

Through a fusion of intellectual assets from within and beyond the company, and through accelerated product development, we are aiming for growth in the health care field, and particularly growth in cancer-related treatment areas.



Haruo Inose
Senior Managing Director
Representative Director
Director of Pharmaceuticals Group

A product lineup aimed at strengthening and streamlining our focused research and development for cancer-related products

In the pharmaceuticals business, we are actively investing our business resources for the development of cancer-related products, and are continually working to strengthen our business base in this area. For research and development in particular, we are working to create a fusion of technologies from within and beyond the company, and also to accelerate the development and marketing of a broad range of anti-cancer drug products. For this purpose, we are actively engaged in alliances with other companies.

Nippon Kayaku currently sells 17 anti-cancer drugs in Japan, and during our many years of experience we have accumulated a wealth of diverse information covering the entire anti-cancer drug field. In order to apply this information in the best way to efficient business practices, we are actively introducing new products and proceeding with joint development to constantly strengthen our product lineup.

Broad-based research activities in the anti-cancer products field

The demand for effective cancer treatment will continue to increase in the future. In addition to demands for improving the utility of anti-cancer drugs that are currently on the market, there is also a strong demand for new anti-cancer drugs. In response, Nippon Kayaku is proceeding with joint development together with NEC Corporation to create a highly advanced "insilico screening system" which can rapidly identify candidate compounds from a vast compound library.

In addition to our conventional research into anti-cancer drugs, we are engaged in research over a broad range of areas. Examples include the development of a drug delivery system (DDS) in which an anti-cancer drug is contained inside nano-size polymer micelles, and the development of anti-cancer drugs that are effective against hormone-dependent cancer. As part of our corporate focus on company-wide research and development, we have also established a development venture (Nanotherapy Co., Ltd.), centered on Nippon Kayaku and incorporating links with universities and industry. Research at this venture company is being conducted for heat immunotherapy, in which heat is applied to treat cancer.

Lineup of cancer-related products

At present, Nippon Kayaku has marketed 17 anti-cancer drugs, two analgesics for cancer-related pain, and two cancer diagnostic agents. Development of new pharmaceuticals is especially focused on anti-cancer drugs, and we will continue to strengthen our product lineup in this important area. Because combined therapy is most often used by medical institutions for cancer chemotherapy, in addition to providing and collecting information concerning our own products, it is also possible for us to collect information concerning the administration, efficacy, and side effects of anti-cancer drugs in general, including the products of other companies. This allows us to collect a greater amount of information concerning anti-cancer drugs for research, production, and sales. We are further strengthening our lineup of anti-cancer products, because this allows us to provide information that is useful for actual treatment and to expand our business. In 2003 we introduced HYCAMTIN® from GlaxoSmithKline and CARBOMERCK from Merck Hoesl, and in 2004 we introduced ONCOVIN and EXAL from Eli Lilly Japan. We will continue to actively pursue the introduction of new products, joint-development products, and similar efforts in the future.

Strengthening our ability to provide information and reinforcing our specialist medical representatives (MRs)

Cancer treatment today is generally conducted by a team, centered on a specialist physician and including a pharmacist and nurse with advanced learning and extensive practical experience. It is therefore necessary to provide a broad range of information to them, and to react quickly to any and all new developments in the cancer field. For this reason, Nippon Kayaku organizes lectures, seminars, and briefing sessions to answer these needs, and we have trained and dispatched specialist MRs equipped with the ability to provide and collect information related to anti-cancer drugs in general.

Nippon Kayaku currently has 500-plus certified MRs. Of these, 90 specialist MRs are assigned to the two fields of anti-cancer drugs and pharmacologically active drugs to meet the growing demand in these fields. To help them in their information-sensitive jobs, each MR is provided with a personal computer containing custom software developed by Nippon Kayaku. This software helps to strengthen the system that allows us to collect and provide information quickly. We have also constructed the MINK web system, which allows us to send information directly to health care professionals who wish to receive it.

Reinforcement of facilities for production of high-potency active ingredients—Expanding contract manufacturing of API

For many years Nippon Kayaku has been engaged in integrated production of anti-cancer drugs that satisfy FDA standards, and we have constructed a complete good manufacturing practices (GMP) system covering every step from active pharmaceutical ingredients (API) to the final pharmaceuticals.

Making use of the vast amount of technology that we have

acquired for the production of high-potency active ingredients, in autumn 2003 we began expanding our contract manufacturing of API. Combining original synthesis and bioscience technologies, we are working to meet the strong demand for integrated production covering API, intermediates, and final pharmaceuticals. In particular, we are striving to differentiate ourselves from the competition in the production of anti-cancer agents and other drugs that contain high-potency active ingredients. The production of anti-cancer agents naturally requires thorough GMP, which are standards related to manufacturing control and quality control of pharmaceuticals. In addition, because the drugs are more potent than other pharmaceuticals and require special hazard-protection measures, control of the production process requires an advanced level of technology and experience. We possess production equipment for our primary anti-cancer drugs, which can be used to safely produce chemically hazardous medical compounds. In 2003, additional multi-purpose production equipment for chemically hazardous drugs was installed at the Takasaki Plant (Gunma Prefecture), completing a system for contract manufacturing of anti-cancer drugs and other high-potency active ingredients.

Active development of anti-cancer drugs utilizing nano-technology

The research into drug delivery systems (DDS) is rapidly advancing with the integration of nano-technology and information technology (IT). Patients and doctors have long awaited life-saving drugs with an innovative mechanism that properly regulates the release of drugs at the lesion site or which is especially effective for a specific population that can be selected through screening and diagnosis. Nippon Kayaku has been successful in new businesses based on the fusion of fine chemical-based knowledge arising from biotechnology, polymers, organic synthesis, and related technologies. Now we are focusing on the development of nano-technology-based DDS. Already we have synthesized a DDS utilizing polymer micelle technology that allows entrapment of an anti-cancer drug and delivery to the tumor site. Development of this promising approach has already progressed to the clinical trial stage and is attracting widespread attention. Unlike those formed by normal cells, the blood vessels generated by cancer tissues to supply nutrients have small openings in the vessel wall. It is through these small openings that drug-carrying polymer micelles 50 to 200 nanometers in diameter can reach the tumor cells and deliver drugs directly. If this highly specific delivery of anti-cancer drugs is realized, the side effects and dosage can be reduced.

We have also concluded a licensing agreement with NanoCarrier Co., Ltd. for paclitaxel polymer micelle DDS pharmaceuticals utilizing nano-technology, and the phase I clinical trials began at the National Cancer Center in April 2004.

Marketing of the arterial infusion IA CALL 100 mg

In July 2004 we began to market IA CALL 100 mg, a cisplatin drug specifically designed for arterial infusion in patients with hepatocellular carcinoma. IA CALL is the world's first platinum drug to be specifically approved for hepatocellular carcinoma, and there are high expectations by cancer specialists for its use. We believe that future research based on the actual clinical use of this drug will firmly establish its high effectiveness.



Expanded use of HYCANTIN® against ovarian cancer and phase III clinical trials of IMMUCYST intravesical

In November 2002 we introduced injectable HYCANTIN® from GlaxoSmithKline K.K., and we began clinical trials aimed at expanding the use of this drug to treat ovarian cancer. HYCANTIN® has been approved for the treatment of ovarian cancer in more than 70 countries worldwide, and its approval in Japan is eagerly anticipated.

In October 2003, we began importing and sale of IMMUCYST introduced from AventisPasteur K.K. In April 2004 we began phase III clinical trials aimed at establishing this drug as a maintenance treatment in order to prevent recurrence after transurethral resection of bladder cancer (TUR-Bt).

Establishment of a research center for development of heat immunotherapy, a new type of cancer treatment

In January 2004, Nanotherapy Co., Ltd. was established in Nagoya by Nippon Kayaku, Dai-Ichi High Frequency Co., Ltd. (Meguro Ward, Tokyo), Toda Kogyo Corp. (Otake City, Hiroshima Prefecture), and the technology-support venture company TTC (Meguro Ward, Tokyo). The purpose of this company is to develop practical applications and commercialize the new heat immunotherapy of cancer originally developed by Professor Takeshi Kobayashi and others at the Nagoya University Graduate School of Engineering. (Professor Kobayashi is now professor emeritus at Nagoya University and a professor at Chubu University.) The ratios of capital investment in the new company are 55% from Nippon Kayaku, 30% from Dai-Ichi High Frequency, 5% from Toda Kogyo, and 15% from TTC and others. The Nippon Kayaku's DDS pharmaceutical technology for targeted delivery of drugs to cancer cells and the Nippon Kayaku experience in commercializing a large number of anti-cancer drugs are combined with Dai-Ichi High Frequency's original high-frequency heating

technology and equipment manufacturing ability, and Toda Kogyo's superior nano-technology utilizing magnetic particles. Together we have entrusted rapid practical development of the drugs and medical devices for this new treatment to Nanotherapy Co., Ltd., and are aiming to commercialize this promising treatment method.

With this approach, heat-generating magnetic particles are covered with lipids and converted into a nano-size pharmaceutical agent. After injection into cancer tissues, an alternating magnetic field quickly heats only the tumor, which destroys it. Compared with conventional heat treatment methods, this revolutionary treatment is thought to cause least physical burden on the patient or adverse side effects. It has also been found that this treatment strongly induces immunological activity to the cancer cells.

By approximately 2010, our companies are aiming for clinical use of this method to treat solid cancers for which no effective treatment is available.

Acquisition of the distribution rights to two types of anti-cancer agents from Eli Lilly Japan

In January 2004, Nippon Kayaku obtained transfer of importation approvals of two anti-cancer agents from Eli Lilly Japan, and acquired their distribution rights. Sales of these two agents began on April 1, 2004. Injectable ONCOVIN 1 mg has been approved for leukemia, etc., while injectable EXAL 10 mg is approved for malignant lymphoma.



ISO9001 certification for all divisions in the Pharmaceuticals Group

In September of 2003, the quality management systems in all divisions of the Pharmaceuticals Group were certified according to the international standard ISO9001. This includes the Research & Development division, all pharmaceutical district offices in our East Japan Branch and West Japan Branch. In the Pharmaceuticals Group, the Takasaki Plant and Tokyo Plant had previously been certified, and now with the current certifications we have established an integrated quality management system that covers research and development, production, sales, and post-marketing activities. We intend to maintain and improve this system in order to raise the level of customer satisfaction and contribute to our business performance.

Status of New Product Development by Stage

Stage	Development code Product name (Generic name)	Dosage form or route of administration	Therapeutic category (Indications)	Domestic developer	Characteristics/Others
				Origin	
NDA	NS75A (NDA Dec. '00) (Cetorelix)	Injection	Anti-hormone drug (Infertility)	Joint dev. with Shionogi, Kayaku Zentaris Zentaris (Germany)	LHRH (Luteinizing hormone-releasing hormone) antagonist
	SL-1100 (NDA Dec. '03) (Estradiol)	Gel preparation	Estrogen (Climacteric disorder)	Joint dev. with Shiseido Besins International (France)	First estradiol gel preparation in Japan. Approved in 61 countries.
P III	IMMUCYST PMCJ-9 (BCG)	Bladder instillation	Anti-cancer drug (for preventing recurrence of bladder cancer)	Own development AventisPasteur (Canada)	Extended indication
P II	NKT-01/ SPANIDIN (Gusperimus hydrochloride)	Injection	Immunosuppressant (Wegener's granulomatosis)	Own development Institute of Microbial Chemistry	Developed overseas. Designated as an orphan drug (Mar. 2001) by the EMEA. Late phase II trial is currently in progress.
	NK911 (Micelle doxorubicin hydrochloride)	Injection	Anti-cancer drug (Pancreatic cancers)	Own development Tokyo Women's Medical University	Macromolecular micelle anti-cancer drug. Early phase II trial for pancreatic cancer was started in October 2003. Development consigned by Japan Science and Technology Corp.
	NK211 (Nogitecan)	Injection	Anti-cancer drug (Ovarian cancer)	Own development GSK	Extended indication
	NS75A (Cetorelix)	Injection	Anti-hormone drug (Hysteromyoma)	Joint dev. with Shionogi, Kayaku Zentaris Zentaris (Germany)	LHRH (Luteinizing hormone-releasing hormone) antagonist
P I	NK105 (Micelle paclitaxel)	Injection	Anti-cancer drug (Solid cancers)	Own development Joint dev. with NanoCarrier	Macromolecular micelle anti-cancer drug.

Major Products

The year in parentheses is when the product was first marketed.

■ Anti-Cancer and Cancer-Related Drugs

- IA CALL (2004)
- ONCOVIN (2004)
- EXAL (2004)
- CARBOMERCK (2003)
- IMMUCYST (2003) ①
- Hycamtin® (2003)
- MS-TWICELON (2001)
- COFORIN (1996)
- FARESTON (1995)
- ODYNE (1994)
- STARASID (1992)
- PINORUBIN (1988)
- LASTET (1987)
- BESTATIN (1987)
- Randa (1984) ②
- PEPLEO (1981)
- BLEO (1969)



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②

■ Immunosuppressants

- SPANIDIN (1994) ③



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■ Cardiovascular Drugs

- MILLISROL for Coronary Infusion (2001)
- ADEHL (1999)
- MILLISTAPE (1998)
- NITROPEN TABLETS (1988)
- MILLISROL (1984) ④
- NITROGLYCERINE TABLETS (1953)



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■ Neurological Drugs

- SALIGREN (2001)
- MUSCALM (1975)

■ Other Drugs

- ASTRIC DRY SYRUP (2002) ⑤



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■ Diagnostic Agents

- LANA MAMMO CARD CEA (2002) ⑥
- LANA TP AUTO (2001)
- LANA 1,5AG AUTO LIQUID (2000)
- LANAZYME BFP PLATE (2000)
- LANAZYME ST-439 PLATE (1999)



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■ Pharmaceutical API and Intermediates