



**Seikagaku engages in research and development of innovative drugs that contribute to health and fulfill the lives 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.

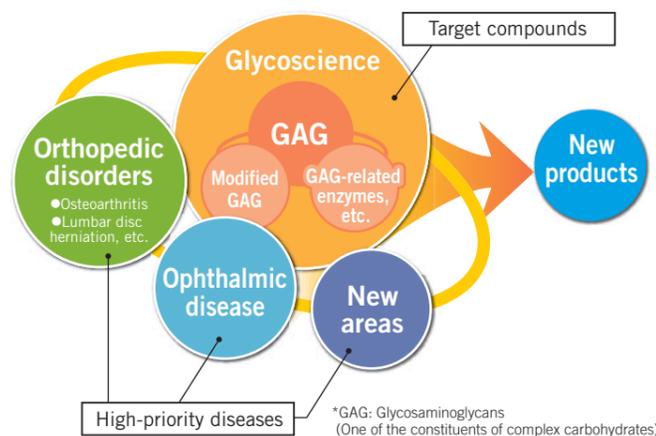
## Seikagaku and glycoscience

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 chondriase, 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 of 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 have given orthopedic disorders and ophthalmic diseases high-priority for research and development. Recently, we have also begun development of adhesion barriers used in surgery as a new R&D area. At the same time, we are considering ways of enhancing the product value (expansion of indications, additional formulations, and improvements in dosage and administration) of products already on the market and themes currently in the development stage.

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 possessed, not only low-molecular compounds, but also proteins and middle molecules such as peptides and nucleic acids.

## Topics TATENO Forum

Each year the Central Research Laboratory holds the TATENO Forum, an internal forum for presentations relating to new ideas and technology creation. The forum showcases oral and poster presentations of research results for about fifty entries. In addition to researchers, many employees from the head office and manufacturing plants participate in the forum, strengthening exchanges and interaction through active discussion and information sharing.

By providing a forum for actively presenting new ideas and further refining them through open discussion, the Central Research Laboratory contributes to enhancement of Seikagaku's R&D and technological capabilities and aims to generate candidate substances for future development.

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



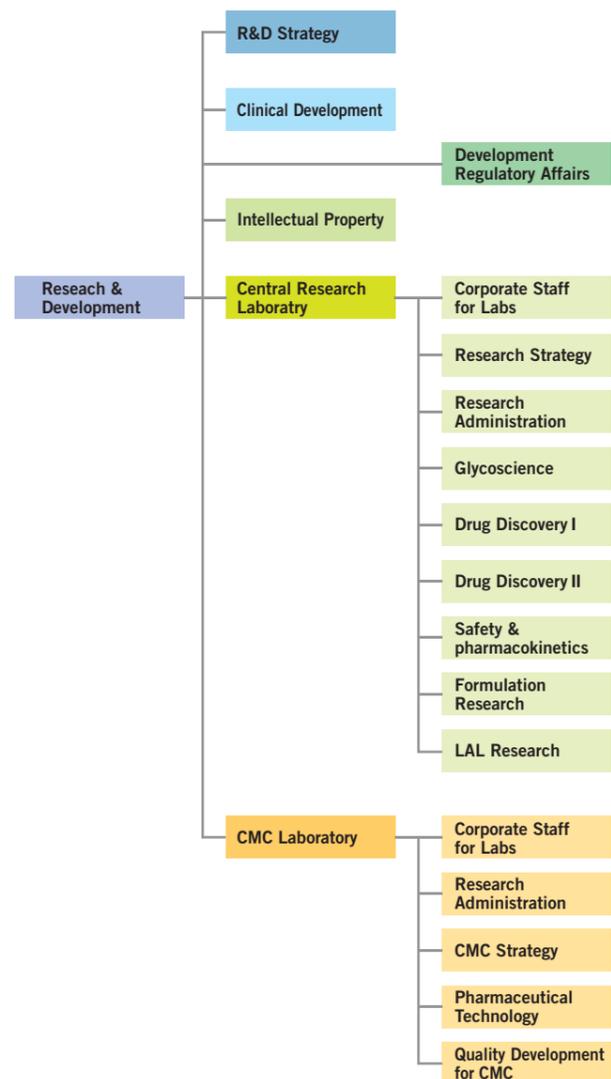
## Research and development organization

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, 2019)



## Central Research Laboratory

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. At the Central Research Laboratory, we accumulate proprietary glycoscience-related knowledge, technologies, and expertise. We also collaborate with academic research institutes and companies in Japan and overseas and actively engage in basic research to promote the search for new 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 Laboratory

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

## 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

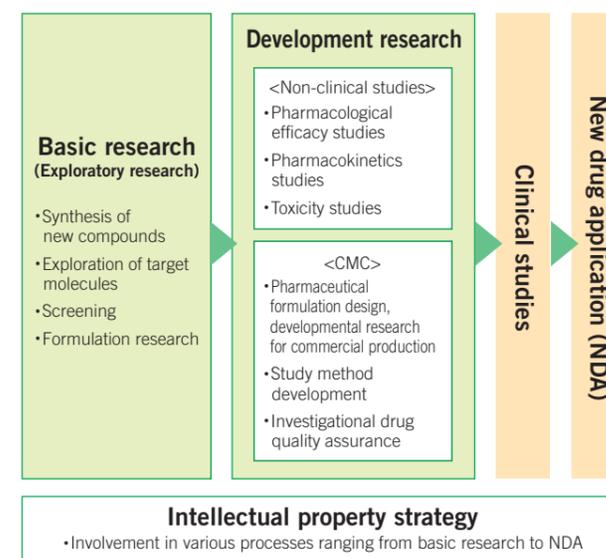
## Ethical considerations in non-clinical studies

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)

## Processes of New Drug Research



## Topics

### SI-449 advances to the clinical study stage

SI-449 is an adhesion barrier original to Seikagaku whose main ingredient is cross-linked chondroitin sulfate developed using a glycosaminoglycan cross-linking technology. A number of issues have been encountered in laboratory basic research and non-clinical studies for SI-449, and numerous employees have invested their experience and enthusiasm to resolve them one by one. As a result, we successfully advanced SI-449 to the clinical study stage in May 2018.

SI-449 is a powdered formulation that has unique physical properties, and little reference information is available for guidance in conducting studies. From the initial development stage until the present, development has been a continuous process of trial and error. The experience and knowledge gained by the developers in the involved departments through this development process will be an important asset in future development.

SI-449 has at last reached the starting point of medical device development. The project team members will unite to proceed with development to enable delivery of a product that will bring smiles to the faces of patients.



SI-449 Project manager and Research, CMC, and Clinical project leaders

## 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.

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. Phase II clinical study examines efficacy, safety, and pharmacokinetics and confirms optimal dosage and usage in a small number of patients. 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.

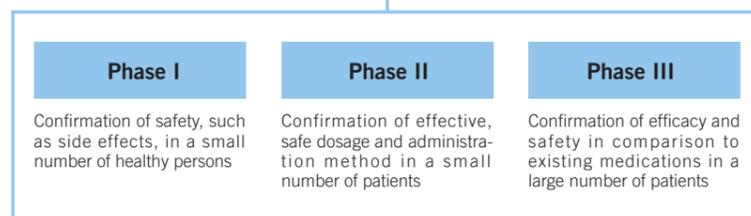
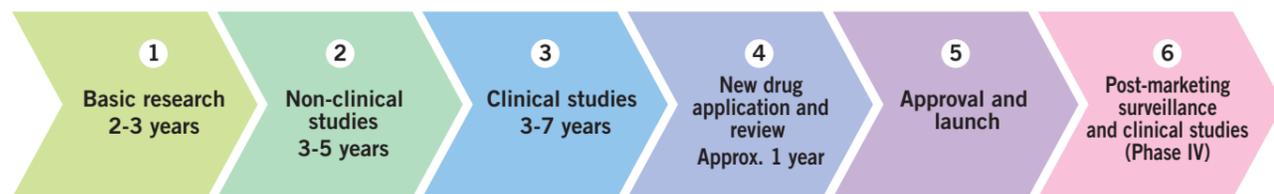
## Clinical development structure

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 the 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

Discovery and origination of new compounds that become drug candidates	New compound efficacy and safety research	Confirmation of efficacy and safety in humans	Filing of new drug application with the Ministry of Health, Labour and Welfare (MHLW) and expert review	MHLW approval and listing in the National Health Insurance drug price list	Post-marketing check of safety and directions for use
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Reference: "JPMA Guide," Japan Pharmaceutical Manufacturers Association

## Development Pipeline

(As of November 7, 2018)

### <Pharmaceuticals>

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	

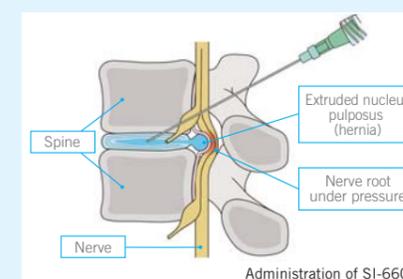
### <Medical Devices>

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 directly injected into the intervertebral disc. A single injection of SI-6603 is expected to reduce nerve root impingement resulting in improvement of the symptoms of lumbar disc herniation by reducing intervertebral disc pressure. Treatment with SI-6603 is less invasive to the patient than surgical removal of the herniation.

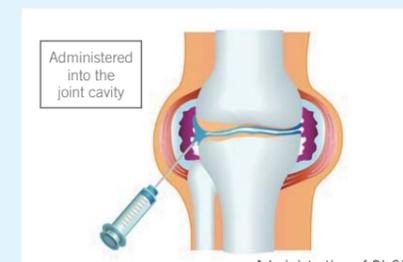
SI-6603 was launched in Japan in August 2018 as HERNICORE 1.25 units for intradiscal injection. In the U.S., although the expected pharmacological effect was demonstrated in a Phase III clinical study, the study did not meet its primary endpoint of improvement in pain. In response to this result, we initiated a Phase III clinical study (an additional study) in the U.S. in February 2018. Together with Switzerland-based Ferring Pharmaceuticals, the sales partner for the U.S. and other overseas markets, we will consider expansion to countries where it is possible to obtain approval using study data from Japan.



Administration of SI-6603

### SI-613 (treatment for osteoarthritis and enthesopathy)

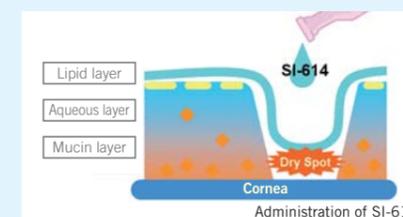
SI-613 is a formulation in which hyaluronic acid and a diclofenac (anti-inflammatory drug) are chemically bound using Seikagaku's own proprietary technology that is expected to provide prompt and sustained relief of the pain associated with osteoarthritis and enthesopathy. In Japan, we are conducting a Phase III clinical study initiated in February 2017 for the treatment of osteoarthritis and a late-stage Phase II study initiated in September 2017 for the treatment of enthesopathy (SI-613-ETP). We concluded an agreement concerning a co-development and marketing collaboration for SI-613 in Japan with Ono Pharmaceutical Co., Ltd. in September 2017. In the U.S., we are conducting a Phase II study for the treatment of knee osteoarthritis initiated in June 2017.



Administration of SI-613

### SI-614 (treatment for dry eye)

SI-614 is a modified hyaluronate that is produced using Seikagaku's proprietary technology. Ocular instillation of SI-614 is expected to protect the ocular surface and promote corneal wound healing. Many factors are involved in dry eye, and SI-614 is thought to have the potential of providing a therapeutic option based on a new mechanism unavailable from existing drugs with anti-inflammatory mechanisms in the U.S. Phase II/III clinical study was completed in January 2015, and Seikagaku is currently proceeding with selection of a development and sales partner.



Administration of SI-614

### SI-449 (adhesion barrier)

SI-449 is a medical device whose main ingredient is cross-linked chondroitin sulfate developed using Seikagaku's proprietary glycosaminoglycan cross-linking technology. SI-449 is expected to prevent or mitigate post-operative adhesion formation by absorbing moisture and swelling to form a barrier between the surgical wound site and surrounding tissues. Since it is a powdered formulation, it adheres well to uneven tissue surfaces and 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 development.



Use of SI-449



**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 build

ings 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

## Takahagi Plant operational improvement activities (improvement project)

The Takahagi Plant is focusing on operational improvement activities to improve production efficiency and quality. As part of this effort, the Plant undertook capacity utilization improvement and defective product reduction by launching a project bringing in an expert consultant, and re-examining practices taken for granted. This activity had the added benefit of enabling employees in the Plant to acquire the expertise to objectively analyze and visualize business operations and processes.

In these activities, the improvement project team has actively solicited and listened to employee input, and they work together to progress the improvement activities. Employee feedback such as "Work times have been reduced and work is getting easier" and "Yield has increased" has provided tremendous motivation for the project.

Currently, Seikagaku is setting up a dedicated organization for improvement activities within the Takahagi Plant and striving for further operational improvements. We plan to roll out the activities to the Kurihama Plant and ensure their penetration throughout the entire Production Division and will foster a corporate culture that encourages these activities and develop personnel who will be responsible for them.



Takahagi Plant improvement project team members

## 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 assures sterility of the products.

\* A kit with 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.





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 the 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

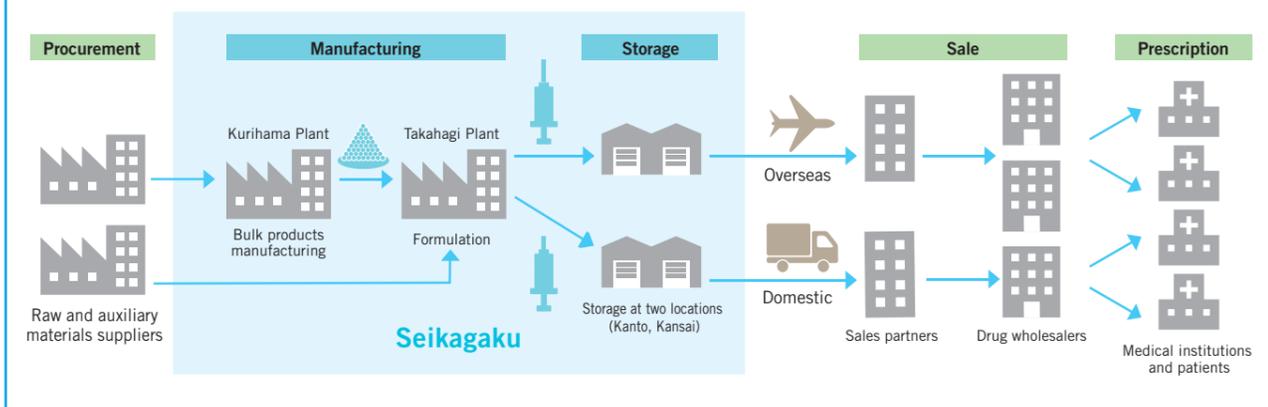
agent ARTZ, from glass to plastic. Through these efforts, we are adding value of our products.

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.

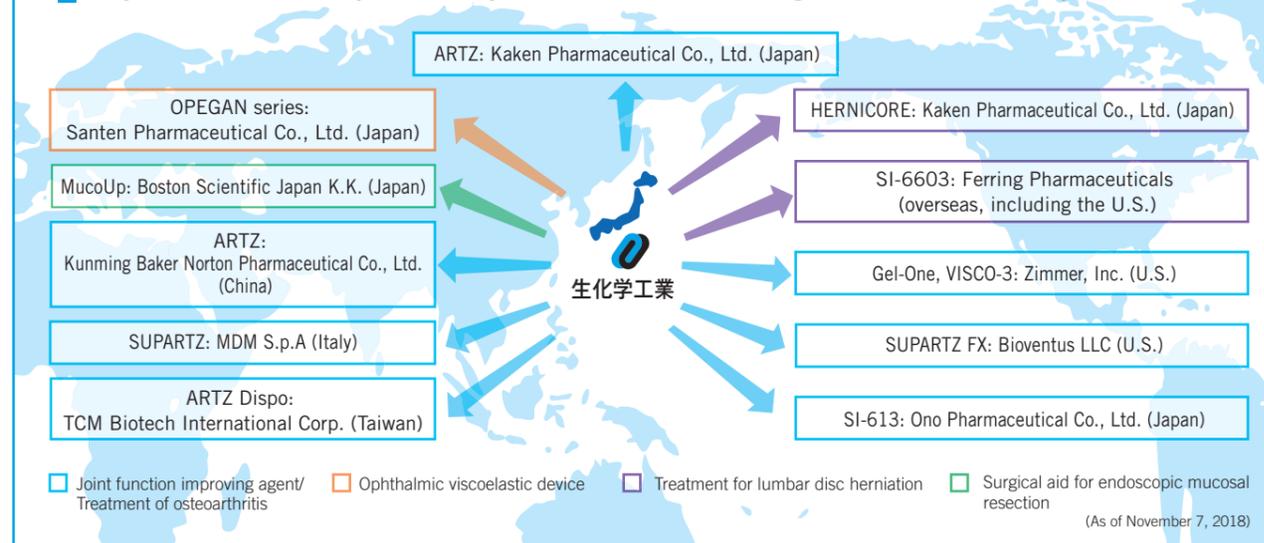
Bulk products

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 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 amoebocyte 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, by manufacturing and sales of endotoxin-detecting reagents, as well as beta-glucan-detecting in vitro reagent to diagnose invasive fungal disease.

Topics Implementing marketing activities in Japan

At Seikagaku, with its unique structure without an in-house pharmaceuticals sales team, the Business Development & Marketing Department is responsible for marketing and promotion activities in Japan. With the aim to improve patients' quality of life (QOL), its activity covers a broad area, such as sales strategy planning together with partners; product information materials creation, academic seminars and workshop arrangements, collection of information at medical institutions, product life cycle management design (including, but not limited to, expansion of indications and product modification), product shipment and inventory control, etc. The Business Development & Marketing Department does engage in direct sales of bulk products in Japan.

To ensure the provision of the new product "HERNICORE" to large numbers of patients from now into the future, we will pursue market penetration with appropriated steps, by gathering safety information and collaborating with academic societies to ensure safety use of the product.



Takahagi Plant has celebrated its first shipment of HERNICORE to the Japanese market.



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

To continuously provide patients and medical professionals with high-quality pharmaceuticals and medical devices, 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 peri-arthritis of the shoulder. We strictly maintain and control quality at all stages from product design and development to post-marketing in conformance

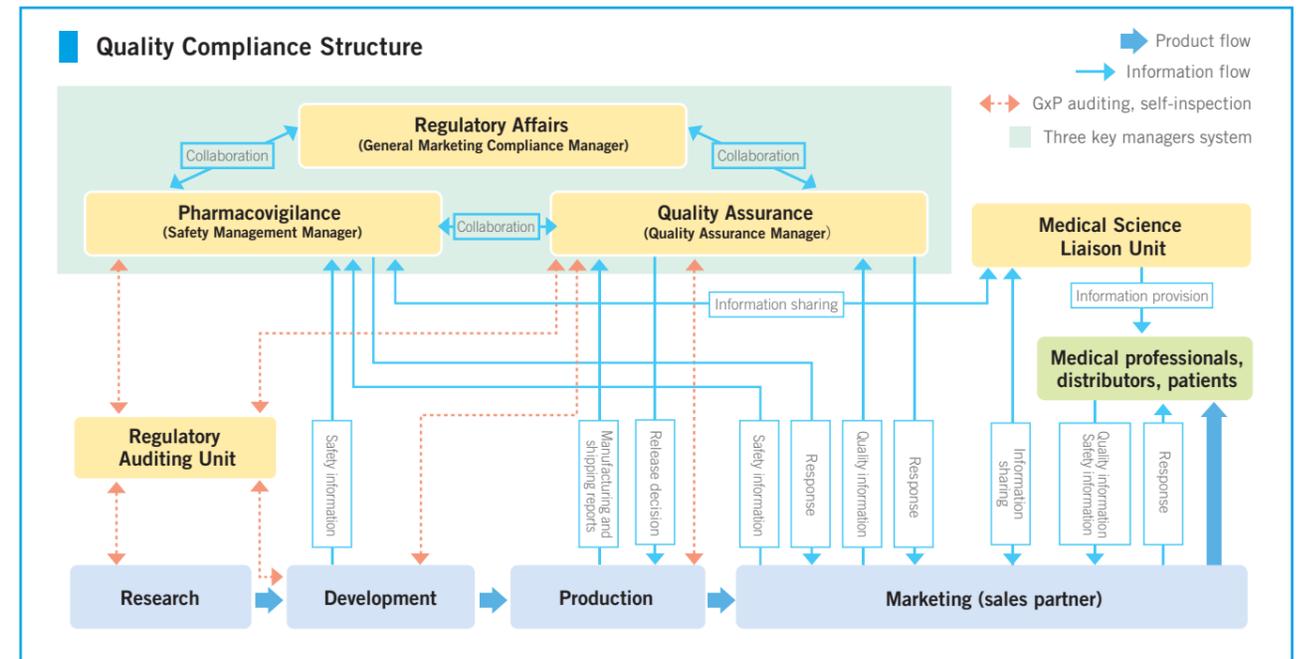
with these manufacturing control and quality assurance systems.

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	2	3	4	5
	Basic research	Development	NDA	Manufacturing, quality control, information provision, and product provision	Post-marketing
Pharmaceuticals	•PMD Act •GLP	•PMD Act •GLP •GCP •GMP for investigational products	•PMD Act	•PMD Act •GMP •GQP	•PMD Act •GPSP •GVP
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



## 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 (Medical Science Liaison)

Seikagaku has established the Medical Science Liaison (MSL) 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

### HERNICORE post-marketing surveys

The Pharmacovigilance Department is conducting post-marketing surveys of HERNICORE, the treatment for lumbar disc herniation launched in August 2018, in cooperation with sales partner Kaken Pharmaceutical Co., Ltd. We are surveying and examining safety and efficacy, and what factors affect them, after the administration of HERNICORE at medical facilities.

HERNICORE is the first drug to be classified as intradiscal enzyme injection therapy in Japan, and this is the largest survey project ever undertaken by Seikagaku, involving more than 3,000 patients for three years after administration. For this reason, we are mounting a concerted effort to reliably conduct the survey in collaboration with numerous physicians of related academic societies and patients as well as with our sales partner. By feeding back the safety and efficacy information obtained through surveys to medical facilities, we promote appropriate use of HERNICORE and contribute to post-marketing drug development.



HERNICORE post-marketing survey team members



**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.

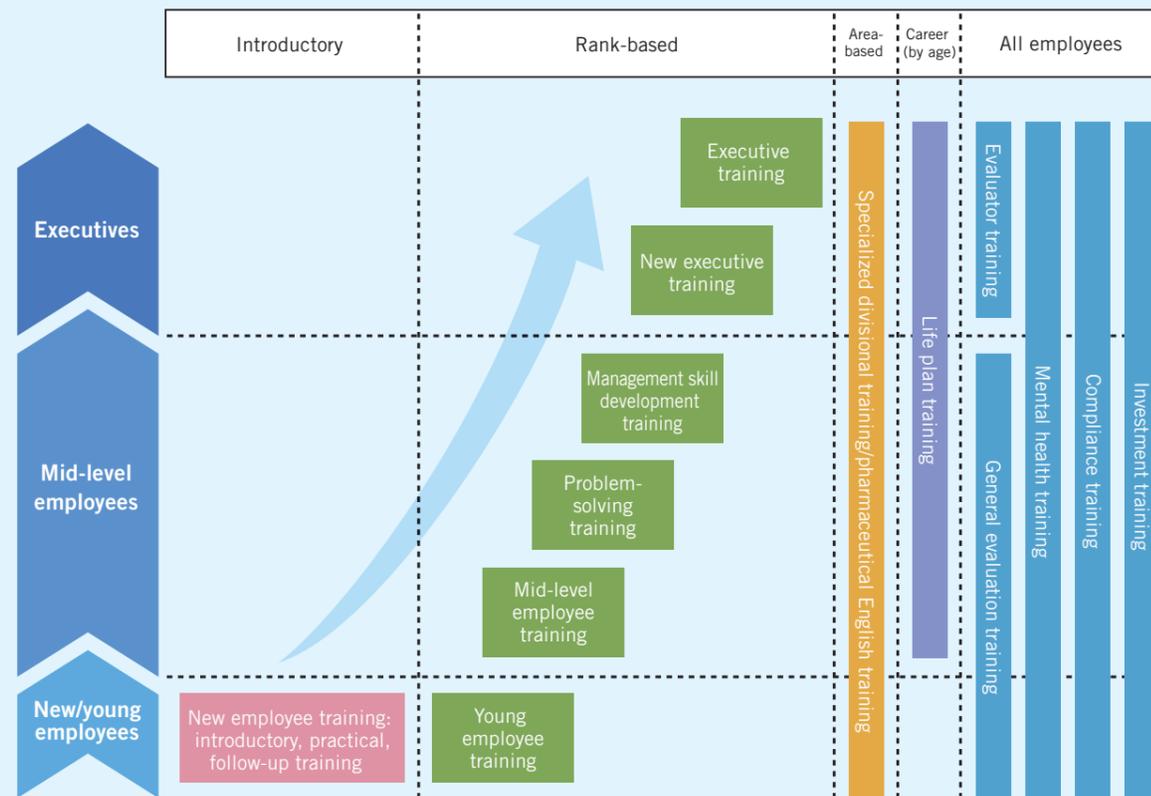
Seikagaku also strives to provide fields for each person to grow and thrive.

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 in-

dividuals 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.

## Training Systems



## 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 2018, employees used an average of 77.5% of their paid leave.

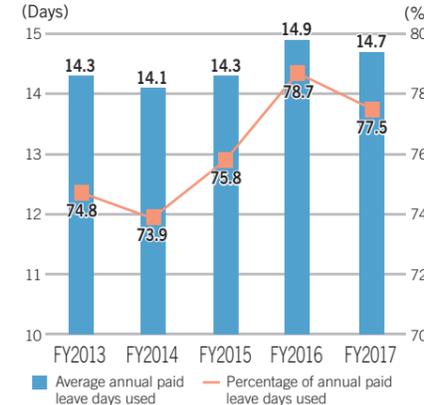
In the period from fiscal 2007 to fiscal 2017, 100% of staff who left work for childcare reasons returned to work. The number of male employees taking childcare leave has also increased in recent years.

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

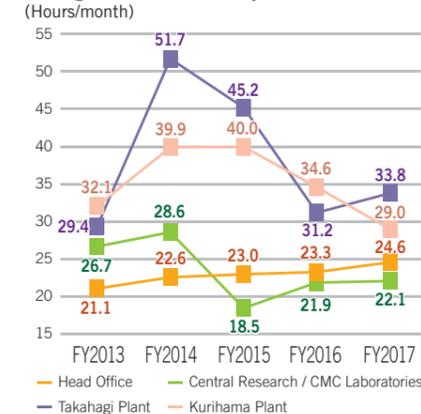
## Career development for female employees

Career development for female employees is an important aspect of diversity management at Seikagaku. Related measures include the creation of environments, systems, and structures that allow female employees to achieve their full potential, and support for career advancement. Specifically, we have set a target of increasing the percentage of executive positions held by women to 10% by the end of March 2019. A variety of initiatives have been implemented since April 2016 under an in-house project led by female employees and the Human Resources Department. Activities include interviews with and surveys of all female employees, a study concerning improvements to internal systems, and workshops and seminars designed to foster a culture of success for female employees. In addition, female employees have been sent to outside executive training programs specifically for women. As of March 31, 2018, 8.9% of executive positions were held by women.

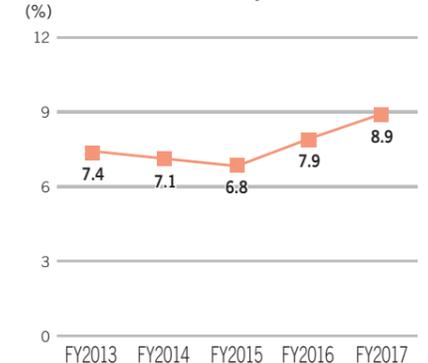
Use of Paid Leave



Average Overtime Hours by Business Site



Executive Positions Held by Women (%)



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

## Topics Participation in J-Win

Seikagaku is helping to promote diversity by sending female employees to participate in the activities of the Japan Women's Innovative Network (J-win), a non-profit organization established to support networking and reciprocal learning among female executives and candidate executives from various companies.

During the year I participated, we ran several projects and implemented problem-solving activities, including lectures by J-Win member presidents, training camps in Japan, and overseas training programs. One of the most stimulating aspects of the activities was the opportunity to discover and discuss issues and find solutions with women working in various industries, and to rethink our ideas based on direct advice from J-Win executives. Repetitions of this process led to accelerating changes in my awareness, and I was able to broaden my horizons and perspectives. I believe that changes in the awareness of individual women are vital to the development of a culture in which women can succeed. I am determined to maintain my sense of mission so that I can inspire others to raise their awareness.



Medical Science Liaison Unit  
Miwako Sato