a bachelor's and a master's degree in chemical engineering from the University of Michigan. He is presently the Co-CEO of Celltrion and the Senior Vice President of Manufacturing



Jong Hyun Kim, Project Manager

Dr. Ing. ETH Kwang Hun Yoon, Senior Vice President
Corporate Engineering and Technology Team



In-Gyu Kim, Project Director

at VaxGen. Prior to joining Celltrion and VaxGen, he had an 18-year tenure at Genentech, where he was responsible for the design, construction, and maintenance of all facilities. Prior to joining Genentech, he spent six years with Eli Lilly in a variety of engineering and development roles. At Genentech, Mr. Panek led the development of manufacturing facilities that enabled FDA approval and the launch of many recombinant products, including Nutropin Depot®, Protropin®, TNKase™, Rituxan®, and Herceptin®. He was also responsible for the purification of all human pharmaceuticals for clinical and market use, and led the successful start-up and licensure of operations for purification of Activase®, the first large-scale cell culture product approved by the FDA.

Seung-il Shin, Ph. D., Chairman of the Scientific Advisory Board

Dr. Shin has more than 18 years of experience in the vaccine industry. Dr. Shin was educated in Korea and the U. S. in chemistry and biochemistry and in The Netherlands in genetics, and further trained in immunology in England. Dr. Shin is presently the Chairman of Celltrion's Scientific Advisory Board. Prior to this position at Celltrion, he had a six-year tenure at VaxGen, Inc., where he was responsible for directing and coordinating the formulation and implementation of international activities, including the development of international partnerships for the production and marketing of AIDSVAX, VaxGen's HIV vaccine. Since 2002, Dr. Shin has also been a member of the Celltrion Board of Directors. Prior to joining VaxGen in 1999, he served with the United Nations, where he founded and directed an initiative that led to the establishment of the International Vaccine Institute. In 1984,

Dr. Shin co-founded Eugene Tech International and, as CEO, led the company's efforts to develop and market a hepatitis B vaccine that was successfully distributed widely in many developing countries. Earlier in his career he served as a Professor of Genetics at Albert Einstein College of Medicine. As the Senior Advisor for International Development at VaxGen, Dr. Shin was responsible for establishing Celltrion. He also conceived, planned and directed the development of the International Vaccine Institute in Seoul Korea.

Don Gerson, Ph. D., Chief Operating Officer

Dr. Gerson has more than 23 years of experience in the pharmaceutical and biotechnology business, with a focus on the establishment, design, construction and operations of large-scale manufacturing facilities in the U. S. and Canada. Dr. Gerson holds a Ph. D. in biology from McGill University and a B. S. in chemistry from the University of Western Ontario. Prior to joining Celltrion, Dr. Gerson spent 3 years at the International AIDS Vaccine Initiative (IAVI) as the Managing Director of Manufacturing. His career also includes 3 years at Acambis as the Vice President of Manufacturing and Development, and a 7-year tenure at Wyeth-Lederle Vaccines and Pediatrics as the Managing Director of Vaccine Manufacturing. Throughout Dr. Gerson's career, he has been involved in the process development and manufacturing of numerous pediatric and adult vaccines against major infectious diseases. This includes the development of the manufacturing process for a new smallpox vaccine, and the manufacturing of the U. S. supply of polio, pertussis, diphtheria, tetanus and pneumonia. Dr. Gerson was also responsible for manufacturing vaccines, including the Sabin/Salk polio vaccines, for Canadian, PAHO and WHO-EPI vaccine programs.

Hyun-Soo Lee, Ph. D., Senior Advisor

Dr. Hyun-Soo Lee was named Senior Vice President of Celltrion in 2002 and is responsible for all technical operations including manufacturing, process development and engineering. Dr. Lee spent most of his professional career with Samyang Corp. and its affiliate companies, where for 35 years he served in various technical and managerial roles, eventually becoming Executive Vice President, Director and COO for the Biotech Division and Biotech R&D of Samyang Genex Corp. He is also a member of the National New Drug R&D Promotion Board of the Ministry of Health and Welfare of Korea, and a Director of the Korea Institute of Science and Technology Evaluation and Planning Committee. Dr. Lee oversaw the development and construction of the world's largest plant-cell-based biopharmaceutical manufacturing facility of 135,000 liters to produce Taxol. Dr. Lee has received many prestigious awards given to leading industrial scientists in Korea, including the Technology Award from the Korean Society for Applied Microbiology in 1998, the Jang Young Sil Award from the Ministry of Science and Technology in 1999, the Grand Prize of the Bio-Industry Award from the Ministry of Energy and Resources in 2000, and the Doyak Medal for the promotion of national science and technology in 2001.

Dr. Lee received his B. S. in Agricultural Chemistry, and Ph. D. in Food Science and Technology from Seoul National University.



Mixing tank for buffer solutions.





Operator interface of 500-liter bioreactors.

Celltrion and Bioengineering AG

Celltrion has chosen Bioengineering as its main contractor to plan and build its production facilities. The trust shown in Bioengineering's services enabled Celltrion to profit from a vast pool of experience and knowledge and ensured that the same solid and state-of-the-art design philosophy was consequently realized throughout all critical installations.

Bioengineering's components

Besides designing all process vessels and reactors Bioengineering also designed all inter-connecting process and utility piping systems including all related accessories. The implementation of Bioengineering's components and instruments in all processing systems guarantees consistent quality and functionality. Bioengineering's engineers wrote all functional design specifications for the automation of the whole processing plant.

For Celltrion, Bioengineering executed basic and detail engineering and procured, fabricated, installed, commissioned and qualified (DQ, IQ, OQ, part of PQ) the following process units:

Media preparation

Three agitated media mixing tanks with capacities between 500 L and 12,500 L with powder delivery system and liquid media sterilization by sterile filtration.

Media hold

Four sterilisable and agitated media hold vessels with a capacity of 2,500 L each.

Fermentation

The fermentation suite is regarded as the heart of Celltrion's plant. There are four fermentation trains arranged in a layout that allows gravitational flow from seed into production fermenters. Each one of the four trains consists of five sterilisable and fully automated cell culture bioreactors with working capacities of 20 L, 100 L, 500 L, 2,500 L and 12,500 L.

Harvest

Harvest is done in a 15,000-liter capacity sterile and agitated harvest tank. The harvested product is centrifuged and over a 500-liter harvest surge tank it is then further cleaned in a depth filtration system.

Buffer preparation and holding

Seven agitated buffer preparation tanks with capacities between 400 L and 20,000 L with powder delivery system and liquid buffer sterilization by sterile filtration.

16 steam-sterilisable buffer holding tanks with capacities between 400 L and 20,000 L.

Initial and final purification

Initial and final purification is done in various ultrafiltration and chromatography steps. Intermediate product between different processing steps is held in eight sterilisable and

agitated product pool and holding vessels with capacities of between 500 L and 8,000 L. Process units are connected by a sophisticated arrangement of sterile transfer panels allowing a flexible process adaptation to different requirements of Celltrion's clients.

WFI system

Bioengineering designed and built the storage and distribution system for ambient and for hot Water for Injection (WFI). WFI is produced in a WFI still with a capacity of approx. 10 m³ per hour and stored in a 50,000-liter hot WFI storage tank at 85 °C. Ambient WFI is produced in large heat exchangers and is kept under constant circulation through two piping systems with various user points throughout the whole facility. Hot WFI is circulated through a single piping system connecting various user points within the production facility.

CIP

Process equipment is designed to allow an automated CIP process. Four independent CIP kitchens which serve various processing units separately provide and recirculate the CIP solutions through a sophisticated CIP supply and CIP return piping system. Hot and ambient WFI for rinsing and flushing during the CIP processes is supplied by separate hot and ambient WFI rinse tanks connected to the CIP kitchens.

Clean utilities

Bioengineering designed and supervised the installation and commissioning for the distribution systems for clean air, clean oxygen, clean nitrogen, clean carbon dioxide and clean steam.





Media preparation tank.

How Bioengineering AG did it

A tailored work process

Bioengineering AG worked closely together with local partners for the detail design of piping systems, fabrication of process vessels and for the installation of equipment and piping. Critical components including bioreactors with a capacity of up to 2,500 L and all bioreactor skids were fabricated and factory tested in Wald.

Other process vessels were fabricated locally in Korea under the supervision of Bioengineering AG. Process and clean utility piping systems incorporating Bioengineering's components were prefabricated and installed on site under constant supervision by Bioengineering's specialists. Commissioning and qualification was done in collaboration with Celltrion's manufacturing personnel under the guidance of Bioengineering's experts.

Bioengineering AG received a comprehensive set of user requirement specifications from Celltrion which were worked out by another engineering company during the conceptual design phase. Based on these documents Bioengineering's engineers worked hard to enhance these concepts and ensure the optimum design of all process systems.

New and innovative solutions were deliberated and discussed intensively between Bioengineering AG and the client during all design phases before a concept was finally realized. Based on such studies the final piping and instrumentation diagrams and all other relevant engineering documents were created.

3D planning

Under the supervision of Bioengineering AG, all process vessels and piping systems were incorporated into a comprehensive 3D model representing the layout and disposition within the manufacturing and utility building.



Purification area: selection of pipe jumpers for transfer panels.





A bright future

Celltrion is increasing its capacity by building a new facility. Since Celltrion's current 50,000-liter capacity is already fully dedicated to a client, Celltrion is proceeding with facility expansion to accommodate increases in demand. The expanded facility will have over 300,000 liters of mammalian cell culturing capacity making it the largest cell culture facility in the world. As a first step, a 90,000-liter (15,000 L x 6 bioreactor trains) expansion is planned to begin in late summer of 2006, and is scheduled for completion of all commissioning and validation by end of 2009. This will allow commercial production and supply to begin as early as 2010.