NIPPON SHINYAKU

by

AERA

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and
One Tablet
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Shigenobu Maekawa

President

I am always thinking about ways to improve and enhance our drug development pipeline. The ultimate goal is "to launch at least one new drug a year." Nothing more, nothing less. This is actually what I set out to do when I became president of Nippon Shinyaku back in 2007. The company was going through a tough time in regard to drug development. Employee morale was low, and I sensed a marked lack of energy. As the top executive I had to find a way to overcome difficulties. So I made this pledge, setting a specific target. I announced that we were going to work hard to achieve the goal. I knew our backs were against the wall and all we could do was fight gallantly.

In those days, the company lacked the willingness to meet challenges, to take speedy action and investigate and analyze information. These values—challenge, speed and investigation—now serve as the company's code of conduct. In order to realize our goal, we have to strictly adhere to these three guidelines: there was no other way. I appealed to the employees again and again until I saw their eyes light up. They knew that I was committed.

Social security expenses were on the rise every year and affecting our business environment. We were facing higher hurdles that made new drug development more difficult. Despite such obstacles, I decided that the way forward for Nippon Shinyaku was to pursue originality by developing our areas of specialty. We would be the first to take on the challenge and research fields that no other company has touched, develop drugs with speed in mind, while carefully investigating the situation. The strategy has served us well. So far, on average, we have managed to launch one or more new pharmaceuticals every year. Compared to existing pharmaceuticals the new drug must be superior in at least one aspect: drug efficacy, safety, or improvement of the patient's quality of life (QOL). If not, we do not pursue development. This is the rule, and I make sure we stick to it.

As long as there are patients in need,

That is why we have strong product development capabilities in the fields of intractable and rare diseases, including pulmonary arterial hypertension (PAH). There are patients out there who are in need, while there are no established treatments. If we could come up with high-quality pharmaceuticals, we could deliver good news for these patients with rare or intractable diseases. We want to become a company that is trusted and respected by society, prove our raison d'être. That is what we strive for.

Specifically, in order to realize our goal, we established primary focus fields that center on urology, hematology, intractable and rare diseases. Through three avenues—in-house drug discovery, in-licensing from other companies and product lifecycle management (PLCM)—we seek to enhance our drug development pipeline lineup. Already, in the past decade, we have seen our revenue nearly double. We expect to achieve the financial target of the mid-term management plan to fiscal 2018 without losing any steam.

Regarding management, I support the "hands-on" management style and push for "all hands on deck"—everyone pitching in. The job site is a treasure trove of information. It is important that I visit every location, any place around the world, and carefully listen to what employees and relevant parties have to say. Sometimes I will pick up on something that I can't let pass—which usually turns out to be an issue that requires immediate attention.

Find the answer in the voice of the employee

When I am faced with such pressing matters, I know I can always make a quick decision. That is because the answer is already there, in the voice of the employee. If a lot of employees get together and brainstorm, they will inevitably come up with the best solution possible. Every employee will feel that he or she "took part in the decision-making process", and give their best when it comes to implementing the project.

The next mid-term management plan will be put together with the same "hands-on" and "all hands on deck" approach. The first year of the next mid-term management plan will be 2019, the year we celebrate the 100th anniversary of establishment of the company. It will be an occasion to express our gratitude to everyone who has supported us. We will be eyeing the future, as we mark a major milestone and renew our commitment for further development. Taking this perfect opportunity, at Nippon Shinyaku, we have just started a productivity enhancement activity project called "Challenge 100." We asked every section to come up with their own "unique challenge theme", to challenge themselves to take up a highly original, brand new assignment; and a "zero waste time theme" that will promote operational efficiency.

That said, these days, I often find myself with not much spare time. In the early days, even after I took on the role of president, my job rarely spilled into my non-working days, except for maybe a special company event or two. Things have changed dramatically. My workload has grown substantially alongside the expansion of our business operations. These few years, I have spent most of my Saturday mornings going through piles of documents and reference material. I tell everyone at the company that I will look for a solution, and I hope you will look for solutions, too. That is what our "Challenge 100" project is all about. Keeping work and life separate is one way to keep people and the workplace energized.

Our company attaches paramount importance to the pursuit of originality. We want people who can think on their own and act on their own volition to come and join us at Nippon Shinyaku. Versatility, to respond to changes in the environment; perseverence, to see things through to completion; ambition, to aim even higher. These are the three qualities that give us the strength to respond to the needs and expectations of patients who are waiting for our pharmaceuticals.

If they see that the top executive is committed, everyone on the frontline gets excited.

Their eyes light up
A new drug is currently under development in the United States and Japan. “NS-065/NCNP-01” was discovered through a collaboration project between Nippon Shinyaku and the National Center of Neurology and Psychiatry (NCNP). The drug is being developed for the treatment of an intractable disease, Duchenne Muscular Dystrophy (DMD). It is attracting much attention around the world as the new drug that could provide a breakthrough for DMD treatment.

DMD is a genetic disorder with the highest incidence found in male children. It causes a severe loss of muscle power due to a deficiency of normal dystrophin, a protein that is indispensable in constructing the “framework” of muscle cells. This deficiency arises from mutation of the dystrophin gene. DMD is a serious disease that presents a dire prognosis. After onset of symptoms, most patients will undergo loss of ambulation by their early teens. Cardiac and respiratory failures are the main causes of death, occurring in their twenties or thirties. It is also a rare disease, with an estimated 5,000 patients in Japan. No effective treatment has been established, other than steroids which delay the loss of muscle power.

The new drug under development comes from the exciting new field of “nucleic acid medicine”. Nucleic acid medicines are pharmaceuticals that are synthesized from nucleic acid, the same building blocks that compose our genes. The new therapeutic technology directly targets the genetic base of the disease and promotes protein production. Thus there are high hopes that nucleic acid medicines will make their mark as effective medical agents for treating hereditary disease. Here in Japan, major pharmaceutical companies, universities and research institutions are involved in research and development of nucleic acid medicine. Among them, Nippon Shinyaku is considered to be the top runner, closest to receiving manufacture and marketing approval of the medicine. Collaborative research with NCNP began in 2009. The whole project—R&D Administration Department, Discovery Research Laboratories, Discovery Research Laboratories in Tsukuba, Clinical Development Division—came together to take on the challenge.

Atsushi Hashimoto works for the R&D Administration Department which overlooks the project. He said: “We believe that the product we are developing will bring good news to young DMD patients. We want to conduct a solid evaluation and make sure that we can deliver the medication to patients as swiftly as possible.”

Let us take a close look at NS-065/NCNP-01 to see what kind of medicine it is (diagram on page 8). Genetic instructions are necessary for generating proteins that play an essential role in maintaining life and growth. Genetic instructions exist in sections of DNA (deoxyribonucleic acid) called “exons”. Multiple exons are linked together, and the entire DNA code is transcribed into a temporary form, to yield mRNA (messenger ribonucleic acid). The precise code for the amino acids that make up the protein is then translated to synthesize protein.

Normally, the genetic code for making the protein dystrophin is contained in 79 exons. For a DMD patient who lacks the exons 48 to 52, exon 47 is joined to exon 53 directly. The mutation results in a disruption of the “reading frame” and hampers production of functional dystrophin.

The drug under development has “ exon skipping” properties. An exon skip induces the cellular machinery to skip over an exon (to skip over exon 53, in this example) and join exon 47 directly with exon 54. Thus the amino acid code can be read, allowing for the generation of dystrophin—which may be shorter, but still functional. This is how the synthesized nucleic acid, NS-065/NCNP-01, prompts the skipping of exon 53.

Nippon Shinyaku has been developing agents for the treatment of rare diseases that affect few people around the world. Our long-term efforts directed towards drug discovery and development are coming to fruition. We have overcome numerous hurdles and are steadily paving the way toward commercialization.

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In developing the drug, the first step was to come up with a sequence for multiple compounds that make up this “nucleic acid”. Discovery Research Laboratories in Tsukuba was established in 1987 as the major research and development center on nucleic acid drug discovery. Discovery Research Laboratories in Tsukuba became the hub that propelled the study forward. Yuichiro Tone has been working with nucleic acid medicine at the Discovery Research Laboratories in Tsukuba, conducting basic research and testing efficacy in cells. Tone said: “With nucleic acid drugs, you only need to build a sequence that targets a specific gene. So coming up with a molecular design is relatively easier compared to working with traditional drugs. That is one advantage. However, when it comes to efficacy, that is another matter. You have to keep on testing to see if it works. Even when you deliberately choose a sequence, knowing it should work—at least theoretically—unexpected things happen. Quite often!” Researchers came up with one design after another. And every sequence was tested using human cells. Each test would take about a week before results could be confirmed. It was a slow and tedious process that had to be repeated countless times before the team managed to come up with the optimal sequence. Tone said that bringing in cutting-edge devices such as a nucleic acids synthesizing system helped speed up the development process.

An investigator-initiated clinical study by NCNP (from June 2013 to March 2015) was conducted, followed by a phase 1/2 clinical study in Japan which began in January 2016. A phase 3 clinical study began in the US in March 2018. At this stage of clinical trials, it is crucial to secure the quality of the drug and ensure safety and protection of human subjects. Rigorous quality control protocols covering a wide range of concerns had to be developed, including establishing a standard procedure to evaluate drug quality, and confirm the levels of impurities were within an acceptable range. Tatsuya Hamamoto is in charge of analysis and quality control at the Discovery Research Laboratories. He said: “There had been almost nothing going on regarding development of nucleic acid medicines here in Japan. So there was limited knowhow available regarding both technology and regulations. We had to overcome a number of challenges.”

One example was how to control the level of impurities. While safety had already been confirmed through animal experiments, it was still possible for internal impurities to appear while the investigational drug was in storage. And this was a drug that affects a particular gene sequence. There was the possibility of impurities affecting a different gene, which then led to another question: “In the field of nucleic acid medicine, does the technology to test for impurities even exist?” Hamamoto and his team kept on going, working closely with people in the production sector to address each difficult task.

We had to start from scratch, and even established procedures to assess efficacy

During this time, Michiyoshi Akagi at the company’s Clinical Development Department was racing around trying to find patients who were willing to take part in the trial. As stated before, DMD is a rare disease. She began her search near the company headquarters, and widened the search, even reaching out to medical institutions far away in Kyushu, to collect detailed information regarding DMD patients. Akagi said: “The investigational new drug needs to be administered once a week by intravenous drip. We were worried whether patients who lived far away from medical institutions could make regular visits for their procedure.”

According to the clinical trial protocol, trial subjects were male patients aged 5 to 17. In reality, most of the participants who took part in the trial are young boys in the lower grades of elementary school. They are youngsters who love to play and horse around. Assessment of the clinical study involves tests that measure how much a patient can walk in 6 minutes, and how long it takes for the patient to get up from the floor. It is important to find ways to get the young patients to cooperate and concentrate on the examination. Doctors, clinical research coordinators and physical therapists are constantly discussing ways to make things easier for the patients.

The most valid approach to assess the efficacy of the investigational new drug is to see if there is an increase in dystrophin levels inside the cells after administering the drug. Initially, the testing technology did not even exist. Akagi reminisced: “Everywhere we looked, we had to start from scratch. But our clinical development project team made it possible, taking us forward, step by step.”

Akagi is now busy visiting medical institutions, collecting data regarding the efficacy and safety of the investigational new drug. She commented: “Every single day, I am reminded how much the young patients and their guardians need this drug.”

Once a week Akagi shares her report with NS Pharma, Inc., a US subsidiary of Nippon Shinyaku, via audio conference. The information collected in Japan is used to help the clinical study in the US.

“We can’t lose out to other companies” It is a race against time

NS Pharma, Inc., based in New Jersey is in charge of development of the drug in the US. Taishi Yamashita moved to the US in May 2014, and quickly became one of the key members of the project team. He was instrumental in setting up the US-based clinical study, seeking out medical institutions that were willing to take part in the clinical trial, and liaising with patient associations. Yamashita collaborated with headquarters in Japan, met with clinical study consultants in the US and prominent researchers, to come up with a carefully thought-out strategy for implementing the clinical study. Yamashita said: “In the US, people in research and development are highly conscious of effective time management. There is a strong demand for speed in every respect.”

And of course, Nippon Shinyaku could not lose out against the competition. This was indeed proving to be a race against time. In Japan, NS-065/NCNP-01 received a “SAKIGAKE designation” from the Ministry of Health, Labour and Welfare in October 2015. The designation allows for a prioritized consultation, shortening the review time for regulatory approval. In the US, NS-065/NCNP-01 was granted Fast Track Designation in October 2014 in Orphan Drug Designation and Rare Pediatric Disease Designation in January 2017, from the Food and Drug Administration (FDA).

Yamashita said: “It is a once-in-a-lifetime opportunity—to see a new drug that you helped develop go on the market. I am grateful to be part of this meaningful endeavours”.

Nippon Shinyaku is aiming for commercialization in Japan at the earliest time possible. The company must prepare for a phase 3 clinical study and apply for approval. There is still a lot of work that must be completed. To “become the pioneer in nucleic acid medicine” and to “bring new drugs to patients who are waiting in hope”—these are the two goals that inspire and motivate the employees at Nippon Shinyaku. Their strong commitment and unwavering passion serve as the driving force for advancement.

| PROJECT History |
| collaborations between Nippon Shinyaku and National Center of Neurology and Psychiatry (NCNP) began |
| 2013 June |
| An investigator-initiated clinical study by NCNP started |
| 2015 March |
| An investigator-initiated clinical study by NCNP completed |
| 2015 October |
| Received “SAKIGAKE designation” from the Ministry of Health, Labour and Welfare |
| 2016 January |
| A phase 1/2 clinical study started in Japan |
| 2016 March |
| A phase 2 clinical study started in the US |
| 2016 October |
| Fast Track Designation granted by the Food and Drug Administration (FDA) |
| 2017 January |
| Orphan Drug Designation and Rare Pediatric Disease Designation granted by the FDA |

First time it was founded, Discovery Research Laboratories in Tsukuba has been advancing research on and has accumulated a large amount of knowledge and knowhow on “nucleic acid” synthesis to develop new drugs.
A wish comes true for the manufacturing department

A state-of-the-art manufacturing plant for highly active solid formulations now completed

Text: Mirei Nishidzuma (Editorial Department)
Photography: Atsuko Ohada

The construction of a new manufacturing plant for highly active solid formulations was completed in July 2017. The new plant, located at Nippon Shinyaku’s Owada Central Factory compound in Kanagawa Prefecture, is equipped with state-of-the-art facilities including a tabletting machine (bottom photograph). The plant has the ability to produce 400 to 500 million medicine tablets a year. For the time being, the plant will be producing Uptravi® tablets, for which the company received manufacture and marketing approval in September 2016. Uptravi® is used for the treatment of pulmonary arterial hypertension (PAH). In the future, the plant will continue to support the company’s endeavors to expand indications for Uptravi® from the production side, in addition to manufactur- ing the upcoming “NS-018”, a new drug now in development.

The company first began considering plans for the new production facility in fall 2014. The decision became official in the summer of 2015, while Nippon Shinyaku awaited marketing authorization for Uptravi® in Europe and the US. Mikiyo Fujiki is Department Manager, Production Planning Department at Owada Central Factory. He reminisced: “For all of us involved in production, we had this burning desire to take care of everything at our own facilities. We wanted to produce all pharmaceuticals, including highly active solid formulations that we couldn’t handle up until then, and every original in-house medicine that we were going to develop—on our own. We needed this new plant in order to provide a stable supply, and also, as a way to work on cost reduction.” According to Fujiki, the plant will also be used for Nippon Shinyaku’s consignment manufacturing business, making full use of the technology and knowhow it has accumulated as an R&D-based producer of new medicine.

The sleek “tabletting machine” manufactured in Germany was designed by a famous sports car designer. It is the first time this type of tabletting machine that compresses and seals the tablet contents has been intro- duced here in Japan.
The successful launch of a new drug does not mark the completion of research and development. The nurturing process goes on—to make the drug safer and more effective, and to seek new indications for treating a wider range of diseases. Nippon Shinyaku is carefully laying the groundwork for further growth and development.

Drugs “grow” too

Uptravi® is headed for a “full life”

The successful launch of a new drug does not mark the completion of research and development. The nurturing process goes on—to make the drug safer and more effective, and to seek new indications for treating a wider range of diseases. Nippon Shinyaku is carefully laying the groundwork for further growth and development.

We can save more patients suffering from different ailments. We can make a difference to such a worthy cause—bringing good news to all patients. On the other hand, there were the doubters: “Are we sure we want to branch out, spreading ourselves thin?”

Employees raised their voices in a mixture of hope and concern. Uptravi® is a drug that is indicated for the treatment of pulmonary arterial hypertension (PAH, diagram on page 14). The medication not only controls the symptoms but also delays disease progression. Uptravi® will provide hope for patients suffering from PAH, a disease with a high mortality rate.

Uptravi® works only on IP receptors. IP receptors bind with a lipid called prostacyclin, or PGI2, relaxing muscles in the walls of blood vessels to dilate them. Uptravi® is the world’s first oral drug that decreases the elevated pressure in the vessels supplying blood to the lungs. As an IP prostacyclin receptor agonist, it can prove effective in many ways. Hopes are high that Uptravi® can become a therapeutic drug used to treat a wide array of illnesses.

New drug development is a long and expensive commitment. It could take as long as nine to 16 years to develop a new drug. Full research and development costs could exceed 100 billion yen. After all this work, the success rate of bringing a new drug to market is a mere one in 25,000. So once you succeed in launching a drug—against such odds—you want to keep on working on it to make sure the success story keeps on “growing”.

The goal is to enrich the “life” of a drug, to make sure the drug fulfills its promise and leads a purposeful life. Nippon Shinyaku president Shigenobu Maekawa eventually came up with an initiative to promote “Product Life Cycle Management (PLCM)” (diagram on page 15), which maps the total lifecycle of a drug or compound still under development. One of the specific measures was to maximize a product’s value by adding new indications to the product. In other words, to “branch out” so the drug could be used to treat other ailments.

“We got the expected results!”

Doubts were dispelled

We were ready for a new challenge

When the scene described above took place, Uptravi® had been in development for seven years or so. It was still called by its development code, “NS-304”. Phase 2 trials were underway overseas with the cooperation of PAH patients. In order to add new indications, clinical trials had to be run for each subject disease—and clinical trials were expensive and time-consuming. And of course, there was no guarantee of success at the end of the road. This was a source of nagging concern.

In order to disperse the dark clouds of doubt from the company corridors, a project team comprised of numerous divisions, including Sales and Marketing, and Research & Development, was set up. The team took on the task of visiting and talking to every department.

Then the results of the phase 2 clinical trial which had been implemented in Europe came in. The drug was proven effective in humans. Shunji Funaki of the R&D Administration Department was a member of the explanatory team. He reminisced: “(When the report came in) the mood around the company changed all at once. We knew that things were going to be all right.”

Nippon Shinyaku took this opportunity to add another indication. The new target was: chronic thromboembolic pulmonary hypertension (CTEPH, diagram on page 14). The drug was expected to benefit CTEPH patients, just like PAH patients, through dilation of blood vessels that supply blood to the lungs.

Uptravi® tablets are packed into little boxes as they move along the conveyor belt to the forefront, where the packages undergo a visual check for spots and stains.
We team up with doctors to find optimal treatment strategy for patients

The team applied for Orphan Drug designation by the Ministry of Health, Labour, and Welfare, proposing the need for the new treatment. Designation was granted, same as PAH, and the drug became eligible for a prioritized review for regulatory approval.

The show of such overwhelming enthusiasm from the Nippon Shinyaku team motivated the doctors and helped build mutual trust. For a clinical trial to succeed, full cooperation from the doctors is a must. It is up to the project monitor, the liaison who is in daily touch with the staff, to forge a good relationship.

For one thing, the doctors have no previous experience using a drug that is still under development. During the trial there will be situations where they falter trying to make the right decision. For example, if a patient experiences side-effects, the monitoring team will receive information from the doctor and propose suitable measures. It takes a team effort to come up with the best treatment for a patient.

Every time she encounters a patient struggling with an ailment, Yamamoto is overcome by a strong wish “to do something to help”. This is what motivates her. She said: “I feel that my job could help patients around the world. The thought itself is quite rewarding”.

Let us turn back the clock a few years.

Actually, Funaki and the project team were already working on another indication. The next target was arteriosclerosis obliterans (ASO). The symptoms, called intermittent claudication, are pain and muscle cramps that occur in the legs when walking for some distance. In severe cases, symptoms include pain, ulceration, and necrosis. Arteriosclerosis obliterans is also caused by the hardening of the arteries which narrows the blood vessels, causing an occlusion. This is not a rare disease that affects few patients. So a clinical trial targeting ASO was going to be a huge one.

Still, Nippon Shinyaku decided to go ahead. There were no domestic drugs that treated intermittent claudication caused by ASO. And there were an estimated 1.5 million patients suffering from the condition. If the company could bring the drug to market, it would save that many people who were in pain. Based on information garnered from the phase 2 clinical trial for CTEPH,

Nippon Shinyaku initiated a phase 1 domestic clinical trial for ASO in 2013.

One of the monitors, Makiko Shibata from the Clinical Development Department Tokyo, took part in the production of a DVD which was to be shown at the medical institutions taking part in the trials. The DVD was prepared with a specific intent. One of the evaluations included an effectiveness measurement test using a treadmill. Every facility was different. And different people were going to administer the test. A slight change in test procedures or room temperature could easily affect the outcome.

In order to obtain a fair evaluation of the effectiveness of NS-304, all conditions had to be standardized. That is why Shibata wanted people to administer the test using a treadmill. Every facility was different. And different people were going to administer the test. A slight change in test procedures or room temperature could easily affect the outcome.

Eventually the clinical trial was on its way, almost on schedule. Eventually the clinical trial was on its way, almost on schedule. Eventually the clinical trial was on its way, almost on schedule. Eventually the clinical trial was on its way, almost on schedule. Eventually the clinical trial was on its way, almost on schedule. Eventually the clinical trial was on its way, almost on schedule. Eventually the clinical trial was on its way, almost on schedule. Eventually the clinical trial was on its way, almost on schedule. Eventually the clinical trial was on its way, almost on schedule. Eventually the clinical trial was on its way, almost on schedule. Eventually the clinical trial was on its way, almost on schedule. Eventually the clinical trial was on its way, almost on schedule. Eventually the clinical trial was on its way, almost on schedule. Eventually the clinical trial was on its way, almost on schedule. Eventually the clinical trial was on its way, almost on schedule. 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To ensure there are no safety issues, Germany. NS-304 now became Uptravi®. In order to keep the drug in 2012. She has taken up golf for a serious adverse drug reaction to occur. carefully following all instructions, there is always the possibility of the slightest harm to the human body, cause and effect will be investigated and analyzed immediately. Even if the patient is closed clinical tests. Changes in the settings and circumstances significantly compared to the time when it was being used in closed clinical tests. Changes in the settings and circumstances become manifold. Side-effects that went undetected before could show up. This is why it is essential for pharmaceutical companies to carry out post-marketing surveillance studies. At Nippon Shinyaku, the PM’s Clinical Research Department fine-tunes the contents and duration of the post-marketing surveillance study. Koyuki Tajima and her team collaborated with PMDA and chose to conduct an all-patient survey in order to collect information regarding the safety and efficacy of Uptravi® at the earliest time possible. The team sent out questionnaires to the doctors and asked them to fill in information regarding treatment. The questionnaires were collected every six to 12 months. The team combied the data to see if there were any problem issues. The findings were reported to the PMDA. More importantly, the results were also relayed to the doctors. Tajima said: “Ultimately it all comes down to the doctors to administer the medicine properly. We want to make sure they use it effectively and safely”. Even after conducting a post-marketing surveillance study, it is not all over. The Safety Management Department then takes over to continue the monitoring process. If a red flag goes up, indicating the slightest harm to the human body, cause and effect will be investigated and analyzed immediately. Even if the patient is carefully following all instructions, there is always the possibility of a serious adverse drug reaction to occur. According to Arihiro Oyamada, this is precisely when you must be ready to step in with the correct response in order to stop the situation from worsening. He said: “If you make the wrong decision, no matter how wonderful the drug—the name gets tainted. The bad reputation may never go away. You can say the drug’s ‘life’ is over”. Study abroad program in the US State-of-the-art environment for research

Nippon Shinyaku is also looking further ahead into the future, in search of the “next generation”. Kazuya Kuramoto at the Discovery Research Laboratories is conducting that important search. He began studying at Stanford University, in California, in July 2016, taking advantage of the company’s study abroad support program. The program was implemented in 2015, and encourages employees to go abroad for a maximum of two years to conduct research. Kuramoto wanted to investigate the mechanism of PAH, to find out what triggers the onset of the disease. If he can unlock the mechanism the study may lead to the discovery of a drug that would truly “cure” the disease. He hopes to find a conclusion to his hypothesis during his study in this state-of-the-art environment. Kuramoto said: “If we could define the mechanism that triggers the onset, we may be able to find a way to return the lungs to a normal condition”.

So, the journey of Uptravi® continues. Will it go on to lead a rich and fulfilling life? That is up to the commitment and good work of the Nippon Shinyaku team.

April 2016—a new project was underway at the Functional Food Division in Nippon Shinyaku. The mission was to bring dietary supplements to market drawing on the company’s strengths attained through development of health food ingredients. Nippon Shinyaku had already been successful in developing a wide range of ingredients and foodstuffs making use of its professional know-how as a pharmaceutical company. This included seasoning spices, preservatives, and protein powder ingredients. More recently, the company has been focusing on developing ingredients for nutritional foods—covering health foods and sports nutrition.

The enhanced effort came to fruition in October 2016 with the launch of a sports supplement that helps solve the problem of “energy drain” for athletes who take part in long workouts and endurance sports like marathons. The dietary supplement has two distinctive characteristics. First, during exercise, the supplement actively prompts the breakdown and conversion of stored fat into energy. Secondly, it promotes faster replenishment of glycogen supplies. The two-pronged approach enhances energy efficiency, thereby preventing energy drain.

It became the first dietary supplement that focused on these two functions. The product has been well-received by athletes in track and field and other sports, in corporate and university teams.

This was followed up by another launch in March 2017. The new dietary supplement contains polyphenols derived from mangosteen that have “glycation care” properties.

Glycation is one of the causes that contribute to accelerating the aging process. About 20 to 30 percent of the human body is made of protein. Glycation occurs as a result of covalent bonding of protein with excess sugar—sugar which was consumed as food and could not be metabolized. Glycation affects collagen and other proteins, causing hardening and other changes that deteriorate inherent functions such as water retention.

Glycation progresses with age. It is thought that irregular lifestyle habits, such as lack of exercise and not getting enough sleep, as well as stress, contribute to raising the risk of glycation. Effective anti-aging care can only be made possible by implementing regular glycation care. Nippon Shinyaku began developing this new dietary supplement to help realize this goal. The company hopes to continue developing and expanding its dietary supplement product lines in the fields of sports nutrition and anti-aging.
We are the key point of contact that connects doctors and the company. Various departments within the company including Medical Representatives (MR) and drug information services work together in collaboration to provide information about the company's products—drug efficacy and special features—along with information regarding diseases, to healthcare professionals.

We are in charge of spreading the word about our company's pharmaceutical products.

Key requirements for MRs are strong communication skills to interact with doctors, as well as expert knowledge regarding drugs and medicine. They must be ready to provide doctors with clinical data for pharmaceutical drugs. Nippon Shinyaku pays particular attention to intractable and rare diseases. Treatment for such diseases sometimes calls for unprecedented approaches. MRs need to communicate the exact information to doctors; and MRs must share the doctors' experience of administering the drug with other MRs around the nation.

We make sure the drugs reach the right people and it's not all about the tools.

Nippon Shinyaku has been putting a lot of effort in promoting Uptravi® which is used for the treatment of pulmonary arterial hypertension (PAH). Yutaka Terayama is the product leader who relays and supervises marketing strategy, market conditions, and accumulated information related to the new drug, to all MRs around the country.

Regarding the marketing strategy for Uptravi®, Terayama focused on preliminary preparations—the low-key approach of laying the groundwork. When Terayama was in sales, right at the front line, he learned from experience that every hospital had its own set of rules when it came to adopting pharmaceuticals—it was necessary to get a grasp of the different rules. Even the greatest drug would be rendered worthless if it did not reach the patients who need it. Terayama said: “MRs who work with clinics and hospitals tend to ask for new tools like pamphlets. Actually, what is most important is that each MR knows and thoroughly understands the drug”.

Terayama reaches out to doctors, mostly those who are involved in PAH treatment, and proposes using Uptravi® in combination with two other lines of medication that are already on the market. PAH is an intractable disease that is also little-known. Konaka makes a special effort to educate patients and their families. In addition to creating a website that helps people achieve a deeper understanding of the disease, he has developed a smartphone app called “PAH Care Notebook” for PAH patients.

A smartphone app helps patients take a proactive approach to treatment

Yuto Konaka supports Terayama’s efforts from his office at the Marketing and Planning Department. His job is to devise ways to promote and find a wider audience for Nippon Shinyaku products, with a focus on planning marketing strategies for Uptravi®.

In developing the app, Konaka considered various elements: What kind of functions are necessary? What could be done to make it more user-friendly? What kind of patient information does the doctor need? Through his work, Konaka offers support to patients who are battling intractable diseases. It is his work that serves as a fresh reminder of the mission of a pharmaceutical company, and brings him satisfaction and joy to be a part of it.
If patients need a remedy that is not available in Japan, we will bring it in from abroad through in-licensing. We train to become connoisseurs. The specialist needs to be aware of the marketability of a drug, and ask the question, "Will this lead us to a drug with the potential to develop?"

Masaaki Shirai of the Alliance Department said: "That is our main focus here. The real goal is to deliver pharmaceuticals to patients who need the drugs—broadly defined. It is a demanding job, but it is extremely rewarding."
Corporate Social Responsibility:
Contributing to people’s health and prosperous lifestyles

In addition to supplying high-quality products, Nippon Shinyaku actively engages in a variety of social contribution activities.

Photograph: Courtesy of Nippon Shinyaku

Baseball clinics for children

The Nippon Shinyaku Baseball Team, which competes in the Intercity Baseball Tournament and the Amateur Baseball Japan Championship, often provides baseball clinics for high school baseball players and children’s baseball teams in order to raise the level of local baseball and promote interpersonal exchanges.

Nippon Shinyaku Children’s Literary Awards

The Nippon Shinyaku Children’s Literary Awards contest was started in 2009. The contest solicits entries in two categories: stories and artwork (Column 3 on page 23).

For People Living with Disease

The Yellow Ribbon drive

Nippon Shinyaku engages in various educational activities related to disease, such as Yellow Ribbons drive to provide accurate information about medicinal plants and endometriosis, and a civic public lecture to spread correct, up-to-date information on illnesses and medicines.

Yamashina Botanical Research Institute

Yamashina Botanical Research Institute preserves and cultivates more than 3000 species of medicinal and useful plants from around the world, including rare species threatened with extinction. The institute contributes to the preservation of biodiversity through plant breeding and cultivation research.

Cultural Activities

Nippon Shinyaku’s newsletter “Kyotogakari” and calendar

Yamashina Botanical Research Institute

Our future lies in the hands of our children. The Nippon Shinyaku Children’s Literary Awards was created in 2009 with the support of the Japan Juvenile Writers Association. The award was created with the hopes of giving wings to young children’s dreams and to nurture their minds and spirits through picture books.

For the 9th Nippon Shinyaku Children’s Literary Awards which was held in 2016, we received a total of 1,965 submissions; 1,538 stories and 427 pieces of artwork from all over the nation. The panel of judges included Dr. Ryota Hosoya, a pediatrician at St. Luke’s International Hospital in Tokyo. The first prize for the story division went to Kotoba Ninpo Onomatopoeia (Onomatopoeia is word magic), which was penned by Hana Tomikawa who is in the fifth grade at elementary school. The first prize for the artwork division was awarded to Yukari Igeta’s Yoru no Ashioto (Footsteps by night).

Tomikawa, the budding young author, said: “I was really surprised. This prize is going to be my first step to realizing my dream.” Igeta commented: “(Tomikawa’s) story is full of movement. It is very different from my style.”

One of the judges, Shozo Taimamoto, creator of children’s picture books, praised Tomikawa’s story-telling: “It is a unique piece of work full of speed and rhythm.”

Igeta, the first prize winner for artwork, added pictures to this story. Nippon Shinyaku produced 30,000 picture books and distributed copies to children nationwide through medical institutions and public facilities. In addition to the literary award, the company established the “Kira Kira Mirai Kodomo Bokin” children’s fund in 2009. When supporters give to the fund they receive a picture book in return. All donations are used for activities to support children.

We are turning lively, carefree ideas into picture books.

Text: Toshizo Shimizu (Editorial Department)
Photographs: Akina Ohtsuka

*22*
I seem to have an intriguing connection with Kyoto. After graduating from university I began working as a pediatrician at St. Luke’s International Hospital in Tokyo. That is where I met Dr. Kozo Nishimura, who was pediatrician-in-chief at that time. It was this encounter that led me to specialize in childhood cancer. Dr. Nishimura was originally from Kyoto. He graduated from Kyoto Prefectural University of Medicine, and soon after World War II, went overseas to train as a clinician at Boston Children’s Hospital in Massachusetts. The hospital was already offering innovative childhood cancer treatment. At a time when childhood cancer was still considered “incurable”, doctors at Boston Children’s Hospital were treating children using chemotherapy, opening doors to new possibilities in the battle against childhood cancer.

After returning to Japan, based on his experience at Boston Children’s Hospital, Dr. Nishimura introduced a new approach to treating cancer. Total care is a coordinated approach that employs every type of treatment available, including chemotherapy and radiation. Team care was brought to St. Luke’s. It was Dr. Nishimura who made the suggestion that I should “go see the progress being made in childhood cancer treatment”. I took his advice. In the late 1970s I began working at the University of Texas MD Anderson Cancer Center. To be honest, I was flabbergasted when I saw former patients who had overcome leukemia, now all grown up, walking into the hospital with their own children in tow. It made me ponder, “What is the medical care that would help us in Japan?” I kept my eyes peeled and my ears open. I wanted to pick up everything I could and study really hard. In those days, the biggest challenge for doctors in Japan was finding a way to prevent childhood cancer from recurring. Especially worrisome were central nervous system relapses of childhood leukemia. In the US, treatments such as administering drugs into the bone marrow cavity, or administering large dosages of drugs intravenously were proving effective. After returning to Japan, I decided that I wanted to use one such drug, “Cylocide”. I found out that the drug was manufactured by Nippon Shinyaku, a company based in Kyoto. So I got in touch with the company’s medical representative (MR) to talk about my request. That was the beginning of my friendship with Nippon Shinyaku.

During the years, I continued to meet with and trade information with many Nippon Shinyaku MRs. I came to realize that there was a “distinctive feel” to the company that was quite different from other pharmaceutical companies. First of all, Nippon Shinyaku puts out a unique public relations magazine. Normally, pharmaceutical companies put together PR magazines brimming with medical information. But Kyo, Nippon Shinyaku’s PR magazine which first came out in 1967, takes a novel approach. The cover art depicts seasonal scenes of Kyoto. Inside, there are many articles that spotlight local cultural assets and discuss traditional crafts. You don’t have to be a doctor to enjoy the magazine.

When the MRs from Nippon Shinyaku came over with new information regarding pharmaceuticals, without fail, they would leave me with a new copy of Kyo. Some MRs were assigned to St. Luke’s for many years and we ended up becoming good friends. Mind you, I have been practicing medicine for more than 40 years but I have rarely made friends with MRs. I heard that in the olden times, during the Edo period, avid sumo wrestling fans would look out for a favorite sumo wrestler, cheering him on as he rose in ranks. In Kyoto, I heard that there is a similar hobby involving young monks. People would make note of a “promising” young monk and be tickled pink when he became a top priest at a renowned temple. It was the same with me. I just loved watching a young MR from Nippon Shinyaku make his way; get promoted, and climb the corporate ladder. It is not only their PR magazine that stands out. The company produces a beautiful calendar every year using Kyoto’s traditional “kataezome” stencil-dyed prints. In 2009, the company created the “Nippon Shinyaku Children’s Literary Awards” for which I am a member of the selection committee. Furthermore, the company has its own baseball club. The team is a regular contender at the Intercity Baseball Tournament and other nation-wide tournaments.

Amateur baseball is a sport that is rooted deep in the psyche of the Japanese people. And the Intercity Baseball Tournament is the pinnacle of authentic amateur baseball. Apparently, Nippon Shinyaku is a company that takes its cultural activities and pursuits seriously. There is nothing half-committed about this business. It shows that they have an extremely mature corporate culture. Lately there has been a surge of mergers and acquisitions (M&A) taking place in the pharmaceuticals industries. Pharmaceutical firms are getting bigger; scaling up. Maybe that is why corporate images seem to blur and their colors blend into one another. Nippon Shinyaku may not be one of the pharmaceutical giants, but manages to stand distinctly independent. The company actively pursues development of pharmaceuticals to treat intractable and rare diseases that big-name companies rarely go after. We are also seeing a new crop of drug companies with special features emerge in the field of generic medicine. It is important that we have a contingent of such companies—with distinct strengths and features—when we consider Japan’s medical scene. And I feel that Nippon Shinyaku is at the forefront, the leader of the pack. I hope the company will continue to grow without ever losing their inherent goodness.

Ryota Hosoya: Was born in 1948 in Yamagata Prefecture. He graduated from Tohoku University School of Medicine in 1972. After graduation he joined the Pediatric Department at St. Luke’s International Hospital in Tokyo. He was with the University of Texas MD Anderson Cancer Center in Texas, USA, from 1987 to 1990. After returning to St. Luke’s, he became deputy director, head of ambulatory care center for children, and now serves as advisor. His field of specialty is childhood cancer. He is also a haiku poet who uses the pseudonym Hosoya Ryoryo.

A writer
With the trained eye of a doctor
My take on Nippon Shinyaku

“The company has a deep, mature corporate culture”

Nippon Shinyaku is a pharmaceutical company also known for its unique CSR initiatives. So how does the company measure up in the medical scene? Ryota Hosoya, a pediatrician and poet, shared his thoughts about Nippon Shinyaku.

“It eventually became close friends with the MR”
From Kyoto We Aim for the Future

Nippon Shinyaku has steadily paved its way supported by creative ideas and solid technology. It is proud of its long history as a unique developer supported by creative ideas and solid technology.

Company History

1911 Founded “Kyoto Shinyakudo”

1919 Founded Nippon Shinyaku Co., Ltd., taking over operations of Kyoto Shinyakudo

1940 Launched Japan’s first domestically produced antihelmintic, Santonin

1953 Opened Yamasaki Plant Materials Laboratory (now Yamasaki Botanical Research Institute)

1954 Completed construction of Nishi-jo Plant

1957 Relocated headquarters to current location in Minami-ku, Kyoto City

1960 Concluded business alliance agreement with Kurakake Pharmaceutical Co., Ltd. (now Nippon Shinyaku subsidiary, New Pharmaceutical Co., Ltd.)

1961 Established Food Division (now Functional Food Division) and entered the food business

1962 Completed construction of Research Laboratory (now Discovery Research Laboratories, Building B) at company headquarters

1964 Completed construction of Odawara Factory (now Odawara Central Factory)

1965 Established Nippon Shinyaku subsidiary, Royal Motors Co., Ltd. (now NS Shared Service Co., Ltd.)

1966 Was listed on Tokyo Stock Exchange

1967 Concluded business alliance agreement with Tajima Starch Manufacturing Co., Ltd. (now Nippon Shinyaku subsidiary, Tajima Food Industry Co., Ltd.)

1970 Completed construction of Food Development Laboratories

1971 Opened Occupational Office in Germany

1973 Completed construction of the Discovery Research Laboratories in Tsukuba

1979 Established US subsidiary, NS Pharma, Inc. (formerly Nippon Shinyaku New York Office)

2001 Completed construction of new plant for pharmaceuticals formulation production in Odawara Central Factory


2009 Created “Nippon Shinyaku Children’s Literary Awards” to mark the 90th anniversary of foundation

2011 Opened Beijing Representative Office in China

2012 Relocated Dasseldorf Office to London, UK

2016 Completed construction of Active Pharmaceutical Ingredient Manufacturing Building at Kyoto Headquarters

2017 Launched Pulmonary Arterial Hypertension agent Uptravi® in the US, which was followed by successive launches in Europe, Japan, and other countries

Completed construction of manufacturing facility for highly active solid formulations in Odawara Central Factory

Corporate Profile

Corporate Name Nippon Shinyaku Co., Ltd.

Founded November 20, 1911

Date of Incorporation October 1, 1919

Representative Shigeru Okawara, President and Representative Director

Capital ¥5.2 billion

Net Sales ¥98.7 billion (for the year ended March 31, 2017)

Ordinary income ¥16.2 billion (for the year ended March 31, 2017)

Employees 2,011 (as of end of March, 2017)

Head Office 14, Nishinosho-Monguchi-cho, Kisshoin, Minami-ku, Kyoto 601-8550, Japan

Phone +81-75-321-1111

Major Offices, Plants and Laboratories

Tokyo Office

Business Office

Sapporo, Tochigi, Kakamoto-Kashihetsu, Tokyo, Saitama, Chiba, Yokohama, Nagoya, Osaka, Kii-Hokuriku, Kobe, Chushikoku, Kyushu

Business Branches

Asahikawa, Komatsu, Kikuchiku, Utsunomiya, Banbi, Niigata, Nagano-Yamanashi, Tokyo, Tama, Yokohama, Shizuoka, Hokuriku, Himeji, Okayama, Shikoku, Fukuoka, Nagasaki-Gaga, Kumamoto, Miyazaki, Kagoshima, Okinawa

Discovery Research Laboratories, Discovery Research Laboratories in Tsukuba, Yamashina Botanical Research Institute, Food Development Laboratories, Odawara Central Factory, East Logistic Center, West Logistic Center

Domestic subsidiaries and affiliated companies

Sioe Pharmaceutical Co., Ltd.

Tajima Food Industry Co., Ltd.

NS Shared Service Co., Ltd.

Overseas offices and subsidiaries

NS Pharma, Inc.

Beijing Representative Office

London Office

Business Philosophy

Helping People Live Healthier, Happier Lives

Corporate Slogan

To build a healthier future

Our goal is for people to live “longer, healthier lives”. Nippon Shinyaku is an R&D-based company that produces medical products and functional food to help people enjoy “fruitful”, “healthy” and “energetic” lives.

Functional Food 13.6%

Drugs for otorhinolaryngology 8%

Other 37%

Drugs for hematology 14.9%

Drugs for rare diseases 5.2%

Drugs for care of the elderly 5.1%

Pharmaceuticals 86.4%