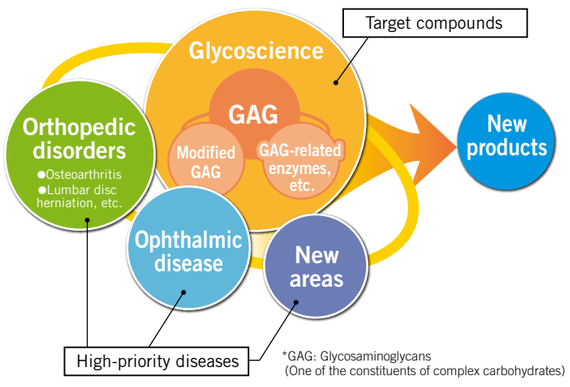
RESEARCH AND DEVELOPMENT

Seikagaku engages in research and development of innovative drugs that contribute to the health and well-being of people around the world.

R&D policy

In order to rapidly and continuously create new products, Seikagaku engages in efficient R&D activities by focusing on target compounds and prioritizing target diseases. The focus of our drug discovery is glycosaminoglycans (GAG), which are the structural components known as glycoconjugates.

In research spanning nearly 70 years, we have accumulated a wealth of experience and expertise related to GAG drug discovery research and GAG production and formulation technologies. Today, we apply hyaluronic acid or unmodified GAG in pharmaceuticals and also engage in research and development of modified GAG produced using a cross-linking technology as well as enzymes and other substances that act on GAG. Given the properties of GAG, we focus mainly on orthopedic disorders and ophthalmic diseases as high-priority areas for now.



Seikagaku and glycoscience

Seikagaku's Management Creed states: "Under the principle of respect for learning, we contribute to human well-being by creating and supplying the world with safe and useful pharmaceutical products based on glycoscience." In keeping with this creed, we have made glycoscience the core foundation of our business and explicitly adopted a stance of respect for learning. Seikagaku's origin is closely bound up with this creed.

In 1950, Seikagaku became the first company in the world to successfully produce chondroitin sulfate, which is a sort of GAG, on a commercial scale. This breakthrough laid the foundation for our current business, which is centered on glycoscience. The manufacture of chondroitin sulfate marked the starting point for expansion of our business to bulk products, as well as reagents and diagnostics, and this has led to the strengthening of our ties to glycoscience-related academia and research institutes.

Through this close relationship with academia, we acquired the idea of applying hyaluronic acid in pharmaceuticals. R&D activities spanning many years culminated in 1987 with the successful development and launch of ARTZ, the world's first joint function improving agent whose main ingredient is hyaluronic acid. The development of HERNICORE, a treatment for lumbar disc herniation that contains condoliase, an enzyme that degrades GAG, also originated from collaboration with academia.

Seikagaku will continue to make glycoscience the central focus of R&D activities and, on the basis of research results in the field of glycoscience achieved in collaboration with universities and research institutes, strive to create pharmaceuticals and medical devices and deliver them to patients around the world.

The difficulty of applying glycoconjugates to pharmaceuticals

GAG are formed when amino sugars (sugars that include nitrogen atoms) and uronic acids (a class of sugar acids) or galactose are linked together to form chain-like structures (sugar chains). GAG exist in living organisms as structural components of glycoconjugates. Sugar chains are known in the life sciences as the third biological chains, along with nucleic acids and proteins. They have complex chemical structures and pose characteristic difficulties in research in areas such as structural analysis, automatic synthesis, and large-scale synthesis.

Some years ago, an industry-government-academia research project focused on glycoscience was formed and its activities advanced the structural analysis and synthesizing technologies for GAG. In addition, the genes of sugar-chain synthesizing enzymes and degrading enzymes have been comprehensively identified, and our understanding of the functions of sugar chains in living organisms is advancing. This progress in glycoscience technologies is closely linked with Seikagaku's drug discovery research.

Direction of R&D and future drug discovery approach

Seikagaku possesses a GAG compound library, GAG-related enzymes, and wide-ranging technologies for manipulating these substances. We actively utilize these assets, accumulated in the course of research spanning many years, in drug discovery activities. We have also developed a global network of collaborating glycoscience researchers and engage in multiple joint research projects with universities and research institutes.

Specifically, we continue to focus on drug discovery for orthopedic disorders and ophthalmic diseases and have also begun utilizing GAG-related technology to enter new fields. At the same time, we make efforts to maximize the value of our products on the market or schenes in development through expansion of indications, additional formulations, changes in dosage and administration, etc.

Until now, Seikagaku has followed a drug discovery approach of increasing the bioactivity of GAG, mainly through GAG modification and processing, and we are currently applying GAG to drug delivery systems (DDSs). Furthermore, going forward, we will also adopt an approach focused on the biological functions of sugar chains to open up new possibilities in drug discovery.

In our DDS, we are researching technologies that utilize the characteristics of modified GAG to freely control drug dose and the location and timing of release. We will pursue drug discovery and development capable of responding to a wide range of unmet medical needs by combining Seikagaku's DDS technologies with drugs and technologies that other companies possess, not only low-molecular compounds, but also proteins and middle molecules such as peptides and nucleic acids.

Message from the Head of the Research & Development Division

Seikagaku Corporation's social mission is to continuously create original, innovative pharmaceuticals and medical devices that respond to unmet medical needs using glycoscience-related technologies and expertise accumulated over many years and to provide them to all patients around the world.

In February 2019, a main confirmatory study among three Phase III clinical studies in Japan for SI-613, a treatment for osteoarthritis being developed as the next-generation ARTZ, met its primary endpoint for patients with knee osteoarthritis. We will aim for a new drug application for SI-613 in the first half of 2020 following consideration of the results of the remaining two studies.

We are also proceeding with a Phase III additional clinical study in the U.S. for SI-6603, a treatment for lumbar disc herniation. To increase the probability of success in this study, we have set rigorous criteria in light of the knowledge obtained from the previous study. Although progress with the study is behind schedule, we will focus on various measures to promote subject enrollment.

To achieve our aspiration of being a professional organization of scientists who think carefully about science and generate outcomes, we will continue to steadily advance the development pipeline and strive to create new drug candidates with potential for global development.

Yosuke Funakoshi
Executive Vice President
Head of Research and Development Division

RESEARCH AND DEVELOPMENT

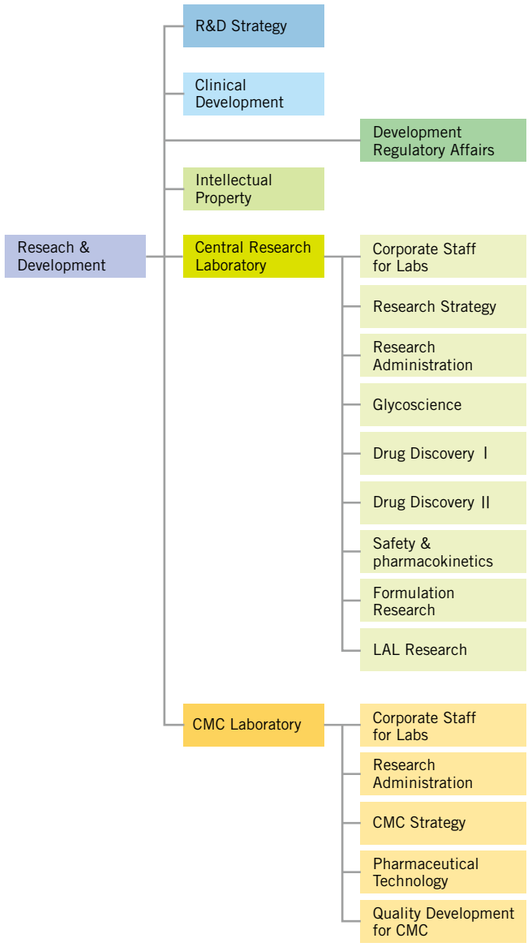
Research and development organization

To ensure close coordination of the drug development process from its upstream to downstream, Seikagaku has put in place an organizational structure in which the departments involved in R&D are consolidated under the control of the Research & Development Division. This integrated organization covers every R&D activity from clinical development to new drug application (NDA) and intellectual property strategy. In this structure, the Central Research Laboratory is in charge of exploring candidate substances and evaluating efficacy, safety, and pharmacokinetics, and the CMC* Laboratory is responsible for production of investigational drugs, design of manufacturing processes, and consideration of commercial production.

* CMC is an abbreviation for Chemistry, Manufacturing and Controls, which refers to the physicochemical properties and standards of active pharmaceutical ingredients (API) and formulations, their manufacturing processes, and quality control.

Research & Development Division Structure

(As of January 1, 2020)



Drug discovery research

The Central Research Laboratory, Seikagaku's drug discovery research center, cultivates the creativity of researchers in a fulfilling research environment, equipped with advanced facilities, and places importance on fostering a self-help culture.

Seikagaku contributes unique knowledge, technology, and expertise related to glycoscience to benefit drug discovery research, and actively collaborates with universities and companies in Japan and overseas to accelerate the search for ideas and development of new technologies.

Through these efforts, we work to create original pharmaceuticals and medical devices on the basis of specialized technologies and creative ideas.

[Overview of Research Units]

- Glycoscience: Exploration of GAG (glycosaminoglycan) and related compounds as pharmaceutical candidate substances
- Drug Discovery: Synthesis of new candidate substances, efficacy evaluation, and research on the mechanisms of action
- Safety & Pharmacokinetics: Evaluation of pharmacokinetics and toxicity profiles of candidate substances *in vivo*
- Formulation Research: Exploratory formulation research by basic physicochemical examination

CMC research

The CMC Laboratory produces investigational drugs, designs manufacturing processes, engages in quality development, and examines commercial production of products under development created by the Central Research Laboratory.

By engaging in development from the R&D stage in collaboration with the Production Division, the CMC Laboratory aims to ensure the stable supply of high-quality pharmaceuticals and medical devices that comply with regulations in Japan, the United States, and Europe and to increase the speed of new drug development under a system integrated from research to production.

[Overview of Research Units]

- Pharmaceutical Technology: Design of active pharmaceutical ingredients, pharmaceutical formulations, packaging, and manufacturing processes for candidate substances and consideration of commercial production
- Quality Development for CMC: Research of physicochemical properties, development of testing methods for quality evaluation, and quality assurance of investigational drugs

Central Research Laboratory / CMC Laboratory

Intellectual property strategy

Appropriate protection of intellectual property relating to Seikagaku's technologies, products, and other assets is essential not only for maintaining corporate competitiveness, but also for continuing to create and supply unique, high-quality pharmaceuticals and medical devices. Seikagaku views intellectual property as an important management resource and engages in global intellectual property-related activities.

The Intellectual Property Department engages in activities related to acquisition of intellectual property rights (patents, designs, trademarks, copyright, knowhow, etc.) and their protection. It works closely with Research and Development Division involved in drug discovery as well as with Business Development & Marketing Division, Production Division, and other relevant company organizations.

The clinical study process and paths of new drug development

To create new drugs, it is necessary to conduct various studies to evaluate efficacy and safety. Clinical studies are conducted to confirm whether drug candidates are actually beneficial to humans, following completion of research processes such as basic research and non-clinical studies.

Clinical studies are ordinarily divided into three phases and conducted at medical institutions such as hospitals in conformance with rigorous standards after the consent of subjects (healthy persons or patients) has been obtained.

A Phase I clinical study, the initial phase, is ordinarily conducted for the main purpose of examining the pharmacokinetics (absorption, distribution, metabolism, and excretion) and safety (adverse events and side effects) of investigational drugs in a small number of healthy subjects. A Phase II clinical study examines efficacy, safety, and pharmacokinetics and confirms optimal dosage and usage in a small number of patients. A Phase III clinical study, the final phase, objectively verifies efficacy and safety in comparison to existing approved drugs or placebos in large numbers of patients.

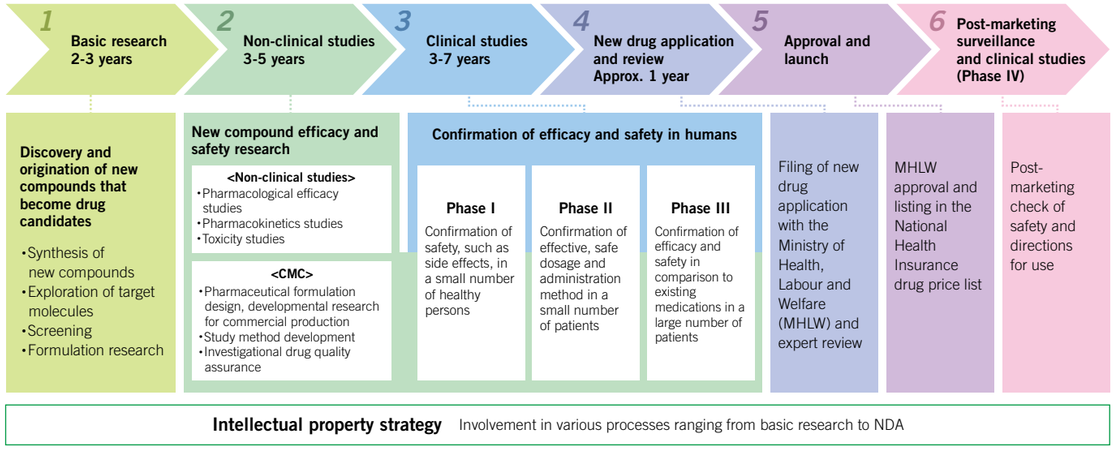
Ordinarily, more than ten years is required from discovery of a candidate substance until its approval as a new drug. Within the long, difficult new drug development process, clinical development is considered to hold the key to whether an NDA can be filed.

Clinical development

Seikagaku conducts various clinical studies in Japan and the U.S. in cooperation and collaboration with medical experts, medical institutions, and external contract research organizations (CROs) and site management organizations (SMOs). The Clinical Development Department is responsible for creating the integrated development plan (protocols); monitoring of clinical studies; planning and execution of enrollment acceleration; and data management and analysis of study results. It also communicates with the regulatory authorities in various countries and develops dossiers necessary at the time of NDA filing.

In developing protocols, the Clinical Development Department closely communicates with medical monitors and regulatory authorities, identifies requirements for NDA approval and finalizes the study design. In monitoring of clinical studies, the Department works through medical institutions to ensure the quality of studies by confirming whether they are being conducted in conformance with Good Clinical Practice (GCP) and regulatory requirements by ascertaining the condition of subjects and reviewing study data.

The Drug Research and Development Process



Ethical considerations concerning research using human biological materials

Progress in biological science has been accelerating in recent years, together with accompanying innovation of medical technologies. In particular, experiments and research using human biological materials, including genetic information, are yielding new knowledge that is expected to lead to the development of novel, highly beneficial pharmaceuticals.

In keeping with the intent of the Japanese government's guidelines on handling of human materials,* Seikagaku has established the Code of Ethics for Research Using Human Specimens to make it possible to conduct comprehensive reviews, including evaluation of ethical and scientific validity, when experiments and research using human materials are conducted. To carry out the intent of the Code of Ethics, we have established the Ethical Review Committee for Research Using Human Specimens and publish a list of committee members and minutes of committee meetings through the Japan Agency for Medical Research and Development's Ethical Review Committee Reporting System.

* Ethical Guidelines for Human Genome and Genetic Sequencing Research and Ethical Guidelines for Medical and Health Research Involving Human Subjects

Ethical considerations in non-clinical studies

In the development of pharmaceuticals and medical devices, research activities using laboratory animals are indispensable to confirm the efficacy and safety of candidate substances, and deeply contribute to the progress and advancement of medical science.

Seikagaku strives to rigorously address ethical considerations in animal experiments and has formulated internal regulations that comply with the Act on Welfare and Management of Animals and Basic Guidelines for Animal Experimentation at Institutes under the Jurisdiction of the Ministry of Health, Labour and Welfare. Also, an ethics committee established within Seikagaku evaluates whether all animal experiments, including outsourced experiments, are planned and conducted in accordance with the 3Rs Principle.* These initiatives at Seikagaku have been evaluated as conformant with the 3Rs Principle by the Japan Health Sciences Foundation's Center for Accreditation of Laboratory Animal Care and Use, a third-party organization.

* 3Rs Principle: Methods that avoid or replace the use of animals (Replacement), methods that minimize the number of animals used per experiment (Reduction), and methods that minimize animal suffering (Refinement)

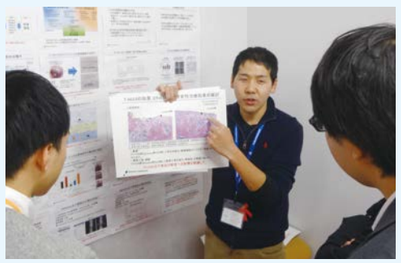
Topics

The TATENO Forum contributes to enhancement of R&D Capabilities

Each year in December, the Central Research Laboratory holds the TATENO Forum, an internal presentation forum for sharing research results relating to new ideas and technology creation. There were 42 entries at the forum in fiscal 2018. In addition to young and mid-career researchers, employees from other business sites participated, actively discussing the future potential and contribution to medical needs of each research theme. Employees who submitted entries expressed their ambitious enthusiasm with comments such as, "I want to press ahead with my research so that someday I will be able to propose a drug-discovery technology unique to Seikagaku" and "I want to increase the feasibility of my research by seriously grappling with the issues and information presented at the forum."

By deepening interaction among employees through the exchange of ideas and information sharing, and contributing to the enhancement of Seikagaku's R&D and technological capabilities, we aim to originate and create development themes, such as new pharmaceuticals that people truly need.

*The forum name was taken from the location of the Central Research Laboratory (Tateno, Higashiyamato City, Tokyo).



A researcher enthusiastically explaining his research at a poster session

Researchers receiving the Head of Research and Development Division's Award and the Head of Central Research Laboratory Director's Award

Development Pipeline

[Pharmaceuticals]

(As of October 1, 2019)

Development code, substance name		Indication	Developed in	Phase I	Phase II	Phase III	NDA
SI-6603	Condoliase	Lumbar disc herniation	USA				
SI-613	Hyaluronic Acid-Diclofenac Conjugates	Osteoarthritis	Japan				
		Knee osteoarthritis	USA				
SI-613-ETP	Hyaluronic Acid-Diclofenac Conjugates	Enthesopathy	Japan			Late-stage Phase II	
SI-614	Modified Hyaluronate	Dry eye	USA			Phase II/III	

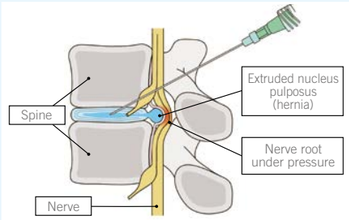
[Medical Devices]

Development code, substance name		Description	Developed in	Pilot study	Pivotal study	NDA
SI-449	Cross-linked Chondroitin Sulfate	Adhesion barrier	Japan			

SI-6603 (treatment for lumbar disc herniation)

SI-6603, which contains condoliase as its active pharmaceutical ingredient, is a treatment for lumbar disc herniation. Since it is a treatment directly injected into the intervertebral disc, it does not require a general anesthesia and is less invasive to patients than surgical treatment. Since a single injection is expected to improve the symptoms of lumbar disc herniation by reducing intervertebral disc pressure and relieving pressure on the nerve root, SI-6603 can contribute to improving patients' quality of life as a new treatment option.

In Japan, marketing approval was obtained from the Ministry of Health, Labour and Welfare in March 2018, and SI-6603 was launched on August 1, 2018 as HERNICORE 1.25 units for intradiscal injection. In the U.S., although the expected pharmacological effect was demonstrated in a Phase III clinical study, the study did not meet its primary endpoint of improvement in leg pain. In response to this result, Seikagaku initiated an additional Phase III clinical study in February 2018.



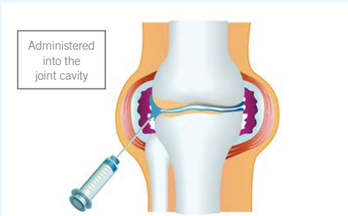
Administration of SI-6603

SI-613 (treatment for osteoarthritis)
SI-613-ETP (treatment for enthesopathy)

SI-613 is a formulation in which hyaluronic acid and diclofenac (an anti-inflammatory drug) are chemically bound using a drug binding technology proprietary to Seikagaku. Since SI-613 combines the pain relief and anti-inflammatory effect of a diclofenac formulation designed for sustained release with the joint function improving effect of hyaluronic acid, it is expected to provide prompt and long-lasting relief of the pain and inflammation associated with osteoarthritis and enthesopathy.

In Japan, a confirmatory study of SI-613 (osteoarthritis) in patients with knee osteoarthritis, one of three Phase III clinical studies, met its primary endpoint. We will aim for a new drug application in the first half of 2020 following consideration of the results of the other two studies: a clinical study on osteoarthritis of four other sites and a long-term administration study.

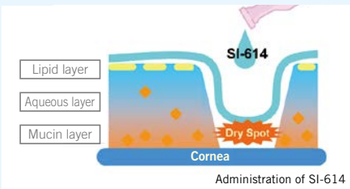
Follow-up observation has been completed in a late-stage Phase II clinical trial in Japan for SI-613-ETP (enthesopathy) and a Phase II clinical trial in the U.S. for SI-613 (knee osteoarthritis), and Seikagaku is currently analyzing the data obtained from these studies.



Administration of SI-613

SI-614 (treatment for dry eye)

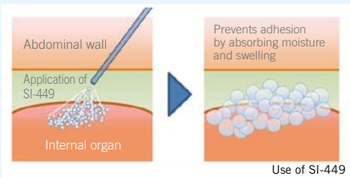
SI-614, an ophthalmic solution, is a modified hyaluronate produced using Seikagaku's proprietary technology. Ocular instillation of SI-614 is expected to protect the ocular surface and promote corneal wound healing. A Phase II/III clinical study was completed in January 2015, and Seikagaku is currently proceeding with selection of a co-development and sales partner.



Administration of SI-614

SI-449 (adhesion barrier)

SI-449 is a powdered adhesion barrier whose main ingredient is cross-linked chondroitin sulfate developed using Seikagaku's own glycosaminoglycan cross-linking technology. SI-449, which has the property of absorbing moisture and swelling, is expected to prevent or mitigate post-operative adhesion formation by forming a barrier between the surgical wound site and surrounding tissues after application. Since it is a powdered formulation, it adheres well to uneven tissue surfaces. It is thought to offer excellent utility in laparoscopic surgery, an increasingly common surgical procedure. Seikagaku initiated a pilot study in May 2018 and will proceed with development with a view to global introduction.



Use of SI-449

PRODUCTION

Seikagaku steadily manufactures high-quality products at its two pharmaceutical manufacturing plants in Japan and endotoxin-detecting reagent manufacturing plant in the U.S.

Production structure compliant with global standards

Companies that manufacture pharmaceuticals and medical devices must comply with the current regional regulations and engage in stable, continuous manufacturing. In order to deliver high-quality products to patients, Seikagaku complies with Good Manufacturing Practice (GMP) in Japan, the U.S., and Europe and strives for ever more rigorous manufacturing processes. We are also working to improve production efficiency through periodic checking and improvement of manufacturing processes using computerized systems for manufacturing and quality control. We will continue to pursue continuous improvement and focus on the manufacture and supply of high-quality products that comply with global standards.

Ensuring a stable supply of products

Providing a stable supply of products is an important mission of a pharmaceutical company. Seikagaku prepares against major disasters and other risks by diversifying raw materials suppliers and maintaining appropriate inventory levels. At the Takahagi Plant, which is responsible for manufacturing the finished products, we have introduced a quake-absorbing structure that reduces shaking for the main production buildings when an earthquake occurs. Through these measures, we have put in place a system capable of stable, reliable product production even in an emergency.

Furthermore, to cope with product supply risk from distribution network disruption following a disaster, we maintain a certain level of product inventory and have product warehouses in two separate locations: within the Takahagi Plant in Takahagi City, Ibaraki Prefecture in the Kanto region and in Hirakata City, Osaka in the Kansai region.

Environmental impact reduction initiatives

Seikagaku is keenly aware of the importance of protecting the global environment. We observe environment-related laws and regulations and voluntarily engage in environmentally friendly business activities. At our plants, in the treatment of water used in pharmaceutical production, we have introduced electro-deionization facilities that use no hydrochloric acid or caustic soda and, in wastewater treatment, we have adopted a system that uses ozone treatment and the activated sludge process.

We have also established the group-wide Energy Conservation Promotion Committee and are engaging in group-level initiatives to save energy, such as information sharing and joint consideration of improvement measures among the Group's business sites.

Topics

Kurihama Plant improvement project and 5S activities

The Kurihama Plant is implementing operational improvement activities focused mainly on improving work efficiency and reducing the burden on workers under the slogan, "Everyone changes, and everyone makes changes." Materials management was identified as an issue, and the plant has launched a 5S (*seiri* [tidiness], *seiton* [orderliness], *seiso* [cleaning], *seiketsu* [cleanliness], and *shitsuke* [discipline]) promotion team, inculcated the practice of "Have nothing unnecessary," and rethought its plant-wide rules for review and retention of stored items.

Although each individual operational improvement is small, the team members are encouraged by employee feedback such as "My work is easier" and "It's easy to find what I need."

Going forward, we will continue to foster a culture in which employees voluntarily work on improvement.

The Kurihama Plant's 5S activities promotion team

Overview of Production Sites

Takahagi Plant (Takahagi City, Ibaraki Prefecture)

The Takahagi Plant, located in northern Ibaraki Prefecture, is responsible for manufacturing finished pharmaceuticals and medical devices, including the joint function improvement agents that are Seikagaku's mainstay products. When the plant opened in 1975, it had 28 employees. Since the launch of hyaluronic acid formulations in 1987, it has steadily expanded production scale as a manufacturing plant that specializes in injectable formulations. Today, the Takahagi Plant occupies a site of approximately 86,000 square meters and has five production buildings and some 300 employees.

The Takahagi Plant is one of the world's largest manufacturing sites for hyaluronic acid pre-filled syringe formulations*, producing more than 25 million units per year for the Japanese and overseas markets. Sterility assurance is strictly required for the manufacture of injectable formulations, and the Plant has minimized the risk of contamination by implementing unattended, automated manufacturing processes. The Plant possesses facilities and equipment that can be adapted to optimal sterilization methods suited to the product characteristics and that assure sterility of the products.

* A kit with an injectable syringe that has been filled with solution.

Kurihama Plant (Yokosuka City, Kanagawa Prefecture)

The Kurihama Plant, which manufactures bulk products, opened in 1947 and is Seikagaku's most experienced plant. The plant has some 100 employees and manufactures high-purity hyaluronic acid and chondroitin sulfate for use mainly as active pharmaceutical ingredients.

The most important characteristic of the Kurihama Plant is that it specializes in the manufacturing of bulk products by extraction and fermentation. The plant applies advanced chondroitin sulfate extraction and fermentation technologies nurtured over many years since the founding of Seikagaku and has expertise in the efficient manufacture of high-purity bulk products from chicken combs, the raw material of hyaluronic acid, and shark cartilage, the raw material of chondroitin sulfate.

The Kurihama Plant is also responsible for some of the manufacturing processes for condoliase, the active pharmaceutical ingredient of HERNICORE, a treatment for lumbar disc herniation. The Plant is currently preparing to start up new bulk condoliase manufacturing facilities to further strengthen the production scale.

Associates of Cape Cod, Inc. (Massachusetts, USA)

Associates of Cape Cod, Inc. (ACC), a wholly owned subsidiary of Seikagaku, was the first FDA-licensed LAL manufacturer. It was established in 1974, became a Seikagaku subsidiary in 1997, and currently plays a central role in the global Bacterial Endotoxin Testing (BET) and clinical glucan detection sectors. ACC employs approximately 230 employees and has operations in the U.K. and Germany.

ACC's reagent production facility, located at their campus in Falmouth Technology Park in Massachusetts, is vertically integrated with an end-to-end manufacturing operation that extends from harvesting horseshoe crab blood cells, a reagent raw material, to manufacturing, testing, packaging/labeling and distributing endotoxin and glucan *in-vitro* diagnostic agents. From that location, ACC also offers customers in-house contract testing services for BET and clinical glucan product testing.

MARKETING

Seikagaku has a unique business model of supplying products through external partnerships in Japan and overseas in collaboration with pharmaceuticals and medical device sales companies. In this way, it intends to focus and develop its business activities without having an in-house pharmaceuticals sales division.

Pharmaceuticals and medical devices

Seikagaku manufactures pharmaceuticals and medical devices with, as their main ingredient, glycosaminoglycans (GAG) such as hyaluronic acid, which are the structural components of glycoconjugates, and also products based on enzymes that act on GAG. To deliver these products to patients globally, Seikagaku forms partnerships with pharmaceutical companies that have expertise in each market, including Japan.

Through their activities, our partners, in conformance with laws and regulations on pharmaceutical sales, provide appropriate information on product efficacy, safety, quality, and other matters to physicians on a timely basis. Seikagaku's activities such as sales strategy planning, market analysis, collaborations with academic societies, and product information materials creation are conducted in close cooperation with these partners for promoting market penetration.

As part of product life cycle management, Seikagaku is implementing product modifications that respond to needs of a changing market. One example is the conversion of the material for syringes, used for the joint function improving agent ARTZ, from glass to plastic. Through these efforts, we are adding value to our products.

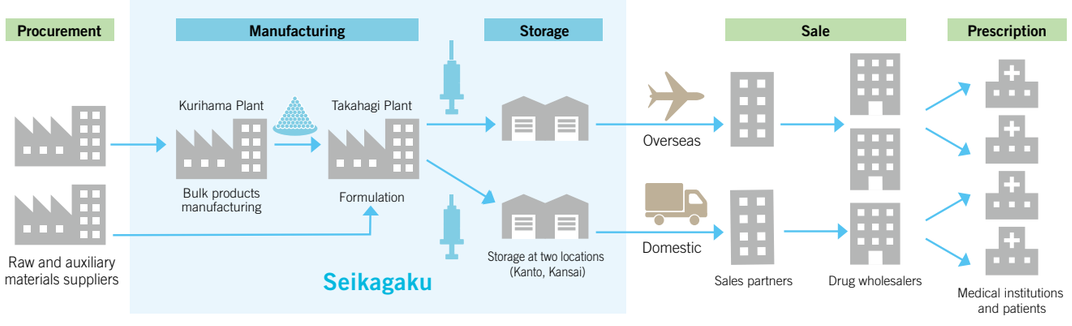
To accelerate and expand our overseas business, Seikagaku is committed to continuously grow in its current markets, and also develop new markets, by responding to global medical needs with its products.

Bulk products

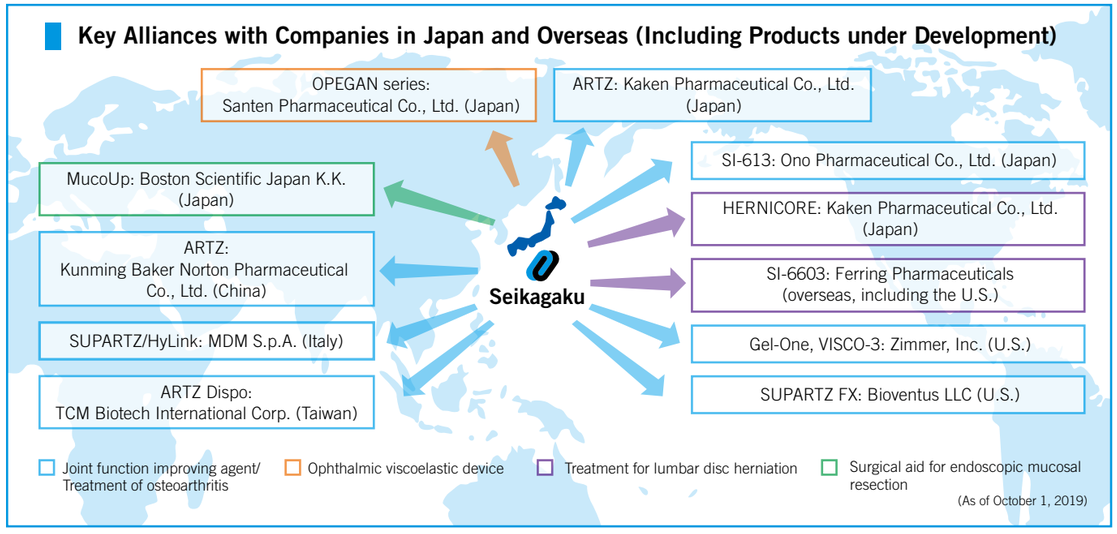
Seikagaku's business can be traced back to 1950 when it became the first company in the world to successfully produce chondroitin sulfate on a commercial scale. The key to success was its unique extraction and purification technologies. With these technologies, Seikagaku manufactures high-purity and high-quality hyaluronic acid and chondroitin sulfate and sells them to pharmaceutical and cosmetic companies, and others globally.

The bulk products are widely applied as active pharmaceutical ingredients for orthopedics and ophthalmology. In recent years, those bulk products are also being considered as new application materials in the regenerative medicine area.

Supply Chain for Main Products



Key Alliances with Companies in Japan and Overseas (Including Products under Development)



Endotoxin-detecting reagents (LAL business)

The endotoxin-detecting reagents that Seikagaku provides are mainly used in quality control of pharmaceutical and medical device manufacturing processes and water quality control of dialysate used in artificial dialysis.

Seikagaku is engaged in the development of the LAL business in Japan, selling endotoxin-detecting reagents and related devices mainly to pharmaceutical companies that manufacture injectable formulations, while wholly owned subsidiary Associates of Cape Cod,Inc. (ACC) handles overseas business development. ACC is the first company in the world to successfully develop endotoxin-detecting reagents from limulus amebocyte lysate (LAL), and it obtained U.S. Food and Drug Administration (FDA) approval in 1977. ACC plays an important role in the overseas business expansion through its global sales network, mainly in the U.S. and Europe, through the manufacturing and sales of endotoxin-detecting reagents, as well as beta-glucan-detecting *in vitro* reagent to diagnose invasive fungal disease.

Topics

Launch of HyLink®, an intra-articular viscosupplement for the treatment of knee osteoarthritis, in Italy

In March 2019, Seikagaku launched HyLink in Italy as medical device through its sales partner MDM S.p.A.. HyLink is an intra-articular single-injection viscosupplement for the treatment of knee osteoarthritis, which contains cross-linked hyaluronate hydrogel as its main ingredient. With its high-viscosity, cross-linked hyaluronate hydrogel has a long-term residual presence in the knee joint cavity, and a single injection with only 3 mL provides pain relief for 26 weeks. The launch of HyLink was announced at Congresso Roma 2019, through a commemorative lecture presentation for local physicians. The inventors from Seikagaku were invited to speak about their success stories and product features.

Seikagaku will continue to support MDM's activities by providing academic information.

HyLink®

180 attendees at Congresso Roma 2019

QUALITY COMPLIANCE

Seikagaku's mission is to provide society with a continuous supply of beneficial, high-quality pharmaceuticals and medical devices. We have constructed corporate quality assurance and compliance systems in accordance with laws, regulations, and standards.

Quality compliance system

Seikagaku makes maximum effort to ensure quality at every stage, from R&D to post-marketing by complying with the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices ("PMD Act") and a collection of regulations and guidelines called GxP.* In Japan, as a marketing authorization holder, we have developed a system with three key roles (general marketing compliance officer, quality assurance supervisor, and safety management supervisor) and implement appropriate quality management and pharmacovigilance operations.

To continue to reliably provide pharmaceuticals and medical devices required by patients around the world, we will strive to maintain and enhance quality assurance and compliance systems in accordance with global standards.

* GxP is an abbreviation for Good XXX Practice, a collective term for standards established to ensure the efficacy, safety, and quality of pharmaceuticals and medical devices from the R&D stage to post-marketing. (See the diagram to the right.)

Quality management system based on global standards

To provide a stable supply of high-quality pharmaceuticals and medical devices, according to our Quality Policy, we have developed a quality management system that ensures the reliability of our products worldwide. At the development stage, we ensure reliability under Good Laboratory Practice (GLP) and Good Clinical Practice (GCP). To guarantee quality assurance in accordance with legal and regulatory requirements after product launch, each year we systematically conduct self-inspections and internal audits to confirm the status of operation of the quality management system and promptly take corrective and preventive actions as necessary.

Seikagaku has obtained ISO 13485 certification for the development, manufacture, and distribution of sodium hyaluronate-based viscoelastic products for the treatment of osteoarthritis of the knee and periarthritis of the shoulder. We strictly maintain and control quality at all stages from product design and development to post-marketing in conformance with these manufacturing control and quality assurance systems.

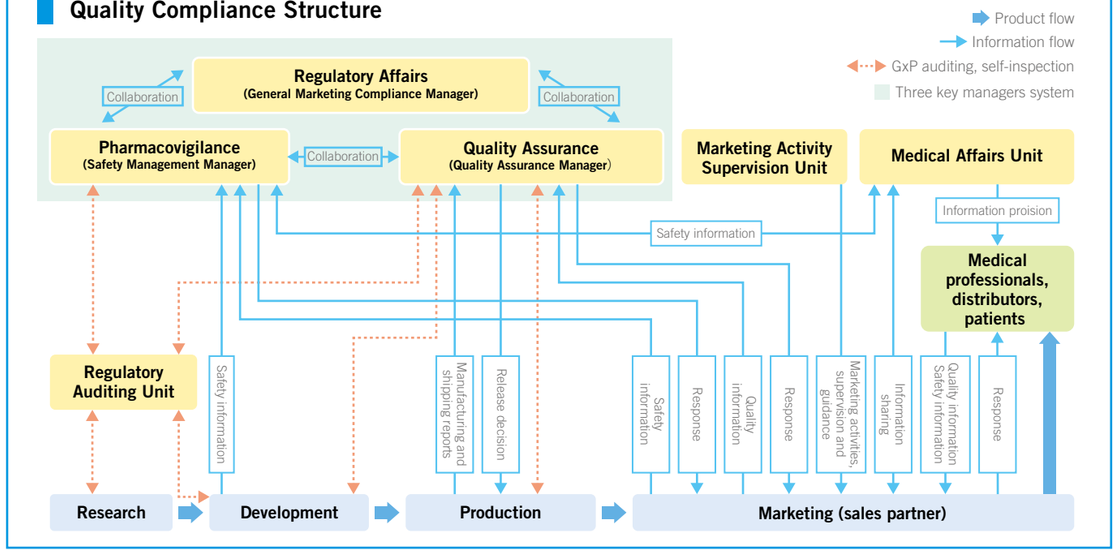
ISO 13485 is an international standard for quality management systems established by the International Organization for Standardization (ISO) that prescribes requirements concerning the design, development, and manufacturing of medical devices. In Japan, ISO 13485 has been adopted as an ordinance on standards for manufacturing control and quality control of medical devices and *in vitro* diagnostics.

Laws and Regulations Governing Pharmaceuticals and Medical Devices

Life cycle	1 Basic research	2 Development	3 NDA	4 Manufacturing, quality control, information provision, and product provision	5 Post-marketing
Laws and Regulations: Pharmaceuticals	•PMD Act •GLP	•PMD Act •GLP •GCP •GMP for investigational products	•PMD Act	•PMD Act •GMP •GQP	•PMD Act •GPSP •GVP
Laws and Regulations: Medical devices	•PMD Act •GLP	•PMD Act •GLP •GCP •QMS	•PMD Act	•PMD Act •QMS	•PMD Act •GPSP •GVP

- PMD (Pharmaceutical and Medical Device) Act
  Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices
- GLP: Good Laboratory Practice
  Standards for conducting non-clinical studies on safety
- GCP: Good Clinical Practice
  Standards for conducting clinical studies
- GMP: Good Manufacturing Practice
  Standards for manufacturing control and quality control in manufacturing
- GVP: Good Vigilance Practice
  Standards for post-marketing safety management of drugs, quasi-drugs, cosmetics and medical devices and regenerative medicine products
- GQP: Good Quality Practice
  Standards for quality control of products
- GPSP: Good Post-marketing Study Practice
  Standards for conducting post-marketing surveys and studies on drugs
- QMS: Quality Management System
  Ordinance on Standards for Manufacturing Control and Quality Control of Medical Devices and *In Vitro* Diagnostic Reagents

Quality Compliance Structure



Safety management

Sometimes side effects not observed in the development stage come to light after the launch of a new drug. In accordance with Good Vigilance Practice (GVP) standards, Seikagaku conducts post-marketing pharmacovigilance activities involving promptly and appropriately collecting, evaluating, and sharing feedback information on the side effects of drugs prescribed at medical facilities. Through these activities, we prevent the expansion of side effects and promote safety assurance and appropriate use of new drugs.

Medical information collection and provision activities

Seikagaku has established the Medical Affairs Unit, which engages in activities to provide current scientific knowledge to external professionals independently from the marketing division. As scientific experts with sufficient ethical perspective, the MSL Unit contributes to medical progress by creating and disseminating medical evidence relating to disease information and products in the fields in which Seikagaku focuses, such as orthopedic disorders and ophthalmic diseases.

Topics

Post-marketing surveillance for further development of HERNICORE®

A year has passed since the launch in August 2018 of HERNICORE, a treatment for lumbar disc herniation, and administration of HERNICORE to patients is steadily increasing. Since the launch, Seikagaku, together with sales partner Kaken Pharmaceutical Co., Ltd., has been focusing on surveying and examining safety, efficacy, and factors affecting them after administration of HERNICORE in medical institutions.

This is a large-scale, long-term surveillance project involving observation of some 3,000 patients for three years after administration. For this reason, we have obtained the cooperation of physicians and patients, developed a framework for close collaboration with Kaken Pharmaceutical, and are steadily working to increase enrollments.

By feeding back the safety and efficacy information obtained through surveillance to medical institutions, we will promote appropriate use of HERNICORE and contribute to post-marketing drug development.

A safety information meeting

HUMAN RESOURCES

Seikagaku aims to develop self-driven and self-disciplined employees who can contribute to sustainable growth.

Development of human resources

Seikagaku Corporation considers human resources to be an important corporate asset and seeks people who understand and put into practice our core values “creativity,” “fairness,” and "dreams and passion” and are capable of self-growth while fulfilling their roles with a sense of responsibility.

Seikagaku also strives to provide fields for each person to grow and thrive in.

We endeavor to cultivate autonomous employees who go about their work with enthusiasm and pride and produce results. We promote upskilling and career development of individuals through a combination of systematic education in various training programs, personnel training in the workplace through day-to-day work, and job rotation.

In addition, to develop the human resources required by each division and department, we conduct age-specific and level-specific training for everyone from rank-and-file employees to executives.

Work-life balance

To help its employees achieve a good work-life balance, Seikagaku has introduced flex-time at all of its business sites except for a few production operations and established a weekly “no overtime day” to encourage employees to leave work at the normal finishing time. To help employees balance the demands of their personal lives with their work activities, Seikagaku encourages employees to develop their own workstyles. For example, we are introducing a reduced working hours system to help employees to take care of childcare and nursing care duties, and there is also a system that allows employees to accumulate lapsed annual paid leave for use during prolonged illnesses or to cope with extended childcare and nursing care responsibilities. In the fiscal year ended March 2019 (fiscal 2018), employees used an average of 79.4% of their paid leave. In the period from fiscal 2007 to fiscal 2018, 100% of staff who left work for childcare reasons returned to work. The number of male employees taking childcare leave has also increased in recent years.

Seikagaku will continue to consider systems to meet workstyle needs as part of its efforts to improve working environments.

Promoting advancement of women

Seikagaku is creating an environment and developing systems to enable female employees to fully demonstrate their capabilities, and is implementing measures to support the advancement of women as part of diversity management efforts.

Since April 2016, we have implemented an action plan for the advancement of women, launched an in-house project with the objective of achieving a ratio of female managers of 10% by March 31, 2019, and engaged in various promotion activities spearheaded by female employees and the Human Resources Department. In this project, we have studied improvements to our internal systems based on the results of interviews with all female employees and held workshops to foster a culture that supports advancement of women. As a result of these initiatives, the ratio of female managers was 11.8% as of March 31, 2019, exceeding the target set when the project was launched. Seikagaku will continue to engage in initiatives to promote the advancement of female employees in the workplace.

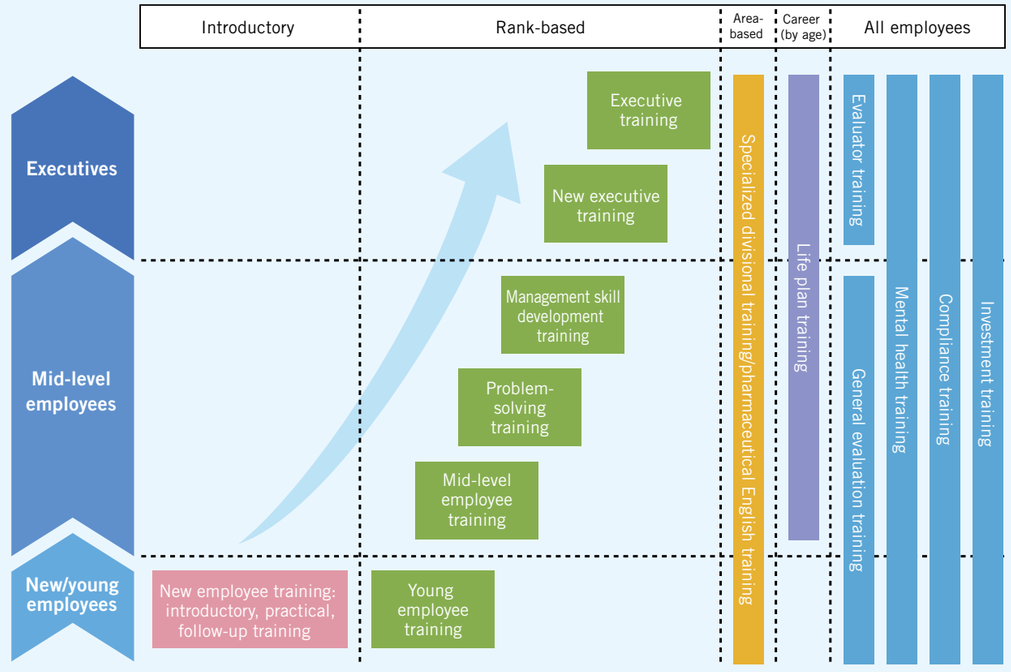
Health and Safety Committees

Seikagaku has formed Health and Safety Committees for the purpose of preventing occupational injuries and maintaining and promoting an appropriate working environment. The Committees meet once monthly at each business site with an industrial physician and public health nurse in attendance to survey the workplace environment and discuss issues. Through the Committees' activities, Seikagaku reinforces initiatives to prevent employee health problems and maintain and promote employee health and is developing a system for obtaining guidance and advice necessary for health management with professional input from an industrial physician and public health nurse.

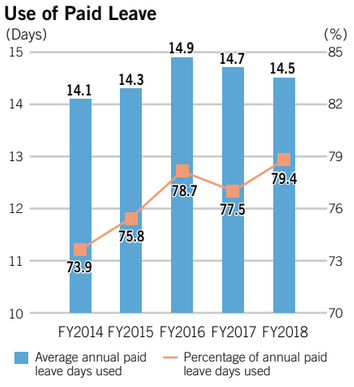
Mental health care (stress checks)

Since 2009, Seikagaku has implemented measures aimed at preventing employee mental illness. Specifically, we periodically aggregate and analyze employee stress values (organizational diagnosis) and, at departments and divisions where stress is high, link the results to personnel allocation corresponding to the nature and amount of work, improvement of the workplace environment, correction of long working hours, and creation of employee-friendly workplaces. We have also instituted an external hotline and counseling service and are developing a framework to enable employees and family members to seek consultation about work-related or personal concerns without hesitation.

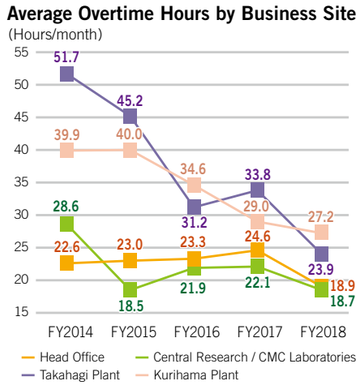
Training Systems



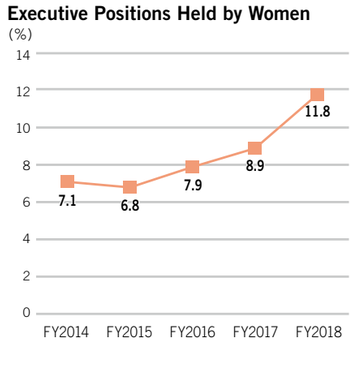
Use of Paid Leave



Average Overtime Hours by Business Site



Executive Positions Held by Women



*The figures provided on this page are all on a non-consolidated basis.