

Pharmaceutical Business

Adapting quickly to changes in the health care environment, and aiming for growth in the “Medicine/Welfare and Care” field.



Haruo Inose
Senior Managing Director
Representative Director
Director of Pharmaceuticals Group

Drastic reform of Japan’s health care system, and an expanded presence of overseas companies in the Japanese market, have led to major changes in the pharmaceuticals market and have heightened the bitter struggle for survival faced by all pharmaceutical companies. The government has designated the following areas that define the directions a pharmaceutical company may take: mega, specialty, OTC (over-the-counter pharmaceuticals), and generic pharmaceuticals.

Moreover, the sharing of expertise and treatment information with patients is progressing with the continued expansion of the Internet. As well, the worldwide trend toward standardization of medical care is changing the health care field faster than ever before. Greater health care business improvements are demanded as a result of social welfare factors that include ranking of health care facilities, a change to an independent administrative institution for national hospitals, the start of Diagnosis Procedure Combination (DPC) at specialized hospitals, and the future shift to the Diagnosis-Related Groups Prospective Payment System (DRG-PPS) at ordinary hospitals.

It is expected that “health care planned from the patient’s perspective” will continue to develop in the future. This entails explanations of latest available treatment regimes, or a “menu,” for each specific illness, including their costs, with treatment started only after agreement is reached between both parties. In order to adapt to these changes in the health care environment, and to continue expanding as a business, Nippon Kayaku is working for growth in the Medicine/Welfare and Care field. Based on our current anti-cancer drugs, we are focused on rapid development of products that benefit patients, from cancer prevention to diagnosis, treatment, and care.

Strengthening cancer-related research and development activities

We expect that the needs for cancer drugs will further increase. The Pharmaceuticals Group has focused its efforts on cancer-related products, and is strengthening our base in this field. We will accelerate the discovery, in-license and development process, and continue to perform R&D specifically for cancer treatment and related business areas. The R&D Division has been involved in developing pharmaceutical agents using applied nanotechnology, and has attracted the attention of the industry with its progress in clinical trials of polymer micelles containing anti-cancer drugs that precisely target and attack cancer cells. As a future corporate research program, this technology will be further studied to apply to fields other than anti-cancer drugs, creating a base for further growth. It is also putting efforts into the early detection of cancer, which is strongly demanded by society.

New drugs to counteract price revisions

The revision of drug price standards is conducted every other year, based on current market prices, and with consideration for a range of other factors. This revision has a major effect on the business performance of all pharmaceutical companies. However, to prevent our own business performance from being affected by the continual lowering of drug price standards, we intend to counteract these changes with new products. In Japan, particular examples include AREDIA (bone resorption inhibitor) licensed in 2001 and VITAJECT (multivitamin product); HYCAMTIN (anti-cancer drug) licensed in 2002 and CARBOMERCK (anti-cancer drug), licensed this year; SALIGREN (drug for dry-mouth symptoms) and MS-TWICELON (sustained-release drug for cancer pain), which were launched in 2001; and IMMUCYST (drug for bladder cancer), which was launched in October 2003. We are also working to expand the applications of RANDA. Overseas, we are planning to expand our company's global sales system, particularly for SPANIDIN, which is being developed in Europe, and 1,5AG, which was approved for the U.S. market in September 2003.

Integration of research, production and sales

The trend in medical practice is to provide fair and open accounting of standard treatment options to patients, with consulting and obtaining patient consent before treatment commencement. To adapt to this trend, this group will focus on the various pharmaceuticals contained in standard treatment regimens for cancer treatments and on areas where our medical information coverage is strongest. We are strengthening the licensing function and integrating the company's system for research, production, and sales to provide pharmaceuticals that are low price and convenient, and which can be administered in a manner appropriate for Medical Risk Management and treatment needs.

Strengthening of the sales division through MRs

An important key in the pharmaceutical market is the expanding use of specially trained medical representatives (MRs) who can promptly respond to the needs of medical institutions, and can both collect and provide accurate information. Nippon Kayaku currently has 500-plus certified MRs. Approximately 60 MRs are positioned in the major cities and assigned to the two strategically important areas of anti-cancer drugs and pharmacologically active drugs such as vasodilators. We plan to increase the number of these specially trained MRs gradually. By assigning MRs possessing wide and updated knowledge of cancer and pharmacology to these areas, we can better understand the needs of medical specialists, and strengthen our promotion activities. To help them in their information-intensive jobs, each MR is provided with a personal computer containing custom software developed by Nippon Kayaku. This software aids in constructing networks with medical institutions, allowing medical information to be provided and collected quickly and efficiently.

Using nanotechnology for active development of anti-cancer drugs

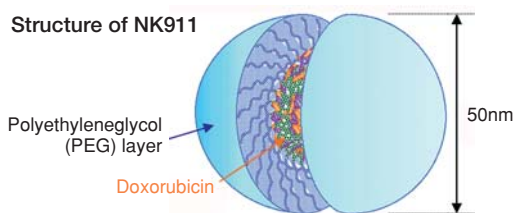
The research into drug delivery systems (DDS) is rapidly advancing with the integration of nanotechnology and information technology (IT). The life-saving drugs patients and doctors have long awaited can be enhanced through an innovative mechanism that properly regulates the release of the drug using DDS at the lesion location 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 nanotechnology-based DDS. Already we have synthesized a DDS utilizing polymer micelle technology that allows entrapment of an anti-cancer drug and delivery to the site of the tumor. Development of this promising approach has already progressed to the clinical trial stage and is attracting widespread attention.

The blood vessels newly formed 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 leach through the blood vessel walls to deliver the drug directly to tumor cells. If this highly specific delivery of anti-cancer drugs is realized, the side effects and dosage can be reduced.

Of the consolidated pharmaceutical net sales of 35.1 billion yen in FY 2003, sales from 13 oncology-related products generated 21.6 billion yen. This world-class lineup of oncology products significantly benefits Nippon Kayaku since multi-drug therapy is the standard for treatment of cancer.

NK911, our first nanotechnology-application DDS, has already reached the clinical study phase. We plan to develop a total of five DDS drugs, adding one each year. The polymer micelle technology is being studied by the Nanotechnology Development Promotion Office to apply it to other anti-cancer drugs.



Phase II for anti-cancer drug NK911

The phase I of clinical trial for NK911, a DDS pharmaceutical based on micelle formulation technology utilizing applied nanotechnology, has been conducted since July 2001 at the National Cancer Center. In the summer of 2003, the early phase II clinical trial started. NK911 containing the anti-cancer drug doxorubicin was consigned to Nippon Kayaku for development by the Japan Science and Technology Corporation. In the future, we will conduct clinical testing from a range of perspectives, and are aiming to market this product in November 2009.

Preparation for clinical trials of DDS pharmaceutical using the anti-cancer drug paclitaxel

We are on track to begin clinical trials in FY 2004 for a joint development project in new pharmaceuticals with the bio-venture company, NanoCarrier Co., Ltd. (Kashiwa, Chiba). In July 2002, Nippon Kayaku concluded a license agreement for paclitaxel DDS pharmaceuticals with this company. NanoCarrier's DDS technology is the formation of a micelle nano-particle with a hydrophilic outer polymer and hydrophobic inner polymer bonded on the molecular level. This nano-particle can contain medication, bio-active agents, or genes, while other compounds or antibodies bond to the outside.

Paclitaxel is an anti-cancer drug used worldwide for the treatment of lung, ovarian, and breast cancer. Although it is injectable, the substance does not dissolve readily in water. A special solvent used in this drug is the drawback for clinical use. However, the exterior of the NanoCarrier nano-particles is hydrophilic. Even when filled with paclitaxel, they will dissolve in a water solution, while the substance is retained inside the nano-particles. This allows longer circulation of the substance in the bloodstream, and provides strong anti-tumor effects.

Alliance with GlaxoSmithKline K.K. for development and sales of the anti-cancer drug HYCAMTIN

In November 2002 Nippon Kayaku concluded an alliance with GlaxoSmithKline K.K. (GSK) for the development and Japan sales of injectable HYCAMTIN in Japan. We have taken over sales from GSK and are conducting joint development for the new indication of ovarian cancer (currently in Phase II).

HYCAMTIN has been sold in Japan since 2001 as a drug for the treatment of small-cell lung cancer. Sales prior to the end of 2001 were approximately 30 million yen, but we are working to increase domestic sales by effectively utilizing our unique sales and development strengths. HYCAMTIN has been approved for the treatment of small-cell lung cancer in more than 35 countries, and for ovarian cancer in over 70 countries. Global sales of this drug in 2002 totaled 17.8 billion yen.



Anti-cancer drug HYCANTIN

Injectable IMMUCYST intravesical for treatment of bladder cancer

Injectable IMMUCYST intravesical, a drug for treatment of bladder cancer, was first marketed in October 2003. The active ingredient of this drug, which is imported from AventisPasteur Inc., is the Connaught strain of BCG. It is injected into the bladder to control cancer cell growth. Nippon Kayaku has positioned cancer treatment as our primary business field, and we are utilizing our system of expert medical representatives (MRs) to expand sales promotion. We expect the annual net sales to peak at 1.2 billion yen.

Application for EU sales approval of NKT-01 for treatment of refractory vasculitis

In February 2003, Nippon Kayaku applied for approval in the EU to sell NKT-01, a promising new drug for treatment of refractory vasculitis, with sales expected to begin in FY 2005. This will be an important product for Nippon Kayaku as it is the first product to be approved by the European Agency for the Evaluation of Medicinal Products (EMEA) in the EU. NKT-01 is intended for treatment of vasculitis which involves lymphocyte anti-neutrophil cytoplasmic antibodies that occur in cases of Wegener's granulomatosis, a type of autoimmune disease of unknown cause.

Originally, NKT-01 was an immunosuppressant used to treat organ rejection in kidney transplantation, and it was found to have a unique ability to inhibit growth of antibody-forming and cytotoxic T lymphocytes. There are approximately 10,000 patients with this disease in Europe and the United States, respectively. NKT-01 has been developed for many years by a contract research organization in Germany and designated as an orphan drug by the EMEA. Additionally, the diabetes diagnostic agent 1,5AG received approval in the United States in September 2003.

■ 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	BESTATIN (NDA Sep. '01) (Ubenimex)	Oral preparation (Capsule)	Anti-cancer drug (For prolonging the survival period after surgery for lung squamous cell carcinoma)	Own development Institute of Microbial Chemistry	Extended indication
	BLEO (NDA May. '02) (Bleomycin)	Injection	Anti-cancer drug (Testicular tumor, germ cell tumor)	Own development Institute of Microbial Chemistry	Extended indication
	NS75A (NDA Dec. '00) (Cetorelix)	Injection	Anti-hormone drug (Infertility)	Joint dev. with Shionogi, Kayaku Zentaris Zentaris (Germany)	LHRH (Hormone that stimulates secretion of pituitary gonadotropin) antagonist
	DDP-H (NDA Mar. '02) (Cisplatin)	Injection (Hepatic arterial infusion)	Anti-cancer drug (Hepatic cancer)	Joint dev. with Bristol Pharmaceuticals NCI (USA)	Extended indications (New dosage form, new route of administration)
	SPANIDIN (NDA Feb. '03) (Gusperimus hydrochloride)	Injection	Immunosuppressant (Wegener's granulomatosis)	Own development Institute of Microbial Chemistry	Developed overseas. Early Phase II study completed in Germany. Currently awaiting approval. Designated as an orphan drug (Mar. 2001) by the EMEA.
P III	SL-1100 (Estradiol)	Gel preparation	Estrogen (Climacteric disorder)	Joint dev. with Shiseido Besins International (France)	First estradiol gel preparation in Japan. Approved in 54 countries.
P II	NK211 (Nogitecan)	Injection	Anti-cancer drug (Ovarian cancer)	Own development GSK	Extended indication
	NK911 (Micelle doxorubicin hydrochloride)	Injection	Anti-cancer drug (Solid cancers)	Own development Tokyo Women's Medical University	Macromolecular micelle anti-cancer drug. Development consigned by Japan Science and Technology Corp.
	NS75A (Cetorelix)	Injection	Anti-hormone drug (Hysteromyoma)	Joint dev. with Shionogi, Kayaku Zentaris Zentaris (Germany)	LHRH (Hormone that stimulates secretion of pituitary gonadotropin) antagonist
PC	NS75B (Cetorelix)	Injection	Anti-hormone drug (Prostatic hypertrophy)	Joint dev. with Shionogi, Kayaku Zentaris Zentaris (Germany)	LHRH (Hormone that stimulates secretion of pituitary gonadotropin) antagonist
	NK105 (Micelle paclitaxel)	Injection	Anti-cancer drug (Solid cancers)	Own development Joint dev. with NanoCarrier	Macromolecular micelle anti-cancer drug.
	NK314	Injection	Anti-cancer drug (Solid cancers)	Own development Own development	Derived from natural substances. Topoisomerase I, II effects + α.