Material Issues to Create New Value for Customers and Society

The Shionogi Group has identified three priority issues it needs to create new value for customers and society – drive innovation, protect people worldwide from the threat of infectious diseases and create a more vigorous society. Leveraging our strengths as a drug discovery-based pharmaceutical company, we aim to help create a society where people can lead more creative, vigorous and healthy lives. In this section, we look at the Shionogi Group's specific initiatives and outcomes in the three priority areas.

Shionogi's Material Issues (Materiality)

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Material Issues to Create New Value for Customers and Society

Drive innovation

At Shionogi, we believe that to grow sustainably as a drug discovery-based pharmaceutical company contributing to a more vigorous society through improved healthcare is impossible without the constant pursuit of innovation contributing to the resolution of social issues. To that end, we seek to continue creating new drugs that balance innovation with healthcare affordability, by investing appropriate sums in R&D and maintaining small molecule drug discovery as a key strength while also diversifying into nonstandard peptide drug discovery and deepening collaboration with all manner of partners including the IT industry, in order to expand into new modalities and acquire entirely new technologies. If we are to meet the needs of both our customers and society as a whole and become a source of new value in the healthcare field, we think it essential that Shionogi remain committed to innovation, particularly as it applies to R&D.

Ryuichi Kiyama, Ph.D.
Corporate Officer, Vice President for Pharmaceutical Research Division

New drug creation balancing innovation with healthcare affordability

Ensuring both innovation and healthcare affordability

With many countries now grappling with the issue of a declining birthrate and aging population, the need to balance innovation with sustainable social security has become a fundamental global issue, to the extent of being taken up by the United Nations. The public is starting to push back against the argument that high prices are warranted by the innovative nature of new drugs. In our medium-term business plan, Shionogi Growth Strategy 2020 (SGS2020), we outline a vision of "to grow sustainably as a drug discovery-based pharmaceutical company contributing to a more vigorous society through improved healthcare," and on that premise we remain committed to supplying drugs that combine efficacy with a reasonable price.

In order to facilitate a focus on creating new drugs balancing innovation with affordable healthcare, we have maintained small molecule drug discovery as a key strength while also building on this platform to further strengthen our drug discovery capabilities by expanding into a new modality—that of medium molecule drugs including peptide-based therapies. In addition to being comparatively inexpensive in the manner of small molecule drugs, peptides rival antibody therapeutics in their target specificity (ensuring high potency with relatively few off-target side effects), while also having a molecular property profile enabling access to intracellular targets, which antibody therapeutics can struggle to reach.

Ensuring both innovation and healthcare affordability through small-molecule and nonstandard peptide drug discovery

	Small molecule drugs	Non-standard peptide drugs	Antibody-based drugs
Molecular weight	500 or below	500 to 2,000	Around 150,000
Specificity	Medium to high	High	High
Side effects	Few to moderate	Few	Few
Intracellular targets	Targetable	Targetable	Untargetable
Manufacturing costs	Low	Low	High

Innovation	×	Healthcare Affordability
Develop drugs with intracellular targets, which are difficult for antibody therapeutics to access		Achieve balance with healthcare affordability by reducing manufacturing costs

Focus on in-house drug discovery

Among pharmaceutical companies, some have scanty pipelines and therefore choose to supply patients with drugs licensed in from other companies. At Shionogi, though, we take a different approach. We believe that our job—and indeed our raison d'etre—is to be of use to patients by supplying them with products discovered in our pharmaceutical research and progressed right through to the stage of regulatory approval. We accordingly are focused squarely on in-house drug discovery. Over the past 14 years, we have succeeded in bringing seven proprietary drugs to market. Whereas the original pipeline ratio at most pharmaceutical companies is said to be 20–30%, we aspire to a ratio of 50–70%, and as at the end of March 2019, our original pipeline ratio was 69%. Given that our vision is to grow as a drug discovery-based pharmaceutical company, we take pride in this high ratio as we think it is indicative of our strength in in-house drug discovery.

Seven proprietary drugs launched over past 14 years

Crestor
Launch: 2005

Finibax
Launch: 2005

Tivicay
Launch: 2014

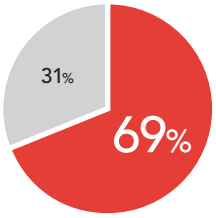
Mulpleta
Launch: 2015

Crestor OD tablets
Launch: 2016

Symproic
Launch: 2017

Xofluza
Launch: 2018

Original pipeline ratio
(As of March 2019)



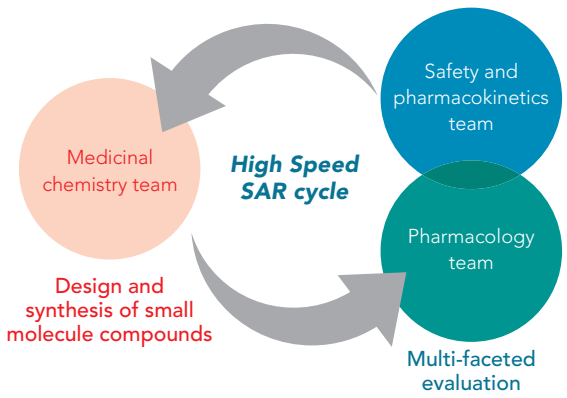
While on the one hand Shionogi is strongly committed to in-house drug discovery, on the other hand R&D into new drugs has become increasingly difficult in recent years, demanding massive resources (people, goods, money) and a lot of time. Against this backdrop, we think innovation rests not just on research and development of pipelines originated in-house, but also on collaboration with academic experts and venture companies, as well as other pharmaceutical makers. In fiscal 2018, Shionogi set a budget of ¥20 billion for strategic investments geared toward sustainable growth, with which we entered into 10 strategic collaborations.

Please refer to page 29 for details of strategic investments

Shionogi's strength in small molecule drug discovery

Capabilities in drug discovery giving rise to innovative new drugs

Shionogi's strength in research stems from our highly efficient SAR engine for small molecule drug discovery. The source of our competitiveness lies in the technological prowess of our medicinal chemistry team (responsible for design and synthesis of small molecule compounds), the pharmacology team (which performs multi-faceted evaluation of the compounds thus synthesized), and the safety and pharmacokinetics team, and in our experience in problem-solving via collaboration between the three. Through strong teamwork, we have been able to speedily and efficiently move through the SAR*1 cycle, giving rise to globally competitive, last-in-class*2 compounds such as the hyperlipidemia treatment *Crestor* and anti-HIV agent *Tivicay*, as well as the flu drug *Xofluza*, with its entirely new mechanism of action. In order to continue discovering competitive new drugs, though, we think it essential to acquire new strengths to augment the base provided by this SAR engine for small molecule drug discovery.



*1 SAR: Structure activity relationship
*2 Last in class: Unrivaled medicines with clear superiority over others that have the same mechanism of action

Shionogi's strengths in antibiotic drug discovery

Shionogi has been engaged in β-lactam antibiotic drug discovery for 30 years now, and we continue to discover new drug candidates. By combining approximately 60 years of antibiotics research with β-lactam chemistry, we have created an original platform for drug discovery that still continuously enables us to generate new drugs. In antibiotics research it is important to spend years collecting clinical isolates and analyzing their characteristics. Shionogi has amassed a considerable library of bacteria over the years, and this now constitutes a considerable advantage in our antibiotics drug discovery.

Shionogi's independent surveillance for resistant bacteria
At Shionogi, we also have spent more than 25 years conducting our own surveillance for resistant bacteria, and the data thus obtained is proving invaluable in promoting antimicrobial stewardship and AMR countermeasures.

1. Evaluate susceptibility patterns of approximately 2,500 clinical isolates of roughly 40 gram-positive and gram-negative aerobic and anaerobic strains
2. Determine MIC*1 for approximately 30 antibiotics, looking for genetic mutations in drug-resistant bacteria
3. Present results at academic symposia, also via published papers
4. The 14th bacterial strain collection initiated (as of July 2018)

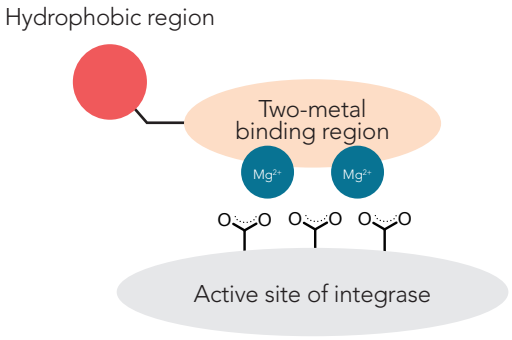
We also participated in joint surveillance programs with three academic groups*2.

*1. MIC: Minimum inhibitory concentration
*2. Japanese Association for Infectious Diseases, Japanese Society of Chemotherapy, and Japanese Society for Clinical Microbiology

Anti-HIV agent *Tivicay* leverages Shionogi's strengths in small molecule drug discovery

Shionogi's research into anti-HIV agents began in the 1980s. At the time, HIV research had not advanced far, and even if a hit compound was identified, subsequent SAR research tended not to proceed very smoothly. Against this backdrop, Shionogi identified a number of candidate compounds. In the process, we discovered a two-metal binding pharmacophore model that later played a role in the discovery of *Xofluza* as well.

In this model, both the metal binding unit and the hydrophobic unit such as benzyl moiety are important pharmacophores in integrase inhibitory activity. The compounds have inhibitory activity when the metal binding unit chelates with two metal ions coordinated by three acidic residues of the active site of integrase*3 and the hydrophobic unit is a certain distance away from the metal binding unit. We had to discontinue development of our first candidate compound owing to concerns about its safety, but then by simultaneously pursuing development of not just one but three candidate compounds, ultimately we succeeded in creating the last-in-class compound dolutegravir (brand name: *Tivicay*). This was the crystallization of a team effort, in which we never gave up no matter how many failures we encountered, and continued aspiring to ever-higher goals.



In 2016, *Tivicay* earned Shionogi the Heroes of Chemistry Award, an award given by the American Chemical Society for innovation in chemistry, and in 2017 we went on to claim the Pharmaceutical Society of Japan Award for Drug Research and Development.

*3 Integrase: Enzyme that catalyzes the integration of virally derived DNA into the host cell DNA in the nucleus

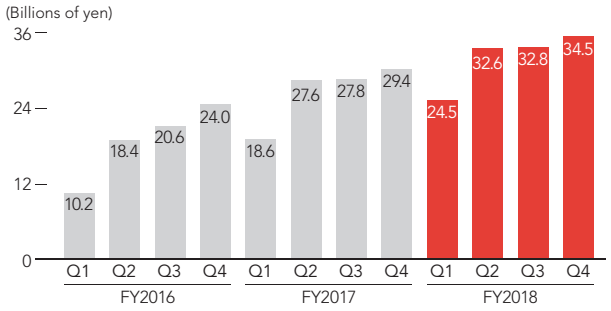
2016 Heroes of Chemistry Award for discovery of *Tivicay* (dolutegravir)

Award presentation ceremony held in August 2016
From left, Takashi Kawasuji of Shionogi, ACS President Donna Nelson, and GSK's Brian Johns

Tivicay gained regulatory approval in August 2013 in the US, in January 2014 in Europe, and in April 2014 in Japan. Our HIV franchise*1 of dolutegravir-based drugs posted global sales of £4,420 million in fiscal 2018, and continues to grow.

*1 HIV franchise: anti-HIV agent *Tivicay* and the dolutegravir combination drugs *Triumeq* and *Juluca*

Quarterly royalty income from HIV franchise



Researcher's voice

Tomokazu Yoshinaga, Ph.D.

Infectious diseases & Immunity Division
Drug Discovery & Disease Research Laboratory
Pharmaceutical Research Division

For Shionogi researchers, the discovery of *Tivicay* represents a great success story, as *Tivicay* is highly potent, has not caused any drug-resistant viruses, has few side effects, can be administered without regard to meals, and has almost no drug/drug interactions. *Tivicay*'s discovery also led to the discovery of *Xofluza*. Talking to patients at international academic symposia, though, we have been made keenly aware of these patients' grave fears about developing side effects that would force them to discontinue medication. This has instilled in us the realization that there is always room for improvement in HIV medications. While it is proving difficult to discover compounds to partner with *Tivicay* in a single-tablet regimen without affecting *Tivicay*'s efficacy, we are working as one to discover a suitable partner as expeditiously as possible, by combining the SAR engine for small molecule drug discovery that is our core strength with innovative ideas. In the knowledge that daily pill-taking is a chore for many, we are working also on a long-acting formulation for injection every three months, all the while also persisting in our search for an HIV cure.

Tivicay
Launch in Japan: Apr. 2014

Triumeq
Launch in Japan: Apr. 2015

Juluca
Launch in Japan: Dec. 2018

Dovato
Launch in the US: Apr. 2019

Past and future of Shionogi's R&D into anti-HIV agents

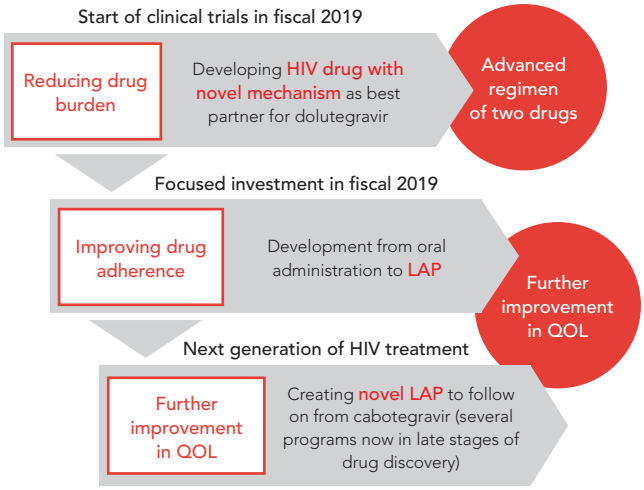
While on the one hand people are now living longer with HIV, they must spend a lifetime taking drugs to suppress the virus. There is a need to improve QOL by exposing newly diagnosed HIV patients to fewer drugs at the start of treatment, thereby alleviating side effects and reducing dosing frequency.

There is now a mountain of clinical data regarding *Tivicay*, demonstrating both potent antiviral activity and a high barrier to resistance. Use of *Tivicay* as the key drug has made it possible to develop two-drug combinations as an alternative to the standard treatment regimen of three or more drugs, resulting in the launch in recent years of *Juluca* (dolutegravir + rilpivirine) and *Dovato* (dolutegravir + lamivudine).

Based on favorable results from Phase III trials, regulatory applications have been submitted in the US and Europe for use of Shionogi's proprietary anti-HIV drug candidate cabotegravir in combination with rilpivirine, as a monthly injectable treatment (long-acting parenteral formulation, or LAP) for HIV. In these trials, patient preference data showed that a majority of participants preferred the LAP over daily therapy. Cabotegravir also is under study for HIV prevention, for which there is clearly a public health need, and as such is expected to offer a new option for both the treatment and prevention of HIV.

We believe that Shionogi carries a responsibility to continuously come up with new treatment options as a means of further improving QOL for people living with HIV, while also preparing for the potential emergence of resistance to *Tivicay*. On that premise, we already have discovered a new anti-HIV drug candidate with a novel mechanism of action, and we are furthermore focusing on research into an HIV cure.

Leveraging experience in developing HIV drugs with novel mechanism in formulation of LAP



Platform for continuous generation of new drugs: Now applying drug discovery know-how to research into flu drugs

The development of *Tivicay* began with a Shionogi researcher's findings concerning the active site binding of HIV integrase. This unique discovery triggered the start of internal competition to synthesize a new superior family of compounds, with the commitment of our research team ultimately leading to the creation of *Tivicay*. This also prompted us to go ahead with research regarding the cap-dependent endonuclease enzyme within the influenza virus, based on the idea of similar binding behavior. Our research team, confident that the science in HIV integrase inhibitors could be adapted for cap-dependent endonuclease inhibitors, took their know-how from *Tivicay* in a new direction, resulting in the discovery of *Xofluza*. This illustrates how passing on expertise and internally cultivating both human resources and technology is a key part of our approach to small molecule drug discovery at Shionogi, constituting a solid foundation for our drug discovery platform.

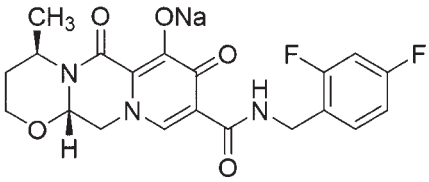
Novel flu drug *Xofluza* has revolutionary mechanism of action

Shionogi launched the novel flu drug *Xofluza* in Japan on March 14, 2018. A cap-dependent endonuclease inhibitor originated by Shionogi, *Xofluza* suppresses the replication of influenza viruses by a mechanism different from existing flu drugs. As *Xofluza* is an oral tablet requiring only a single dose, it is expected to improve compliance as well as convenience, and contribute to improving QOL for patients suffering from influenza.

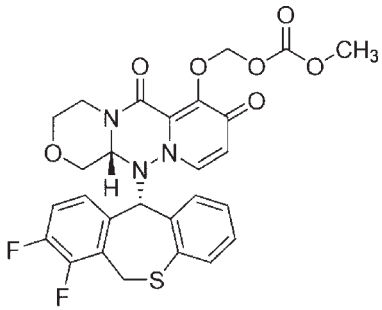
Roche plans to take a leading role in developing and marketing the drug globally, except for Japan and Taiwan. We believe that partnering with Roche will enable us to hasten delivery of *Xofluza* to patients around the world.

Tivicay

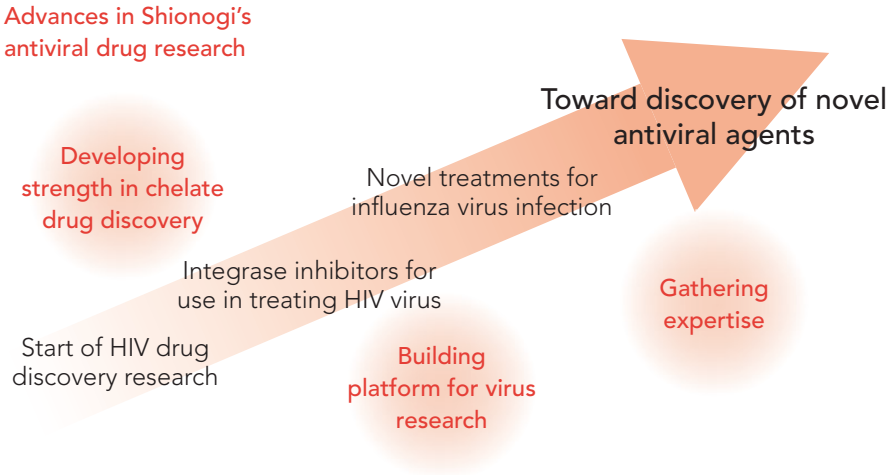
- HIV integrase inhibitor
- Potent activity and high barrier to development of resistance



Xofluza



Antiviral drug research x original compound design



Peptide drug discovery

Shionogi currently is engaging in nonstandard peptide drug discovery as a new modality offering potential synergies with our existing strength in small molecule drug discovery. We previously have had peptide drug candidates that were in-licensed from other companies, but now we plan to undertake our own peptide drug discovery research.

(1) Use of PDPS drug discovery platform to enhance drug discovery efficiency

In February 2016, Shionogi entered into a joint research and development agreement with PeptiDream Inc., with a view to utilizing the latter's proprietary Peptide Discovery Platform System (PDPS) to identify nonstandard cyclic peptides against multiple drug discovery targets. Nonstandard peptides are expected to reduce side effects, given their high affinity and selectivity for specific intracellular and extracellular targets. In June 2017, Shionogi went on to become the first Japanese company to enter into a non-exclusive license agreement for the use of PDPS. Under this agreement, we have taken on new joint R&D projects with PeptiDream, and accelerated innovation by bringing together the strengths of both companies.

Nonstandard cyclic peptides

- Quick screening, with low costs and small tasks
- Generates highly selective and highly active peptides
- Hits can be acquired even for challenging targets

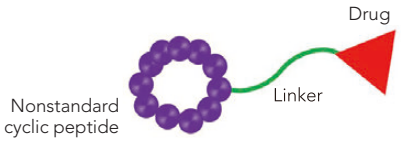
(2) PeptiStar Inc., a CMO*1 specializing in nonstandard peptides

Currently, no country in the world is home to a CMO that can stably provide high-quality peptide APIs at low cost. With this in mind, Shionogi, PeptiDream and Sekisui Chemical inked a joint venture accord in August 2017 to establish PeptiStar, Inc. to engage in research and development, manufacturing, and sales of peptide APIs, in the view that a new CMO possessing specialized technology for peptide therapeutics could help expand the market for these drugs. This joint venture is the world's first CDMO*2 to engage in research and development and manufacturing of a broad range of peptide APIs, from standard peptide APIs to nonstandard peptide APIs with a cyclic structure incorporating non-natural amino acids, and it aims to provide stable supplies of high-quality peptide APIs at low cost. Japan leads the world in peptide drug discovery, and it is expected that this new venture will bring together expertise and know-how from across Japan to create a CDMO specializing in this area, underpinned by the knowledge and technologies related to nonstandard peptide drugs possessed by PeptiDream. PeptiStar will be capable of manufacturing at least 100 kilograms of peptide APIs annually, more than any other company in Japan. Peptide therapeutics are cheaper to manufacture than antibody drugs, and by commercializing peptide manufacturing we seek to strike a balance between innovation in drug discovery and costs.

PeptiStar

(3) Using PDCs*3 to strengthen our presence in the CNS area

In January 2019, Shionogi entered into a joint venture agreement with PeptiDream for the discovery and development of peptide drug conjugates (PDCs). Shionogi is active in drug discovery for CNS indications, and as this technology improves the migration of drugs to the brain, we expect it to add to our strengths in this area.



*1 CMO: Contract Manufacturing Organization
*2 CDMO: Contract Development and Manufacturing Organization
*3 PDC: Peptide Drug Conjugate. A conjugate that connects a drug and nonstandard cyclic peptide with a linker. This joint research aims to establish a new approach to discovering drugs targeting the brain, through the discovery of nonstandard cyclic peptides that can pass through the blood-brain barrier.

Discovery story for *Xofluza*, a drug capitalizing on group value chain

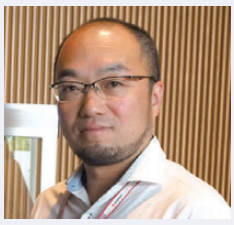
抗インフルエンザウイルス剤
ゾフルーザ®
XOFLUZA®

Promptly providing medicine to those in need through value chain evolution

Xofluza is an innovative new drug designated under the Sakigake scheme for accelerating the approval process. Through a concerted effort to deliver this product to patients even one day sooner, the Shionogi Group succeed in gaining approval for and launching *Xofluza* within roughly three years of commencing Phase I trials. If Shionogi is to continue advancing innovation and growing as a drug discovery-based pharmaceutical company, we think it essential that all value chain actors not only play their own roles, but also pull together to promote evolution of the value chain as a whole.

Research

Innovative new drug discovery in the infectious disease area is Shionogi's strength



Takao Shishido

Drug Discovery &
Disease Research Laboratory

Even before the discovery of the HIV integrase inhibitor, researchers recognized the structural similarities between HIV integrase inhibitors and cap-dependent endonuclease inhibitors, forming the belief that if HIV integrase inhibitors were brought to market, the science could be adapted for cap-dependent endonuclease inhibitors. However, when it actually came to deployment in other programs of the chelate drug discovery know-how gained from *Tivicay*, many things did not go as expected, leading to much trial and error. Some programs even needed to be suspended halfway, so it came as something of a shock when I observed binding of our seed compound*1 to the active center of cap-dependent endonuclease.

*1 Compound found in early screening to have certain level of activity against drug discovery target

Makoto Kawai

Medicinal Chemistry Research
Laboratory

When problems became evident with our first drug candidate, and the realization came that development could go no further, I was the only person left out of a team once composed of several researchers. I was shattered and didn't think I could go on, but I was urged not to quit and took up the challenge again, resulting in *Xofluza*. The active form of *Xofluza* has a chemical structure that is highly unusual in medicinal chemistry, in order to heighten its efficiency. That we were nonetheless able to create *Xofluza* is testament to our researchers' never-failing passion, innovative ideas and chemical knowledge base.

CMC

CMC technologies led to design and development of optimal formulation

Project members

In order to complete development in as short a time as possible, work on finding the optimal formulation proceeded at unprecedented speed. Not all activities were successful, and we experienced disappointments. Nonetheless, when tablets of an unplanned strength were required during clinical development, we were able to supply the investigational medicinal product (IMP) three to six months earlier than usual. At the manufacturing stage, too, we were able to keep the technology transfer period 11 months shorter than normal. Facing the pressure that failure would not be tolerated, members of the IMP Manufacturing Center were involved in the establishment of a small-scale commercial manufacturing process at the Settsu Plant, and this allowed a smoother shift to commercial manufacturing. In this manner, CMC personnel took on the strategic challenge of minimizing the product development period, thereby bringing the best conceivable drug to market in the shortest possible time.

Development

Global development also completed in quick time

Takeki Uehara
Global Project Leader

Kenji Tsuchiya
Project Manager

Undeterred by difficulties, the project team worked tirelessly to come up with the best strategy that would enable us to launch the drug in fiscal 2017, so that we could fulfil our mission of delivering *Xofluza* to patients as soon as possible. The development schedule called for *Xofluza* to launch within roughly three years of clinical trials commencing, and to that end it made full use of the influenza season every year. Starting Phase III studies in the season following completion of Phase II studies was quite a challenge and likely appeared nearly impossible, as did completion of the global Phase III study with about 1,500 enrollments in a single season. In the global trial in particular, a single mistake could lead to major delays, especially if a flu season was missed, so the team worked together to cover each task, going beyond national borders, divisions and roles to make sure there were no blunders. I think that the secret to our success was strong teamwork. The team shared the same goal and played their roles in a cooperative spirit based on mutual trust, enabling them to work together as a single unit. Members of other projects also cooperated on all fronts to make *Xofluza* a success, so our achievements were really due to everyone's strengths, not just to those of *Xofluza* project members.

Japan has the highest standard of influenza treatment in the world, built on early diagnosis and treatment. Shionogi's next mission is to take this impressive level of treatment to the rest of the world and reduce, if even by one, the number of people who become ill and die of influenza—a serious problem all over the world.

Regulatory affairs

Approval in first round of Sakigake designation system for pharmaceutical products

Yuko Kinoshita
Regulatory Affairs Department

Hitomi Ikemoto
Regulatory Affairs Department

Under the Sakigake designation system, the process from filing to approval takes six months or less, as there already has been a prior assessment consultation process. In 2015, applications were received for over 50 drugs in the first round of the Sakigake designation system. *Xofluza* received Sakigake designation in the expectation that it would prove efficacious in patients at high risk of complications, such as the elderly and children, and this focused the public's attention on the drug. Even for drugs with Sakigake designation, though, the requirements are the same as for drugs undergoing the normal process, in terms of the documentation needed to support filings for manufacturing and marketing approval, and the aspects screened by authorities. For this reason, shortening the review period hinges on finding solutions ahead of time to issues deemed likely to be raised by the regulators. This required us to quickly reach a mutual understanding with the authorities and address potential issues without delay. In order to realize our goal of bringing *Xofluza* to the world as soon as possible, we pulled together as a team and achieved Shionogi's maiden approval under the Sakigake designation system.

Active use of diverse partnerships

At Shionogi, we think sustainable growth hinges not only on new drug creation, but also on consolidating our strengths in areas of strategic focus. In this era of diversifying healthcare needs, there seems to be risk in having both a great deal of infrastructure and not much infrastructure. To maintain large infrastructure, it is necessary also to keep a bulging pipeline. However, this adds to the volume and type of work that in theory should be performed in-house. Through external partnerships, we seek to enhance overall productivity through collaboration in areas where it would be difficult for us to go it alone. By keeping our head office functions comparatively lean while at the same time retaining certain strengths in this ever-changing world, we aim to stay nimble and ensure that our presence is felt.

Strategic alliances geared toward sustained growth after 2020

While Shionogi will continue to develop pipeline projects created in-house, we think expansion of pipeline projects and technologies through alliances also is essential for driving innovation. In order to flesh out our product pipeline over the medium and long term, in fiscal 2018 Shionogi set aside a special budget of ¥20 billion for strategic R&D investment in addition to ordinary R&D expenses, and entered into a number of strategic business alliances.

In the field of infectious diseases, Shionogi traditionally has focused on HIV, influenza virus, and multidrug-resistant bacteria. In recent years, though, we have expanded the scope of our research to include the three major infectious diseases (HIV as well as tuberculosis, and malaria) and intractable infectious diseases. To that end, we have in-licensed research assets geared toward accelerating our research into the three major infectious diseases, while also investing in entirely new technologies for the treatment of intractable infectious diseases.

In the pain/CNS area, we have in-licensed assets that should enable us to provide a broader range of treatment options, thereby fleshing out underpopulated portions of our pipeline. We also have expanded into new modalities in order to address medical needs that have not been met by small molecule drugs, acquiring new technologies that will further our research into medium molecule drugs.

Against this backdrop, we plan to harness our competitive edge in small-molecule drugs and develop an order of priority for investment of our limited resources, in order to achieve ongoing improvement in R&D efficiency, both in-house and at partner companies. To further contribute to better health through the use of IT, we look to deepen our collaboration with the IT sector and other industries, tackling new modalities including digital therapeutic apps. In this manner, we aim to provide patients with an increasingly diverse range of treatment options.

Strategic Business Investments

Infectious Disease	Drug candidates for mycobacterial diseases (Hsiri Therapeutics) Research collaboration on anti-RS virus agent (Ube Industries) Collaborative research on prophylaxis and treatment of malaria(Nagasaki University) Nitric oxide inhaled antimicrobial drug candidates (Vast Therapeutics) Technology for antimicrobial resistance (Nemesis Bioscience)	Research on the 3 major infectious diseases (HIV, Tuberculosis, Malaria) and refractory infectious diseases ➡ Establish Shionogi's presence in infectious diseases globally
Pain CNC	Antidepressant candidate S-812217(Sage Therapeutics) Drug candidate for cognitive and memory deficits BPN-14770(Tetra Discovery Partners) Digital therapeutics AKL-T01, AKL-T02(Akili Interactive)	Expanding into wider range of treatment options ➡ Provide new treatment options with novel mechanisms
Modality	PDC technology (PeptiDream) Regenerative medicine product candidate ADR-001 (Rohto Pharmaceutical)	Acquiring new modalities ➡ Solve unmet needs that cannot be met with small molecule drug

Entered into 10 new strategic partnerships with view to sustained growth after 2020

Protect people worldwide from the threat of infectious diseases

As a drug discovery-based pharmaceutical company, we must ask ourselves what Shionogi can do for society. One answer springs to mind, and that is "freeing people from the threat of infectious diseases." Throughout history, mankind has been under constant threat from infectious diseases. No sooner is a new agent introduced than the pathogen develops resistance to it; this has been a persistent battle that continues today. As globalization gathers pace, borders are becoming more porous and people are able to move freely around the world, creating an urgent need for pandemic preparedness. At a time when other large pharmaceutical companies have moved away from the infectious disease area, I believe it is incumbent on Shionogi to maintain and further develop this particular strength, not just in the treatment of infectious diseases, but also in their prevention and diagnosis.

Takuko Sawada
Director,
Executive Vice President

Deaths attributable to AMR per year by 2050, if no action is taken
More than **10 million**

Estimated economic impact
$100 trillion

Address the problem of antimicrobial resistance (AMR)

A significant unmet need: "Time is running out"

Antimicrobial resistance (AMR) is a real and immediate global threat.

The damaging effects caused by resistant bacteria are already responsible for an estimated 700,000 deaths per year globally, and future projections of the impact of unresolved AMR surpass the projected number of deaths caused by cancer by 2050. As AMR also could have a grave impact on the global economy, it potentially could pose a high direct and indirect cost to society.

In the future, lack of effective antibiotics could make routine medical interventions extremely dangerous or even impossible.

For these reasons, AMR must be regarded as a global, regional, and national priority for health organizations and governments, to be addressed with the utmost urgency on a global scale.

WHO and United Nations Initiatives to Tackle AMR

WHO Global Action Plan

- **Global cooperation spearheaded by World Health Assembly**
- **Global Action Plan setting out five strategic objectives**

1. Improving awareness and understanding of antimicrobial resistance
2. Strengthening the knowledge and evidence base through surveillance and research
3. Reducing the incidence of infection through effective sanitation, hygiene and infection prevention measures
4. Optimizing the use of antimicrobial agents in human and animal health
5. Developing an economic case for sustainable investment

United Nations High-Level Meeting (September 2016)

- World leaders signaled an unprecedented level of attention to curb the spread of multidrug-resistant infections.
- Countries reaffirmed their commitment to develop national action plans on AMR.
- Leaders recognized the need for stronger systems to monitor drug-resistant infections and the volume of antimicrobials used in humans, animals and crops, as well as increased international cooperation and funding.
- Leaders also called for new incentives for investment in research and development of new, effective and affordable medicines, rapid diagnostic tests, and other important therapies to replace those that are losing their power.

Combating worldwide public health challenge of AMR

The reality is, though, that many pharmaceutical companies have moved away from infectious disease area, as despite being a public health challenge of utmost importance, from a business perspective this is an area in which profits are hard to come by. Not only is it becoming more and more difficult to conduct R&D into new antibiotics, but also initiatives that restrict the use of new antibiotics have led to uncertainty around market size. It has been reported that only five of the world's top 50 pharmaceutical companies currently have an antibiotics pipeline.

Against this backdrop, Shionogi has made an on-going commitment to the R&D of new antimicrobial therapies, and we will vigorously pursue such activities to ensure that both patients and society as a whole will benefit from new antibiotics.

SGS2020 identifies "Protecting people from the threat of infectious diseases" as one of major social issues we should address, and declares that Shionogi will remain committed to developing new drugs against infectious diseases that lack effective medical treatments, and to promoting antimicrobial stewardship. In 2018, we published the Shionogi AMR Position Paper detailing our point of view and efforts in this regard, and we will continue driving forward our commitment to becoming a leading company in the fight against AMR, by promoting antibiotic R&D, proper use, and access to antibiotics.

Detailed information on Shionogi AMR Position Paper
http://www.shionogi.co.jp/en/company/csr/activities/amr.html

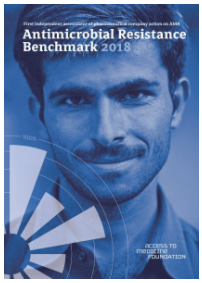
Long-term commitment to improving R&D to provide novel treatments for infectious diseases

Shionogi's involvement in the field of infectious diseases essentially began when we began importing streptomycin in the years following World War II. Subsequently, we commenced sales of *Ilotycin* (licensed in from Eli Lilly) in 1952, and in 1959 we launched the long-acting sulfonamide *Shinomin*, the first proprietary product to come out of our research. The drug was out-licensed to Roche, helping to treat patients with infectious diseases worldwide. We also released the sulfamethoxazole and trimethoprim combination *Baktar*, which is still widely used by patients worldwide. Shionogi now has been involved in infectious disease R&D for over 60 years, either independently or via strategic alliances with other companies/organizations, and we seek to continue generating new products in this field by drawing on that extensive experience in antibiotic drug discovery.

At Shionogi, we also have spent more than 25 years conducting our own surveillance for resistant bacteria, and the data thus obtained is proving invaluable in promoting antimicrobial stewardship and AMR countermeasures.

Shionogi's efforts to combat AMR also have been recognized externally. In a recent Antimicrobial Resistance Benchmark 2018 survey, Shionogi was the only Japanese pharmaceutical company to qualify for inclusion, and was recognized along with the seven other large research-based pharmaceutical companies. Especially, Shionogi was highly recognized in the survey as having the highest annual ratio of investment in R&D for anti-infectives of any of the companies surveyed (based on investment as a proportion of net sales).

Shionogi is also active in the field of antiviral treatments. Over the years we have released a number of innovative anti-infectives including the anti-HIV agent *Tivicay* and related pipeline drugs, and the flu drug *Xofluza*.



Antimicrobial Resistance Benchmark 2018

Please refer to page 22 for details of Shionogi's strength in antibiotic drug discovery, and its independent efforts in surveillance for resistant bacteria.

Shionogi and Industry Efforts to Combat AMR

Shionogi also actively participates in various national and international initiatives addressing AMR, as a means of contributing to global resolution of this public health challenge.

Davos Declaration (January 2016)

- **Declaration by the pharmaceutical, biotechnology and diagnostics industries on combating antimicrobial resistance**
- **Signed by more than 100 companies, including Shionogi, who committed to:** work to reduce the development of antimicrobial resistance; invest in R&D that meets global public health needs with new innovative diagnostics and treatments; improve access to high-quality antibiotics and ensuring that new ones are available to all; and remove financial incentives that reward the prescribing of antibiotics in greater volumes.

Industry Roadmap for Progress on Combating Antimicrobial Resistance (September 2016)

Signed by 13 major global pharmaceutical companies, including Shionogi, and laying out a roadmap for four key commitments:

acting on environmental pollution associated with antibiotic manufacturing;
supporting improved stewardship of antibiotics;
facilitating improved global access to antibiotics; and
supporting open collaboration between industry and public researchers.

AMR Industry Alliance Board

Seven pharmaceutical companies—Shionogi, Pfizer, Merck, Johnson & Johnson, GlaxoSmithKline, Sanofi, and Roche—form the Board of the AMR Industry Alliance, a coalition of over 100 research-based pharmaceutical, generics, biotechnology and diagnostics companies committed to slowing the spread of AMR and promoting industrywide advances in life sciences.

Stimulating Research and Development of New Antibiotics

Various initiatives to stimulate sustained investment by the public and private sectors in R&D into antibiotics

Push & Pull Incentives

Push-type: Provision of financial support for R&D

▷ Includes CARB-X, GARDP, IMI, JPIAMR, NIH/NIAID and BARDA

Pull-type: Reward for innovation through funding that will enhance return on investment (ROI) and improve the accuracy of demand forecasting

▷ In recent years, the G20 has acknowledged the importance of such incentives, debating whether or not to introduce a market entry reward.

WHO List of Antibiotic-Resistant "Priority Pathogens"

On February 27, 2017, the World Health Organization (WHO) published its first-ever list of antibiotic-resistant "priority pathogens," a catalog of 12 families of bacteria that pose the greatest threat to human health. Stating that "Antibiotic resistance is growing, and we are fast running out of treatment options," the WHO stressed the need to develop new antibiotics. The 12 pathogens on the list are divided into three categories according to the urgency of need for new antibiotics, with carbapenem-resistant bacteria slotting into the critical category where the need for new antibiotics is considered particularly urgent.

WHO Priority Pathogens List for R&D of New Antibiotics

Critical Priority	
Acinetobacter baumannii	carbapenem-resistant
Pseudomonas aeruginosa	carbapenem-resistant
Enterobacteriaceae	carbapenem-resistant

Cefiderocol shows potent antibacterial activity against these three pathogens

High Priority	
Enterococcus faecium	vancomycin-resistant
Staphylococcus aureus	methicillin-resistant vancomycin-resistant
Helicobacter pylori	clarithromycin-resistant
Campylobacter	fluoroquinolone-resistant
Salmonella species	fluoroquinolone-resistant
Neisseria gonorrhoeae	cephalosporin-resistant fluoroquinolone-resistant

Medium Priority	
Streptococcus pneumoniae	penicillin-non-susceptible
Haemophilus influenza	ampicillin-resistant
Shigella species	fluoroquinolone-resistant

Prepared by Shionogi, based on WHO press release

Development of cefiderocol

Many of the pathogens in the critical category (deemed in the most urgent need of new R&D) are resistant to carbapenem-type antibiotics, and drugs effective against these pathogens are in high demand worldwide. Shionogi is developing cefiderocol as a candidate for the treatment of multidrug-resistant gram-negative bacterial infections, and we believe it could evolve into a valuable weapon in the fight against the three carbapenem-resistant pathogens positioned by the WHO as the highest priorities.

Clinical trials with a view to gaining approval are proceeding as planned—including a Phase III study in carbapenem-resistant gram-negative bacterial infection and another Phase III study in nosocomial pneumonia—and applications have been filed in the US and Europe.

Shionogi remains fully dedicated to tackling the global public health threat of AMR.

New initiatives for hard-to-treat bacterial infections

Looking ahead, Shionogi's strategy for AMR drug discovery will be to continue research into small-molecule anti-infectives targeting multidrug-resistant bacteria, while also expanding our horizons to include research into hard-to-treat bacterial infections.

To that end, in fiscal 2018 we made strategic investments in companies possessing entirely new modalities for the treatment of hard-to-treat bacterial infections. By combining our alliance partners' unique strengths with our own knowledge and experience in small molecules and infectious diseases, we aim to discover new therapies that would be beyond the scope of other companies.

Please refer to page 29 for details of our strategic investments in fiscal 2018.

Nemesis Bioscience Ltd.

A technology to inactivate antibiotic-resistant genes by weaponizing bacteriophages with CRISPR-Cas genome-editing technology

▷ A new approach to treatment that regains sensitivity to antibiotics in drug-resistant bacteria

Vast Therapeutics

A technology to manufacture drug formulations to stably and continuously emit nitric oxide, which has broad-spectrum antibacterial activity

▷ Toward a new treatment approach for respiratory infections

Tackle the world's three major infectious diseases

The three major infectious diseases (HIV/AIDs, tuberculosis and malaria) constitute a grave threat and massive challenge from the perspective of global health. Swiftly halting the spread of these diseases is an important theme of the United Nations' Sustainable Development Goals (SDGs). Shionogi's strategic investments in fiscal 2018 also included the in-licensing of research assets with potential to accelerate drug discovery, with a view to helping beat these three major infectious diseases.

Please refer to page 29 for details of our strategic investments in fiscal 2018.

HIV

Shionogi has contributed greatly to the treatment of HIV through the discovery of *Tivicay* (dolutegravir), an HIV integrase inhibitor that has high levels of efficacy and safety and minimal risk of drug resistance. Currently, US, European and domestic HIV treatment guidelines recommend *Tivicay* as one of the first-line drugs for treatment-naïve patients, making it an important new treatment option for all HIV positive patients.

Although HIV treatment has come a long way, there remains a need for further improving patients' quality of life (QOL) by exposing them to fewer drugs and reducing dosing frequency. With a view to meeting these unmet needs, Shionogi is supplementing research work already under way with a focus on long-acting parenteral (LAP) formulations and realizing a cure for HIV.

Please refer to pages 22–23 for details of R&D into *Tivicay*, and our future plans for HIV research.

Tuberculosis and non-tuberculous mycobacterial (NTM) diseases

Each year, more than 10 million people reportedly fall ill with tuberculosis, and co-infection with HIV is another significant public health issue. Shionogi is actively engaged in addressing these challenges, by such means as licensing in the anti-tuberculous drug candidate S-004992 from China-based C&O Pharmaceutical Technology, as well as research assets from Hsiri Therapeutics.

Hsiri Therapeutics, Inc.

In the tuberculosis area, Shionogi has started joint research with Hsiri Therapeutics, which has an asset of small molecule lead compounds with a novel mechanism of action and extremely potent activity to mycobacteria. By entering into external alliances in this manner, we seek to pursue drug discovery targeting both tuberculosis and non-tuberculous mycobacterial (NTM) diseases.

Malaria

Along with HIV/AIDs and tuberculosis, malaria is one of the three major infectious diseases. Although it is most prevalent in tropical and subtropical regions, there are reports that malaria distribution has been altered by global warming and other aspects of climate change, potentially leading to an increase in infections. Shionogi started joint research with Nagasaki University, to form the core of a new open innovation base for industry-academia collaboration both inside and outside Japan, and establish a platform aimed at eradication of malaria.

Nagasaki University

The idea is to combine the malaria research assets and network of Nagasaki University, which has a worldwide presence in emerging and re-emerging infectious diseases, with Shionogi's expertise in small molecule drug discovery, to engage in world-class malaria research. There are plans also for Shionogi and Nagasaki University to form the core of a new base for open innovation incorporating external institutions with a range of technologies.

Promote proper use of anti-infectives

Initiatives to promote proper use of medicines

By promoting the proper use of anti-infectives, Shionogi works constantly to prevent the emergence of new drug-resistant bacteria and viruses, and to ensure that patients can continue to receive treatment, both now and in the future.

In our sales activities, Shionogi does not remunerate sales staff based on sales volume of antibiotics, as highly recognized in the Antimicrobial Resistance Benchmark 2018 survey. We expect that delinking of sales volume from revenue reward will support more proper use over the long term, leading to better patient outcomes and improving antibiotic sustainability.

In manufacturing antibiotics, Shionogi is working to reduce environmental burden.

In addition to promoting proper use of antibiotics, Shionogi

supports global and national action plans to conduct more timely and coordinated surveillance for resistant bacteria. We organize and provide relevant information to promote proper use and stewardship of antibiotics, by such means as conducting surveillance programs aimed at gathering accurate epidemiological data, and rigorously analyzing industry guidelines.

In order to promote proper use of our flu drug *Xofluza*, we also have been assiduously conducting further analysis on mutant viral strains and drug safety, and making our findings public.

Please refer to pages 58–59 and our EHS Report for details of Shionogi initiatives to reduce environmental burden as an antibiotics manufacturer.
http://www.shionogi.co.jp/en/company/csr/activities/environment.html

Public awareness and education programs

To promote proper use of anti-infectives, it is absolutely essential to conduct awareness-raising and educational activities that result in the understanding and spread of correct information concerning the prevention and control of disease and infection. Shionogi is actively engaging in such activities.

In an industry-government-academia collaboration geared toward combatting infectious diseases in children under five years of age, in fiscal 2018 Shionogi hosted a total of five seminars (attended by 339 nursery school operators and staff), to raise awareness about the MHLW's "Infection Control Guidelines for Nurseries," as revised in 2018. As a means of raising awareness among the general public as well, Shionogi has created a video explaining the guidelines and a website (Kodomo Kansensho Navi) to help parents navigate the subject of infectious diseases in children.

Shionogi also invited experts from across Japan and Asia to attend the SHIONOGI Infectious Disease Symposium 2019 for a discussion of AMR countermeasures in each country. Our aim in doing so was to broaden engagement in efforts to address the threat of AMR, and promote international cooperation.

Broadcast of Shionogi-sponsored program, Kansensho TODAY, on Radio NIKKEI

感染症TODAY

Targeted at medical professionals, this program seeks to convey a broad range of knowledge concerning infectious diseases by enlisting the aid of specialists to delve into the latest topics and offer educational content. In order to reach as many people as possible, the program keeps a library of past broadcasts to enable relistening.

Initiatives to combat neglected tropical diseases (NTDs)

Neglected tropical diseases (NTDs) such as leishmaniasis and Chagas disease also continue to threaten lives, particularly in developing countries. There has been limited progress, though, in developing effective antibiotics, giving rise to an international public health problem. Shionogi has been working with partners with various expertise in the healthcare area to find workable solutions to the numerous unmet needs in infectious diseases, and are applying the same approach to NTDs.

Contributing to the GHIT Fund*1

Shionogi has been a contributor to the Global Health Innovative Technology Fund (GHIT Fund) since it was founded in 2013, as Japan's first public-private partnership. In addition to contributing to the GHIT Fund, we also have received funding. Under the auspices of the fund, Shionogi is actively working to eliminate the threat not just of NTDs but infectious diseases in general, including by taking part in a program to discover candidate compounds to treat leishmaniasis and Chagas disease.

Participation in DNDi*2 drug discovery consortium

Together with several other pharmaceutical companies, Shionogi has been a participant in the DNDi's "Neglected Tropical Diseases Drug Discovery Booster" consortium since its establishment in 2015.

This consortium is an attempt to accelerate drug discovery for the world's most neglected diseases—leishmaniasis and Chagas disease—and also reduce associated costs. The consortium has started several screening projects for the parasites that cause leishmaniasis and Chagas disease, and most have discovered promising compounds with improved antiparasitic effects. Already, each project has reduced the costs of synthesizing compounds by tens of thousands of dollars and shortened the drug discovery period by roughly 50–70%. In recognition of these achievements, the consortium received the DNDi Project of the Year Award for 2016.

*1 GHIT Fund: Established to support R&D into revolutionary new drugs to fight infectious diseases in developing countries
*2 DNDi: Drugs for Neglected Diseases initiative

Material Issues to Create New Value for Customers and Society

Creating a more vigorous society

Among the social challenges that Shionogi seeks to address, one is the "creation of a more vigorous society." New drugs and other medical advances have extended average life expectancy around the world, but we still see room for improvement from the standpoint of healthy life expectancy. For example, we seek to help those with chronic pain (against which earlier drugs did not have sufficient analgesic effect) to lead more active lives. We also seek to relieve patients, their families, and friends from the impact of psychiatric/nervous system disorders and restore fuller participation in society. These aspirations inform many aspects of our daily activities.

Yoshiaki Kamoya
Senior Executive Officer

Help end suffering from pain

Helping to alleviate cancer pain over a period of 30 years

Back in the late 1980s when the WHO released its cancer pain treatment guidelines, prescription narcotics (opioid pain relievers) for cancer pain were not widely used in Japan. Shionogi already was supplying drugs for pain relief, and we received a request from the then Ministry of Health and Welfare to develop prescription narcotics. This proved to be a major turning point for Shionogi in the area of pain relief. In line with our Company Policy of striving constantly to supply the best possible medicine to protect the health and wellbeing of the patients we serve, we took on the development of MS *Contin* tablets, which we launched in 1989. In the 30 years since then, Shionogi has worked in tandem with regulatory authorities, academia, and medical professionals, to promote the proper use of palliative care and cancer pain relief. In recent years, we have launched *Symproic* tablets for the alleviation of opioid-induced constipation (OIC), with a view to realizing better pain management and improving the QOL of patients troubled by OIC.

Amid changes in the healthcare environment including the promotion of community-based healthcare and an accompanying rise in the importance of in-home care, we released tamper-resistant *OxyContin* TR tablets designed to encourage proper use of prescription narcotics in Japan, and prevent their misuse and abuse.

Going forward, we will continue striving to develop and market products that provide appropriate relief for cancer pain, addressing both the needs of patients and medical professionals, and changes in the social climate.

Measures to encourage proper use of pain relievers

Shionogi seeks to create a society in which patients suffering from cancer pain are able to use prescription narcotics with peace of mind. Recently the problem of prescription drug abuse, notably the opioid crisis in the US, has spread throughout the world, becoming a serious social problem.

To ensure that this problem does not arise in Japan, not only are we working to expand our lineup of drugs to alleviate cancer pain, but also we are taking steps in advance against misuse of opioids. In addition to helping create a society in which patients can get relief from cancer pain without causing abuse of opioids, we will work toward realization of Target 3.5 in the United Nations' Sustainable development goals (SDGs), "Strengthen the prevention and treatment of substance abuse, including narcotic drug abuse and harmful use of alcohol."

Drug abuse prevention campaign with Aichi Prefecture

May 2018: Shionogi is collaborating with Aichi Prefecture on a campaign to prevent drug abuse. To ensure that this problem does not arise in Japan, Shionogi pledges to do more to help create a society in which steps are taken in advance to prevent misuse of opioids, so that patients can get relief from cancer pain without causing abuse of opioids.

From left, Shionogi President and CEO, Isao Teshirogi, and Hideaki Ohmura, Governor of Aichi Prefecture

Dina Mired, UICC President Princess Dina Mired of Jordan pays a courtesy call on Shionogi

November 2018: Princess Dina Mired of Jordan, who serves as President of the Union for International Cancer Control (UICC), paid a courtesy call on Shionogi. We are focusing efforts on the treatment of cancer pain, and we were commended by Princess Dina for our support in helping to alleviate the pain of cancer patients by promoting the proper use of opioids and increasing access to such drugs.

From left, Princess Dina and Shionogi President and CEO, Isao Teshirogi

Combatting psychological and CNS disorders

Expanding treatment options for ADHD

ADHD is a neurodevelopment disorder characterized by three main symptoms—inattentiveness, hyperactivity, and impulsivity—and is a brain function impairment treatable by psychosocial therapy/support and medication.

Shionogi has been developing *Intuniv* and *Vyvanse* as treatments for ADHD, under a 2011 licensing agreement with Shire plc. (now Takeda Pharmaceutical) concerning joint development and commercialization in Japan.

Intuniv is a selective α2A adrenergic receptor agonist, the novel mechanism of action for the treatment of ADHD, and is a non-stimulant administered once daily. Launched in May 2017, *Intuniv* is now widely used in Japan. Furthermore, in June 2019 *Intuniv* won approval for the additional indication of treatment for ADHD in adults (aged 18 and over).

Vyvanse is a once-daily drug that stimulates the release of dopamine and noradrenaline, and blocks their reuptake. It is a prodrug that is therapeutically inactive until it undergoes gradual conversion to an active pharmacologic agent in the body, thus preventing a rapid rise in the active agent's serum level while ensuring that a steady serum level is maintained thereafter. Shionogi received manufacturing and marketing approval for *Vyvanse* in March 2019. Because *Vyvanse* is designated as raw material for stimulant, it was approved for marketing on the condition that certain measures be taken—that it should be given only to appropriate patients under prescription by medical experts well-versed in diagnosis/treatment of ADHD, and that it should be handled only by medical institutions and pharmacies, where risks including dependence can be fully controlled.

Shionogi seeks to contribute to treatment of ADHD patients by providing *Intuniv* and *Vyvanse* as new treatment options.

Support environment for more vigorous society

Support for children's bright future

Japan now leads the world in terms of its declining birthdate and graying population. Shionogi intends to build a sustainable society by creating an environment in which the children who will become our future leaders are able to maximize their potential and lead fulfilling lives.

The Office for Children's Bright Future at Shionogi seeks to lighten the psychological burden on children with a developmental disorder, with a twin focus on gaining greater understanding from society, and building and realizing a support system. As a partner in the support of children with a developmental disorder, we work together with local governments and academia, with an eye to harnessing the core competencies of all involved.

Partnering with local governments

In order to achieve earlier detection and intervention and realize lifelong support, Shionogi works in tandem with local governments to identify challenges particular to each region, and implement the necessary countermeasures.

Promoting understanding

Public seminars designed to promote wider and greater understanding of a developmental disorder
(Osaka, Hiroshima, and Iwate prefectures)

Improving the knowledge and practical skills of support staff

Workshops to enhance knowledge and practical skills among the various professions supporting children with a developmental disorder
(Osaka Prefecture, Hiroshima Prefecture, Sanuki City and Higashikagawa City in Kagawa Prefecture, Iwate Prefecture, and Yokohama City)

Training event for nursery and kindergarten teachers

Partnering with academia

With a view to building and realizing a support system for children with a developmental disorder, Shionogi is working alongside academic institutions to develop and promote useful new tools and methodologies.

Development of new tools

Development of tools to gauge the support needs and challenges faced by children with a developmental disorder, based on observation of such children at school
(Universities: Education field)

Promote training of support staff

Creation of training packages for special needs education coordinators at dedicated special needs schools and at elementary, middle, and high schools with a focus on special needs education
(Osaka Ohtani University: Faculty of Education)

Improving the knowledge and practical skills of support staff

Creation of guidebooks to support occupational health staff in assisting workers with adult ADHD symptoms
(University of Occupational and Environmental Health, Japan: Institute of Industrial Ecological Sciences' Occupational Health Practice and Management Department)

Shionogi has participated in a number of collaborative initiatives, and in May 2018 we entered into a new business alliance with Iwate Prefecture. In Hiroshima Prefecture, with which we had earlier formed a partnership in March 2018, we received recognition as a company conducting leading initiatives that can serve as a model for supporting people with disabilities.

Through this proactive approach, we aim to promote the growth and health of children who will become future leaders. We also seek to lighten the psychological burden on such children in order to help build a society in which individuals can tap their innate potential and thrive.

March 2018: Partnership with Hiroshima Prefectural Government to support our children's bright future
From left, Hidehiko Yuzaki, Governor of Hiroshima Prefecture, and Isao Teshirogi, Shionogi President and CEO

Initiatives to remove communication barriers for sight- and hearing-impaired people

Communication Barrier-free Project (CBF-PJ)
Ensuring that all patients have access to necessary information to receive benefits of best possible medicines

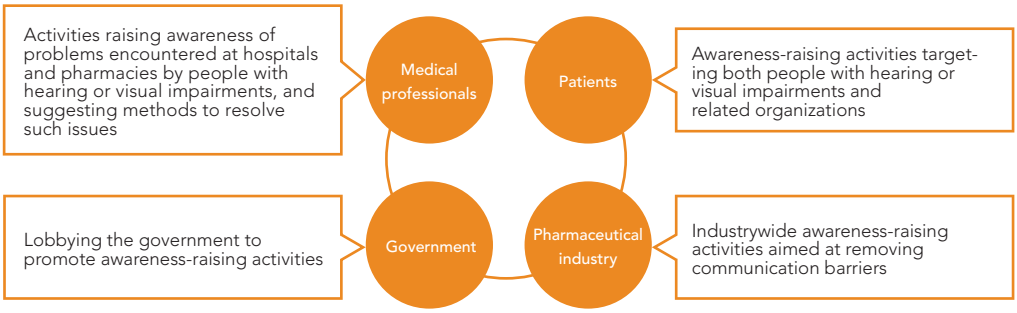
CBF コミュニケーションバリアフリー
気づきをカタチに、マイナスをプラスに

Pharmaceutical products have a direct impact on human health and life, and as such patients are provided with information—for example, through medication guidance from medical professionals—to ensure that drugs have maximum efficacy and minimal side effects.

At Shionogi, we think it extremely important that all patients—whether able-bodied or disabled—have access to the information necessary for medications to work properly. To that end, Shionogi has instigated the Communication Barrier-free Project, which seeks to improve the manner in which information is conveyed and eliminate communication barriers when people with disabilities receive medication instructions.

People with disabilities—in particular those with hearing or visual impairments—sometimes do not take medications as prescribed if they have not received sufficient information. While people with disabilities may struggle to take in information, this problem also can stem from the manner in which information is conveyed. Shionogi conducts activities aimed at educating various parties about the existence of such communication barriers. In 2018, we held a number of awareness-raising seminars targeting medical professionals, attended by 712 doctors, nurses, pharmacists, and so forth, from ten university and public hospitals.

Our aim is to contribute to creating a more vigorous society by ensuring that every individual—able-bodied or otherwise—receives the best possible medicines to protect their health and wellbeing, and is able to take these medicines in the appropriate manner.




Disability awareness seminar targeted at medical professionals


Booth exhibit at external event held by an interested party (All Japan Association of Hard of Hearing and Late-Deafened People)

The awareness-raising activities carried out under the banner of this project not only have contributed to greater understanding, but also have led to changes in behavior on the part of medical institutions.

Example: Addition of new "Ear mark" card*1 varieties

There are varying degrees of hearing impairment, and as such the type of consideration paid to patients also needs to vary. The university hospitals that hosted our seminars have since taken steps to better meet the needs of hearing-impaired individuals by adding new "Ear mark" card varieties and taking greater care when communicating with such patients.

Cards already available		Newly added cards
• "Please write it down" • "Please speak in a loud voice"	+	• "Please take off your mask" • Cards enabling patients to outline specific concerns

*1 "Ear mark" cards: Cards for presentation to hospital staff, signaling that a person is hard of hearing, and indicating the need to pay special consideration when communicating with a person who is hearing-impaired.

Create new value in the healthcare field

The current approach to social security provision is under question amid increasingly stretched healthcare budgets in advanced markets. Meanwhile, AI and ICT have opened the door to new ways of doing business in the pharmaceutical sector that were not possible in the past. Those trends mean we can no longer rely on our existing business model based solely on selling pharmaceutical drugs.

We seek to continue contributing to patients' treatment and QOL through our strength in the creation of innovative drugs, while also drawing on our expertise, skills, and experience in R&D to explore the possibilities of therapeutic and preventive vaccines, digital treatment option such as healthcare apps, and information services. By doing so, we aim to identify and address the issues that people face in all areas of healthcare, from pre-symptomatic and preventive care through diagnosis and treatment.

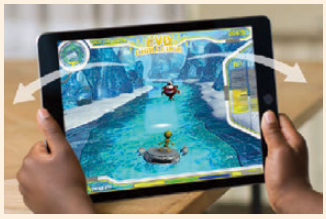
Investigational digital therapeutic, AKL-T01 (SDT-001)

AKL-T01 (Shionogi Group development code: SDT-001) is an investigational digital therapeutic for ADHD in-licensed from US-based Akili Interactive. Shionogi has acquired the development and commercialization rights for this product in Japan and Taiwan. In clinical trials conducted by Akili in the US, AKL-T01 showed a good therapeutic effect. Shionogi seeks to address the needs of ADHD patients by providing a new digital treatment option with SDT-001, along with the proprietary drugs *Intuniv*, which is currently on the market in Japan, and *Vyvanse*, which won approval in Japan in fiscal 2018.

SDT-001 operation screen

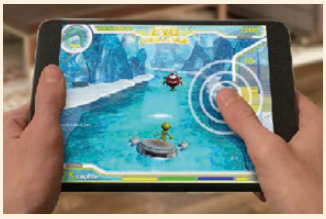
Stimulating the cerebral cortex by simultaneously performing dual tasks (steering and tapping) optimized for each patient

Steering



Steering: Avoid obstacles

Tapping



Tapping: React to specific objects

Initiatives of Shionogi Healthcare

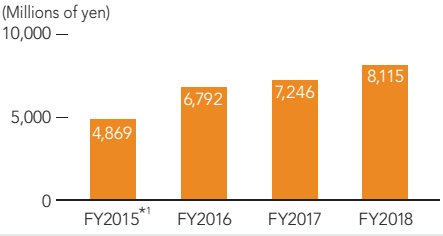
Against the backdrop of a shrinking birthrate and aging population, the role of self-care has expanded to include not just treatment, but also preventive and pre-symptomatic care, in order to extend healthy life expectancy.

Since its establishment in April 2016, Shionogi Healthcare has registered three consecutive years of growth by responding flexibly to changes in the operating environment. Going forward, Shionogi Healthcare remains committed on a daily basis to delivering new health value to patients through the provision of excellent products and service and appropriate information.

Products launched in fiscal 2018

2018	July	*Popon ai*
	August	*Isodine Clear* gargle Apple/Mint
		Pylon PL granules (24)
		Cinal EX chewable tablets e
		Cinal EX granules e
2019	March	*Kenkotsu Keikaku*
		Cinal L white EXIA

Net sales



*1. Sales in fiscal 2015 are those of Shionogi Pharmaceutical's Consumer Health Care Business Division; those for fiscal 2016 onward are for Shionogi Healthcare

Responding to societal changes arising from social security system reforms

In light of the pressure on public finances due to rising healthcare expenditures, consumers are being called upon to take responsibility for their own health, and practice self-care. In 2017, Shionogi launched *Pylon* PL granules as a cold medicine. The product was very well received by consumers, leading to the 2018 release of a larger packet. By supporting self-medication in this manner, Shionogi aspires to further improve consumers' QOL.

Addressing the evolving needs of the self-care market

June 2018: Capital alliance with Rohto Pharmaceutical

Shionogi formed a collaborative relationship with Rohto Pharmaceutical, with a view to meeting the diversifying needs of consumers looking to extend healthy life expectancy. The aim is to draw on the respective strengths of each company in working to improve QOL for as many people as possible.

Capturing the needs of a super-aging society

シオノギヘルスケア
シオノギ健康通販

January 2019: Launch of Shionogi Health Mail-order Service, offering mail order sales of functional foods

In order to strengthen our presence in support for the pre-frail and promote the long-term health of seniors, Shionogi took over the Takara Group's functional food business, commencing direct sales of health foods.

As a company seeking to support consumer health, Shionogi will focus not just on pharmaceuticals for the treatment of illness, but also on developing foods contributing to preventive and pre-symptomatic care, and on the supply of information.