The Source of Value Creation—Strengths in Science & Technology

We have been delivering many revolutionary, in-house developed products to patients all over the world, while fulfilling our purpose, "Contribute to the enrichment of quality of life around the world." Our aim has always been to safely deliver drugs to patients as quickly as possible. We create new drugs by combining all of our people's passion and utilizing our strength in Science & Technology. This is the source of our value creation.

Here, we introduce our strengths in Science & Technology, as the source of value creation, from the following three aspects: Organizational culture and talent that nurture drug discovery capabilities, cooperation organically connected with science, and global R&D in the future.

Organizational Culture and Talent That Nurture Drug Discovery Capabilities

Daiichi Sankyo's proprietary ADC Technologies

Enhertu®, an anti-cancer agent DS-8201, is Daiichi Sankyo's product that symbolizes our high level of scientific assessment capabilities and technological capabilities to refine drugs. *Enhertu* received priority review and breakthrough therapy designation*1 from the U.S. Food and Drug Administration in August 2017 for its first indication, third line treatment of HER2-positive breast cancer. We obtained marketing approval for *Enhertu* only two months after the application. In January 2020, we launched *Enhertu* in the U.S. ahead of other countries. After that, we launched in Japan in May 2020 and in Europe in February 2021. For gastric cancer, SAKIGAKE designation*2 was granted in Japan in March 2018, and indication for third line treatment of HER2-positive gastric cancer was approved in September 2020. In the U.S., breakthrough therapy designation was granted in May 2020, and the indication for second line treatment of HER2-positive gastric cancer was approved in January 2021. We are successfully obtaining approval for additional indications and expanding marketed countries through our strategic collaboration with AstraZeneca.

Our proprietary technologies used for *Enhertu*, an antibody drug conjugate (ADC)*3, are the product of research in which hundreds of compounds were made and tested by screening and optimizing over hundreds of combinations of antibodies, linkers, and payloads to address issues that were identified back then. It was no coincidence that Daiichi Sankyo was able to launch *Enhertu* in only ten years (which is relatively short period for the development of pharmaceuticals) after a research team with an objective to develop ADC technologies was officially organized in 2010. This is an example that our strategies to develop competitive products succeeded based on our strengths in Science & Technology ("S&T") that have been accumulated for many years. We also established our proprietary ADC technology platform *4 that is helping us create new ADCs after *Enhertu*.

*1: A system in the U.S. that expedites the development and review of medicines that may be more effective than existing therapies in treating serious diseases.
*2: Items designated by the SAKIGAKE designation system. The SAKIGAKE Designation System is a core measurement of the "Strategy of SAKIGAKE" (formulated by Ministry of Health, Labor and Welfare and released on June 17, 2014). The system aims to lead the world in the practical application in Japan of innovative pharmaceuticals, medical devices, in-vitro diagnostics, regenerative medicines, etc. The system's objective is to designate medical products including pharmaceuticals and regenerative medicines that have the potential of prominent effectiveness against serious and life-threatening diseases in order to make them available to patients in Japan ahead of the rest of the world. The system designates innovative new drugs that meet certain conditions in the early development phases. The drugs designated are prioritized for consultation and reviews for regulatory approval.
*3: Antibody-drug conjugate is a medication formed by connecting an antibody and drug (small molecule compound) via an appropriate linker. The antibody connects with the targeted protein that causes cancer to deliver the drug directly to the cancer cells, thereby maximizing the anticancer effect while minimizing the body's systemic exposure to the drug. For *Enhertu*, our proprietary ADC technology is used where Daiichi Sankyo's proprietary drug-linker covalently combined with an anti-HER2 antibody. https://www.daiichisankyo.co.jp/investors/individual/cancer/
*4: Daiichi Sankyo has been promoting several ADC projects including 3ADCs (*Enhertu*, *Dato-DXd*, and *HER3-DXd*), using our proprietary ADC technology.

The Source and Driving Force of S&T

Enhertu is the first product utilizing our proprietary ADC technology, which we expect to be the biggest growth engine for us. Typically, research and development of a new drug takes 9 to 16 years, but *Enhertu* only took 10 years to commercialize. This achievement was made as a result of our high level of scientific assessment capabilities and technological capabilities to refine drugs, the source of S&T. As a drug discovery-oriented pharmaceutical company, we have cultivated techniques and experiences of drug development over many years. In addition, we set a strategy to thoroughly differentiate our products from competitors by utilizing our high level scientific assessment capabilities. Based on the techniques and experiences under the strategy, we have been taking advantage of the techniques for refining drugs—technologies originated from craftspersonship.

It takes many years of experience for a researcher to acquire techniques and experiences to find drug development candidates and to refine them. This applies to the researchers who developed our proprietary ADC technologies. They went through a long period of preparation to obtain scientific assessment capabilities through continuous practices in advanced basic

▶ "Characteristics of Daiichi Sankyo's ADC" on pages 71 to 72 of Value Report 2020

Reference https://www.daiichi-sankyo.es/fileadmin/daiichi-sankyo-contents/DS_ES/Value_Report_2020_EN.pdf

▶ Video: Antibody drug conjugates (ADCs) and Daiichi Sankyo's ADC technologies

Reference https://www.daiichisankyo.co.jp/investors/individual/cancer/

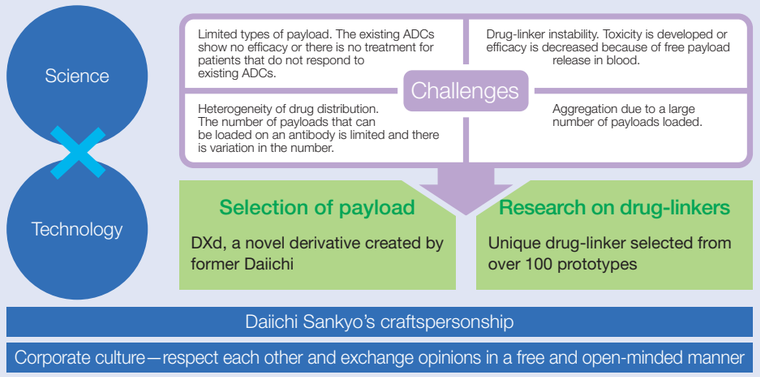
How *Enhertu* Was Developed—An Example of S&T ✕ Driving Force

We started research activities leading to *Enhertu* in the 1990s, dating back to the days of our predecessor companies (Sankyo and Daiichi). These activities were started through bottom-up suggestions from research laboratories and were not then included in each company's key research areas. And it is because of the visionary leaders with strong leadership that we succeeded in the biopharmaceuticals discovery area after establishing Daiichi Sankyo. Our proprietary ADC technologies were based on researchers' bottom-up and self-directed leadership. Later, the ADC technologies were invented and developed by combining our own research insights and research assets of our predecessor companies. In 2013, Daiichi Sankyo established the Biologics Function in R&D to develop and accelerate discovery research and manufacturing technologies for new modalities including biosimilar antibodies and nucleic acid medicines, in addition to ADCs. Before the aforementioned initiative, we worked on in-house development of biosimilar antibodies, which we had to give up from business perspectives. However, know-how in antibody production gained through biosimilar development greatly helped the research and development of *Enhertu*.

With regard to our proprietary research in ADCs, at first, there were some talks that it was too late to start to achieve successful results. Despite those views, people in our research laboratories thoroughly examined ADC literature, eagerly formulated hypotheses against the difficult challenges associated with ADCs (see the figure below) and validated their hypotheses.

To solve the difficult challenges, they focused on the selection of payloads and research on drug-linkers, which turned out to be the key to success. As the payload, we selected a novel derivative (DXd) of the DNA topoisomerase I inhibitor DX-8951, which was created by our predecessor company. The achievement is owing to the fact that we already had sufficient data on DX-8951. This is because we had progressed the development of DX-8951 to clinical trials, although we discontinued it due to safety concerns perspective. One of the reasons we succeeded is that ADCs can reduce the development of toxicity. The drug-linker was selected from more than 100 prototypes. It is unique and has great features where it can be conjugated with various antibodies and demonstrates high stability in human blood.

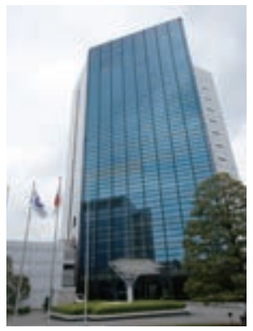
Our "capabilities of refining drugs" accumulated through research and development of small molecules contributed to the development of our ADC technologies. The technique that refines candidates to differentiate and to optimize them through continuous efforts is what we call Japanese artisans' skills—craftspersonship.



We worked on the development of *Enhertu* with highest priority across the organization as it showed encouraging efficacy in Phase 1 clinical trial. The Biologics Oversight Function established in R&D Unit was upgraded to Biologics Unit. In Japan, a project that aimed large number of workforce re-assignment had started. Outside Japan, we were also making efforts to strengthen and expand the organizations including the development function in the US. We focused on obtaining approval and preparing for the launch of *Enhertu* across the organization, not only in R&D but also in functions like Pharmaceutical Technology, Supply Chain, Quality Assurance, Marketing, Medical Affairs, and Pharmacovigilance. The culmination of all the hard work done across the organization brought the outstanding achievement to obtain marketing approval only four years after starting clinical trials (it takes four to nine years normally).

fields, aiming to develop new drugs needed by patients. Our driving forces to discover innovative new drugs are researchers' passion for drug development, their perseverance of not giving up nor being afraid of failure, and their eagerness for innovations. Going forward, we will give to the next generation the experiences and lessons learned from success and failure as well as the dedication of Daiichi Sankyo to create the best drugs possible so that we can develop pillars of our research that leads to future drug discovery.

Shinagawa R&D Center



Kasai R&D Center

R&D Organizational Culture and Talent

For our best-in-class products including *Enhertu*® and *Lixiana*® (anticoagulant), we conducted research aiming to thoroughly differentiate our drugs from existing products. On the other hand, for our first-in-class products including *pravastatin* (cholesterol lowering agent) and *HER3-DXd*, which is under development, research has been conducted focusing on researchers' ideas and imagination to change the Standard of Care (SOC: universally applied best treatment in today's medical practice).

We allow our researchers to work on their individual research in addition to high priority tasks for the entire organization, and senior members encourage them to accumulate a wide range of experience in drug discovery. Our researchers obtain scientific assessment capabilities and scientific intuition through lessons they learn from success and failure as well as discussions with colleagues, while learning the basics of drug development through daily research.

The keys to in-house developed products are our talent and the organizations that bring out the best in them. One of our advantages is that we can hire top students as researchers due to recognition of our high-level research and development capabilities. Every year, we employ many, diverse talent with high level of expertise in a wide range of fields, such as pharmacology, synthetic chemistry, pharmacokinetics, and toxicology. After they join Daiichi Sankyo, we develop them in the organizational culture where people are dedicated to create the best drugs possible. In addition, we develop and enhance talent who support S&T through systems such as programs to gain experience at international academia and research laboratories conducting cutting-edge research; training systems for drug discovery capabilities; and fair evaluation, awarding, and appointments.

In addition, we are proactively hiring people who have a proven track record as researchers in and outside of Japan. In our corporate culture, researchers respect each other as a specialist in science, and exchange opinions in a free and open-minded manner regardless of positions and tenure. This is also one of our major strengths.

Deep Trust in the R&D Organization

A high level of trust from senior management to the R&D organization is one of the reasons we were able to create an organizational culture where bottom-up suggestions are encouraged in research laboratories. Also, R&D leaders grant a wide range of decision-making authority to each research laboratory. In that way, trust from management strongly motivates researchers to obtain good results from organization-wide and individual research activities.

Additionally, we have been maintaining R&D expense ratio to sales (see next page) at about 20% on average since FY2006, which is higher than the average of the industry in Japan at 14%. This is a reflection of senior management's high confidence in our research and development capabilities that are backed up by high level of expertise and accumulated techniques and experiences.

Major Products in the History of Daiichi Sankyo

The history of the Daiichi Sankyo Group as a pharma innovator goes back to the founding of its predecessor organizations, Sankyo and Daiichi Pharmaceutical. Sankyo started its business with the launch of digestive enzyme *Taka-Diastase* which also appeared in *I Am a Cat*, a novel by Soseki Natsume, while Daiichi Pharmaceutical started with the domestic manufacturing of *Salvarsan*, a therapeutic drug for syphilis, a disease prevalent in Japan at that time. We have continued to produce various drugs needed in Japan, including drugs in the field of infectious diseases. They include *Transamin*, a hemostatic and anti-inflammatory drug listed in the WHO Model Lists of Essential Medicines.

We started global business expansion in the 1980s and promoted the development and launch of new drugs. The launch of antimicrobial agents *Tarivid* and *Cravit* in the field of infectious diseases contributed to the suppression of infectious diseases in Japan as well as in the world. While lifestyle diseases draws attention as a social challenge, we have also developed drugs in the area of cerebral and heart diseases, such as the hypercholesterolemia treatment *Mevalotin*, antihypertensive agent *Olmetec* / *Benicar*, and anticoagulant *LIXIANA*.

On the other hand, we have worked on research and development of new drugs in oncology, the largest unmet medical needs at present, as the top priority area. We successfully launched *ENHERTU*, an innovative new anti-cancer agent that utilizes the Group's proprietary ADC technology, a technology that is garnering much attention, in the United States and Japan in 2020 and in Europe in 2021.

1899
Digestive enzyme ***Taka-Diastase***

1902
Adrenalin, an adrenal cortex hormone agent

1910
Dr. Umetaro Suzuki, a future Sankyo scientific adviser, made the world's first discovery of vitamin B1 (***Orizanin***) in rice bran and established a foundation for the theory of vitamins

1915
Dr. Shozaemon Keimatsu (founder of Arsemin Shokai, the predecessor organization of Daiichi Pharmaceutical) began domestic manufacturing of ***Salvarsan***, a therapeutic drug for syphilis

1921
Began manufacturing of ***Bosmin***, a vasoconstriction/ hemostasis and asthma medicine

1965
Transamin, a hemostatic and anti-inflammatory agent

1985
Tarivid, a broad-spectrum oral antimicrobial agent

1985
Loxonin, an anti-inflammatory analgesic

1989
Mevalotin, hypercholesterolemia treatment

1993
Cravit, a broad-spectrum oral antimicrobial agent

2002
Olmesartan (***Olmetec*** in Japan, ***Benicar*** in the United States), an antihypertensive agent

2009
Efient, an antiplatelet agent

2010
Inavir, anti-influenza treatment

2011
Lixiana, an anticoagulant

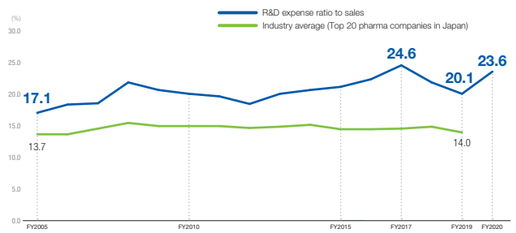
2019
Tarlige, pain treament

2020
Enhertu, an anti-cancer agent (HER2 directed antibody drug conjugate)

* The launch year as the Daiichi Sankyo Group unless otherwise stated.

The Source of Value Creation—Strengths of Science & Technology

▶ R&D Expense Ratio to Sales (FY2005 to FY2020)



Source: Ministry of Health, Labour and Welfare, Statistics on Pharmaceutical and Medical Device Industry
Cited from the Japan Pharmaceutical Manufacturers Association DATA BOOK 2021.

Leadership That Guide the Entire Organization to Transform

Leaders of our R&D are required to be science leaders, and to have capabilities for providing strong leadership in managing organizations.

For instance, leaders of R&D need to organize research teams that can maximize the strengths of the individual researchers. At R&D, typical researchers include those with scientific points of view to correctly judge researchers' suggestions, who have high capabilities for coming up with ideas, and who are good at verification through experiments.

We proactively hire leaders from outside. Junichi Koga, former Global Head of R&D, is one of those leaders. His enthusiasm strongly inspired members of R&D, that is: Push the level of biopharmaceuticals in Japan to the global level and realize that at Daiichi Sankyo. The organization smoothly metamorphosed (like an insect that grows with flexibility) so as to focus on research activities with a venture spirit.

Another example is a leader who had experience as a clinician. The leader significantly raised our global clinical development skills through his world-class experience in clinical development strategies for cancer drugs and his enthusiasm to deliver new drugs to cancer patients as quickly as possible.

As described above, R&D leaders from outside brought a new wind to the entire organization. Specifically, we have transformed into a global organization that can quickly achieve goals in clinical development, manufacturing, and product launches in oncology including ADCs.

In our corporate culture, people are flexible enough to candidly accept new ideas, and they respect each other and exchange opinions in a free and open-minded manner.

Cooperation Organically Connected with Science

Researchers Supporting Our Strengths around Research Base

One of the sources that support our research base is a rich pool of researchers who have accumulated diverse expertise in drug development. Recently, there is a trend of outsourcing drug discovery. However, we believe that it is important to retain core technologies internally so that we can maintain and strengthen our research and development platform that lies underneath drug development. We have been developing talent to have diverse expertise in various fields including medicinal chemistry*1, protein engineering*2, drug evaluation, and computational science. This also contributes to demonstrating a high level of scientific assessment capabilities, which is important when discovering drugs using the latest technologies such as Artificial Intelligence, and global drug discovery networks such as external collaboration.

*1: Study to synthesize new pharmaceuticals after obtaining seed compounds for drug discovery through studies on physiologically active substances at the molecular level and high-throughput screening, based on approaches such as structure–activity relationship.
*2: A method of artificially creating new proteins by adding new functions to natural proteins such as enzymes and antibodies that play an important role in our body, or by improving the function of the protein itself.

Clinical Development Driven by Science & Technology

Translational research is an approach that aims to improve the productivity of drug discovery by using outcomes from research into clinical development. We expect translational research to help us to efficiently perform research and development as follows: Information obtained through basic research such as the mechanism of diseases is provided to clinical development. Then, insight obtained through clinical trials and clinical practice are fed back to the research function, which helps in formulating new research hypotheses.

We noticed the importance of this concept early, and in 2009, established Translational Medicine function by integrating groups that are in charge of early phase clinical development and omics research*1. Our Translational Medicine function has expanded since it started with about 50 staff members. Currently, 300 members are involved in this function, including members in the Early Clinical Development Department, Quantitative Clinical Pharmacology Department, and Translational Science Department, as well as the Translational Research Department at Daiichi Sankyo RD Novare Co., Ltd., and our organizations outside of Japan.

In particular, the early-stage development function, which we are focusing on, plays an important role in conducting Proof of Concept (POC)*2 for clinical trials and connecting the project to late-stage development after obtaining POC. If POC shows expected efficacy or better than expected efficacy, late-stage development can be accelerated by determining appropriate dose, which is key for submission of a marketing approval application. On the other hand, if POC shows no efficacy or the efficacy does not meet the pre-determined criteria, we need to decide whether or not to stop the development as quickly as possible. To achieve this, we assign to early-stage development function the personnel with expertise in development and researchers with long-term experience so that scientific discussions with specialists in research laboratories and external medical institutions can be made more closely.

In addition, Daiichi Sankyo RD Novare established a clinical research laboratory with cutting-edge technologies, where pathological data and omics data obtained from samples from patients are analyzed. Having own clinical laboratories, we can take advantage of cutting-edge technologies to respond to fine-grained clinical needs. This is one of our strengths to conduct high-quality clinical trials.

*1: Comprehensive analysis of the molecules, DNA (genomics), RNA (transcriptomics), protein (proteomics), etc. that make up the cell for the purpose of clarifying life phenomena.
*2: An approach of verifying the efficacy and safety of new drug candidates under research and development in human trials.

Capabilities to Accomplish Clinical Development

To conduct late phase clinical trials quickly and with high level quality, operational capabilities that facilitate global cooperation is necessary. To establish such capabilities, we are working on initiatives for seamless global research and development. Starting from the development phase of a project, we proactively discuss development strategies for the project globally, and use those strategies aiming to increase the probability of success through translational research. Further, we conduct clinical trials based on science in order to implement the development strategies formulated.

In addition, we have capabilities for leading science discussions with regulatory authorities for marketing approval applications, etc., from the patient's perspective with the aim to deliver drugs to patients in each region and country as quickly as possible. One of the examples that demonstrates our strength in quality of clinical trials and flexibility around strategies is when *Enhertu* was approved in the U.S. for gastric cancer with data from a clinical trial conducted only in Asia.

Global R&D in the Future

Our global products, *Enhertu* and our ADCs that follow *Enhertu* are being developed using our proprietary ADC technologies. Development of these ADCs contribute to the growth of our global talent, which are our development base. We have been expanding our R&D bases in Europe. Further, we started to expand our global R&D bases including in China. We are making steady progress in establishing an infrastructure where we can conduct agile development globally.

Additionally, in FY2021, we welcomed Ken Takeshita as our new Global Head of R&D, who has previously demonstrated his skills in the development of many cancer drugs. With him, our research and development entered into a new stage.

R&D leads our sustainable growth as the source of innovation. Under the new Head of R&D, we are further focusing on improving the efficiency of global clinical trials, increasing the speed of decision-making, and developing global talents and next generation leaders, for our growth post 3ADCs. Going forward, we will formulate a unique, global R&D development organization by taking advantage of the strength at each base so that we can capture innovation around the world. At the same time, with our S&T, we aim to continuously discover innovative new drugs that bring hope to patients suffering from diseases including oncology, rare, and CNS diseases.

▶ Global R&D Structure