**Business Activities**

**Pharmaceuticals R&D**

Focused mainly on the four key areas of urology, hematology, intractable and rare diseases, and gynecology, we are targeting areas of disease with unsatisfied therapeutic needs and supplying distinctive products of high quality to patients.

Having the R&D capabilities we have developed to date, we are continuing to create new value by widening the scope of drug discovery through the addition of new modalities and technologies to the drug-discovery platform that produced the small molecule drug Uptravi and nucleic acid drug Viltepso. We are focused on in-licensing and product life cycle management (PLCM) to enhance the R&D pipeline so that we can launch a stream of new products in Japan and target overseas markets.

Akira Matsuura Managing Director, Head of R&D

**FY2019 Review**

Two drugs launched for diseases with unsatisfied therapeutic needs

We launched Defilixio (development code NS-73, generic name defibrotide sodium) in Japan in September 2019 after the drug received regulatory approval in June 2019 for treatment of sinusoidal obstruction syndrome. It was granted orphan drug designation in May 2019. As the first product approved for this indication, it is expected to make a significant contribution to treatment of DMD patients. An NDA was filed in the US in February 2020, and we are currently preparing for launch once-US regulatory approval is received. Joint international Phase III clinical trials for this drug are also underway.

Originally launched in 2016, pulmonary arterial hypertension treatment Uptravi (development code NS-304, generic name selexipag) is in Phase III clinical trials that are being conducted jointly with Janssen Pharmaceutical K.K. for the additional indication of chronic thromboembolic pulmonary hypertension (CTEPH). The drug has received orphan drug designation from MHLW for the CTEPH indication. We are also conducting two separate clinical trials for selexipag for the indications of arterial stiffness obliterans (late-stage PI) and lumbar spinal stenosis (early-stage PI).

**Medium-to-long-term Outlook**

Build pipeline by creating products offering new value through broad-based R&D program

Building on our successes in small molecule and nucleic acid drugs, we are working to broaden our drug-discovery capabilities by integrating new technologies such as AI and induced pluripotent stem cells as well as new modalities such as gene therapy. Our aim is to maximize the potential of our internal and external resources by promoting open innovation.

Creating new value via such R&D activities, we aim to generate a constant stream of distinctive products to treat diseases with unmet therapeutic needs. Moreover, by building an organization with global R&D capabilities, we plan to provide these distinctive drugs to patients worldwide.

**Growth Strategy**

Develop pipeline by strengthening in-house drug discovery, in-licensing and product life cycle management (PLCM), and via higher productivity

**Our Will**

The challenge of R&D for intractable diseases

As a project manager for development themes, I craft strategic proposals for our success in R&D and sales, and I work on time management issues. Recently, I have been focused on the nucleic acid drugs to succeed viltolarsen. This global project aims to create products to help patients worldwide with diseases that currently have no treatment. Nucleic acid drugs also offer potential solutions to treat intractable conditions. Delivering these products is our goal, but we are also conscious of the need for speed because patients suffer while waiting for treatment. In the future, we also hope to develop products that offer value for patients by pursuing development themes based on the introduction of new treatment modalities.

Jin Hiruta Project Management Section, R&D Administration Department

**Our Code of Conduct**

Customer First

Customer First

Customer First

Customer First
Business Activities

Pharmaceuticals Sales

The mission of the Sales and Marketing Division is to provide medical professionals with high-quality information about appropriate therapies so patients can access them as early as possible.

Acting as a treatment partner for patients based on the trust of the medical profession, our basic policy is to ensure integrity in everything we do as we seek to provide information promptly to health professionals based on proper evaluation of related needs.

Shouzou Sano Managing Director, Head of Sales and Marketing

Growth Strategy

With healthcare evolving at the community level in Japan, develop systems to provide information to cater to the increasingly diverse needs of each area; realize faster and more advanced provision of information, supplementing the detailing by MRs by deploying regional and central technical specialists in each therapeutic field.

FY2019 Review

Results driven by rapid market penetration of new products in core areas of focus

We strove to provide high-quality information in the three areas we have identified as core areas of focus: urology, hematology, and specialty domains.

In the urology field, we launched two new prostate cancer treatments in Japan, Erleada in March 2020 in co-promotion with Janssen Japan, Erleada in May 2019, and Zytiga in February 2018, in co-promotion with Janssen Japan. We are contributing to the penetration of new products in the urology field.

In the field of hematology, in August 2019 we launched Defitelio as Japan’s only treatment indicated for sinusoidal obstruction syndrome. This supplement’s Vidalta for myelodysplastic syndromes and Gazyva, a treatment for CD20-positive follicular lymphoma. In serious cases, sinusoidal obstruction syndrome in the liver can be fatal at a high rate due to multiple organ failure.

There has been rapid take-up of this drug since previously there was no approved treatment in Japan.

Nippon Shinyaku is the only company in the world that offers three oral treatments for pulmonary arterial hypertension – Adcirca, Opsumit and Uptravi – that each have a distinct mechanism of action. Elsewhere, in May 2020, we began selling Vilepsio, Japan’s first nucleic acid drug for treatment of Duchenne muscular dystrophy (DMD). MHKJ had earlier granted Sakagane designation (for accelerated approval) and conditional early approval. Since it represents the first-ever treatment for DMD, we are focused on detailing this drug so patients can gain early access to it.

We have deployed specially trained MRs to each region to focus on detailing this product.

Development of technical support system at regional level

Nippon Shinyaku MRs receive ongoing training to improve their knowledge since many of our products treat rare or life-threatening conditions. We have an internal system of examinations to grade MRs on their level of medical knowledge. By providing training to help MRs ascertain the varied needs of medical professionals accurately, as well as role-playing and other training, we are raising the quality of our detailing activities.

From fiscal 2019, we began deploying technical specialists in each therapeutic field across the regions to provide highly specialized detailing to supplement information provided by MRs. Each technical specialist coordinates with local MRs to ensure rapid responses to the needs of medical professionals. Independent market research done in 2019 awarded Nippon Shinyaku high marks for the quality of medical detailing.

Launched in Japan in May 2020, the nucleic acid drug DMD treatment Vilepsio demands a high level of specialized knowledge for detailing.

Creation of system to cater to regional healthcare needs

Sales set-up and detailing activities

The recent shift in Japan to systems that promote comprehensive healthcare solutions tailored to local needs means we must ensure detailing activities meet these diverse requirements.

In response, we have reorganized our sales force into 113 sales teams, spread across 13 business offices and 43 business branches, so that we can provide information quickly. Each MR draws up a detailing plan for their sales territory, and these are used as the basis for planning the provision of information at the team, office and branch level.

Besides MR detailing, we strive to provide information on appropriate use of products by holding briefings, lectures, seminars, and other events.

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We continue to develop our training systems and sales set-up to ensure our medical professional detailing activities meet high quality standards.

Medium-to-long-term Outlook

Shift to “omni-channel” detailing approach that combines MRs with digital channels

Traditionally, MRs have collected information and provided detailing to medical professionals in person. However, the use of digital detailing channels has increased in recent years. With the COVID-19 pandemic severely restricting the opportunities for face-to-face detailing by MRs, the shift to digital channels can only accelerate. More medical professionals are also accessing information via digital channels, in line with the trends at pharmaceutical companies.

In future, we expect a shift towards an “omni-channel” approach to medical detailing combining MRs with the use of digital platforms.

We are already using various digital channels to provide information to medical professionals, including e-detailing, webinars, web-hosted interviews, and remote detailing methods. At the same time, MRs fulfill a critical role in helping to gauge the true needs of medical professionals and respond appropriately. We are shifting to an “omni-channel” approach that emphasizes the respective roles of MRs and digital platforms so we can fulfill our core mission in Sales to help patients gain access to the proper therapies as quickly as possible by focusing on providing information on appropriate use of products.

Finding the way with colleagues sharing their wisdom and passion

Conditions in the pharmaceutical market are changing rapidly, and it is sometimes hard for MRs to perceive the correct option. Yet we must continue to overcome the challenges posed by changing conditions so that as many patients as possible can gain early access to these valuable medicines.

While the correct option may be difficult to see, I have many Nippon Shinyaku colleagues across Japan who stimulate me to face these challenges by imparting wisdom and sharing their passion. Working across interdepartmental boundaries and united by traditional thinking, together we can find a way to meet every new challenge and contribute to better patient treatment.
Pharmaceuticals Production

We set four goals as part of achieving the 6th Five-Year Medium-term Management Plan, and formulated 20 specific policies to achieve them. We achieved most of the intermediate fiscal 2019 targets on our policy roadmap. In particular, we made steady progress in preparing the global supply chain needed to support future in-house sales of Viltexpo in the US market, reflecting the huge collective efforts of the Departments in Resource Procurement, Production & Assurance.

We remain focused on achieving the goals and broader objectives of this plan, based on our mission of providing patients with a stable supply of pharmaceutical products.

Hitoshi Saito
Director, Head of Resource Procurement, Production & Assurance


Growth Strategy
Establish global supply and reliability assurance systems

In fiscal 2019, we continued establishing global supply and reliability assurance systems ahead of the planned launch of Viltexpo in the US market in fiscal 2020. Specifically, we prepared for FDA inspections of related manufacturing sites; built up our local sales network in the US, along with regulatory and medical operations; and compiled a safety database and operating procedures. We also analyzed gaps in our Odawara Central Factory operations relative to global standards, assuming in-house production, and assembled a coordination team to handle any adjustments.

Building on the success of the previous medium-term management plan, we enhanced supply chain productivity by reinforcing our stable supply framework while improving operational efficiency and cost management practices. Specifically, we focused on ensuring the quality, efficacy and safety of APIs and finished products through the development of quality management systems. We also targeted cost reductions for API procurement and logistics with our mainstay products as part of our lowest-cost management approach. In terms of risk mitigation, we maintained inventory target levels and managed our supply chain to ensure uninterrupted supply of products, and we reviewed emergency manuals as part of the promotion of the Business Continuity Plan (BCP).

Medium-to-long-term Outlook
Focus on establishing global supply system while evaluating nucleic acid drug-related capex

The overseas markets of the US, Europe, China and other developing economies are increasingly important for us as conditions become more competitive within the Japanese pharmaceuticals market. To develop these markets aggressively, we are building a global supply system as well as developing logistics infrastructure compliant with Good Distribution Practice (GDP) and reliability assurance systems to handle overseas inspections and regulations.

In addition, we are adapting the Odawara Central Factory to the market shift into specialty domains and to more diverse pharmaceutical modalities. Specific measures include production of highly bioactive small formulations as part of the PLCM development of setipivox and the evaluation of potential capital investments relating to nucleic acid drugs. Alongside this, we continue to focus on boosting profits by cutting procurement and logistics costs as part of our cost management approach.

Quality Assurance and Supply Stability
Ensuring reliability from R&D to production and post-marketing

Efforts at Nippon Shinyaku to ensure the required quality, efficacy and safety of pharmaceuticals are led by the Regulatory Affairs, Safety Management and Quality Assurance Divisions. Non-clinical and clinical studies are conducted at the R&D stage, after which we prepare application documents to obtain manufacturing and marketing approval. These documents are audited by the Regulatory Affairs, Safety Management and Quality Assurance Division at the appropriate stage to ensure the reliability of data from all R&D studies.

After manufacturing and marketing approval is gained, work continues to ensure full compliance with the terms of approval via close cooperation between the general marketing supervisor, QA manager and safety manager. This ensures compliance with approved matters and proper maintenance and management of the license for marketing and license for manufacturing as part of ensuring the quality and safety of the products, thus fulfilling our responsibilities to the market.

Pharmaceutical products reliability assurance

<table>
<thead>
<tr>
<th>Non-clinical tests</th>
<th>Clinical tests</th>
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<tr>
<td>Raw data reliability assurance based on GDP and reliability criteria</td>
<td>Clinical trials reliability assurance based on GDP and reliability criteria</td>
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The Quality Assurance Department develops our pharmaceutical QA systems in full compliance with Good Quality Practice (GDP) and Good Manufacturing Practice (GMP). We constantly work to improve quality systems, product quality and resource allocation via management reviews. As we develop our US business, with the aim of creating world-class pharmaceutical QA systems, we are building local QA infrastructure in the US, investing in English communication skills, and recruiting and training people with QA-related knowledge and experience in overseas markets.

Securing stability of supply

In fiscal 2014, we introduced an in-house accreditation system for qualifications at the Odawara Central Factory to support multi-skilled development by employees. In addition, as part of our vision to make the factory competitive in terms of cost and quality, we have introduced BSC management to help us formulate and realize strategy based on a multifaceted perspective that covers financials, customers, business processes, human capital and workplace reforms. We are also using KPIs to evaluate progress. On the logistics side, we have developed systems to manage temperature during storage and transport and to distribute inventory across multiple sites to mitigate disaster-related risks while preserving quality.

Building QA systems for pharmaceuticals

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Outlook

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- "Build QA systems for pharmaceuticals
- Securing stability of supply
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Outlook

Sustained growth through a global supply chain

I am leading our project to build a global supply chain for Viltexpo, from the procurement of raw materials to the supply of products to Japan and overseas markets. Building a supply chain in the US in particular is a first for Nippon Shinyaku, and it has been a case of trial and error. However, we have been conscious of the need to get innovative drugs to patients as quickly as possible through the efforts of the whole company. The process involves not only NS Pharma, the Group’s US subsidiary, but also many other divisions. My role is to ensure it flows smoothly based on good interdepartmental cooperation and communication. Establishing a US supply chain that is compliant with local laws and regulations has been a challenge, but we have solved the issues one at a time by working out how best to succeed together. My hope is that future business development based on this global supply chain will translate into sustained growth.
Functional Food

The Functional Food business takes a different approach from the Pharmaceuticals business in helping people to lead healthier and happier lives. Besides supporting people’s daily dietary habits, we aim to promote better health using health food ingredients and supplements and address societal challenges such as food waste. We aspire to be a significant contributor to people’s improved health and longevity by bringing to market a continuous stream of highly innovative products, based on our efforts to upgrade R&D capabilities.

Kenro Kobayashi  Director, Head of Functional Food

In supplements, which are a growth driver for the Functional Food business, we are focusing on the two sectors of sports supplements and aging care products. Our aim is to develop supplement ranges that are brand leaders among athletes, while also leveraging our status as a pharmaceutical maker to be a pioneer in supplying supplements that help to prevent disease or provide aging care benefits.

In the bulk materials business, which is the major part of the earnings base, we are investing in R&D in three core focus areas: health food ingredients, preservatives, and protein preparations. Distinctive products in each of these areas were released in a systematic fashion in fiscal 2019.

Based on these initiatives, we posted higher sales and profits in each of the three core focus areas of health food ingredients, preservatives, and protein preparations.

FY2019 Review

Higher sales and profits achieved via introduction of innovative high-value-added products in every core area of focus

In an era when more people are reaching 100 years of age, the goal is not merely to live a long time, but also to lead a rich and meaningful life. The low birth rate and aging population in Japan has caused huge growth in social healthcare spending, prompting governments to try to lower healthcare costs by promoting early diagnosis and treatment of diseases, greater use of OTC medication, and taking more responsibility for one’s own care.

These trends have cultivated increased health consciousness among Japanese, and this is magnifying the role of evidence-based health supplements and health foods.

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TOPICS

Mangostia: Japan-first FFC (Food with Functional Claims)

Known as the “queen of fruits” for the delicate flavor of its white flesh combining sweetness with acidity, the mangosteen is a tropical evergreen of the family Hypericaceae. We were the first in the world to discover in mangosteen peel a functional ingredient called rhodanthene B that possesses strong anti-glycation properties.

As discussed recently in the media, glycation is an internal process in which proteins react with any excess sugars. It is now known that glycation can cause proteins to lose their original function, with various negative effects on the body. Our studies have demonstrated improved water retention in the skin among a group taking a mangosteen extract compared with the placebo control group, pointing to the benefits of glycate stress reduction in terms of enhanced moisture retention by the skin.

We have since developed and launched Mangostia as Japan’s first approved Food with Functional Claims (FFC) where the underlying mechanism of action is based on glycate stress reduction. This product has made a big impact within the industry. Its designation as an FFC prompted many inquiries from consumers.

Kikuo no Kobako “Little Box of Memory”: a supplement designed to support cognitive function

Kikuo no Kobako is the first FFC to use bacopa saponins* as the functionally active ingredient. It has been reported that taking three capsules per day can help to enhance memory (the cognitive function enabling the memorization and recall of information used in daily life, which deteriorates with age).

According to the WHO, the number of dementia sufferers worldwide increases by one every three seconds. This is a serious problem in Japan, where the population of dementia patients is forecast to exceed 7 million by 2025 due to the rapid aging of society. With no effective treatment for dementia yet established, and with lives developing in the brain for 10-20 years before symptoms appear, the early use of evidence-based supplements offers one potential approach to disease prevention.

Going forward, we will seek to develop various aging care products.

* Bacopa saponins are contained in the Bacopa monnieri plant, an herb used in traditional Indian Ayurvedic medicine for its memory-function benefits. It has been reported that these substances work by boosting neural transmission, adding the process of laying down and recalling memories.

Medium-to-long-term (see pg. 28) Outlook

Expand revenues from supplements business while helping to address societal issues

We see our mission as contributing through food the prevention of disease and the extension of healthy longevity. In the bulk materials business, which constitutes most of the earnings base of the Functional Food business, we face a contraction of the processed foods market due to Japan’s falling population, with fierce price-based competition as ingredients become commoditized. Leveraging our R&D expertise as a pharmaceutical maker, we have sought to create new markets and transition to a higher-margin business by bringing to market high-value-added products that satisfy market needs. Moreover, based on these R&D capabilities, we are positioning the development and supply of final products that can translate in-house concepts directly into consumer benefits as a major growth driver, with the aim of improving profit margins further.

Our efforts to develop preservatives contribute to the realization of SDGs by helping to reduce food loss via wasteage. We expect this contribution to continue as we try to develop original technology to extend shelf life while preserving taste, thereby reducing how much food is destroyed.

In this way, our policy is to increase profits from the Functional Food business while contributing to efforts to address societal issues.

Developing original health food ingredients

I am searching for original health food ingredients to use in innovative Nippon Shinyaku aging care products. In particular, my work focuses on the field of anti-glycation materials, a critical area for the Functional Food business. We are doing joint research with universities in this area, based on our in-house library of plant extracts.

The material search processes are conducted by a team, and part of my job is to motivate the team. For example, by increasing the opportunities for team members to communicate, it helps everyone understand the purpose of the process and makes us more aware of what we can do. The enhanced awareness helps work to proceed more efficiently. In addition, in collaboration with universities and other groups, we are trying to gather information from as wide a range of contacts as possible so our materials development work produces truly unique results.

Kenjiro Hayashi  Food Development Labs, Functional Food Division