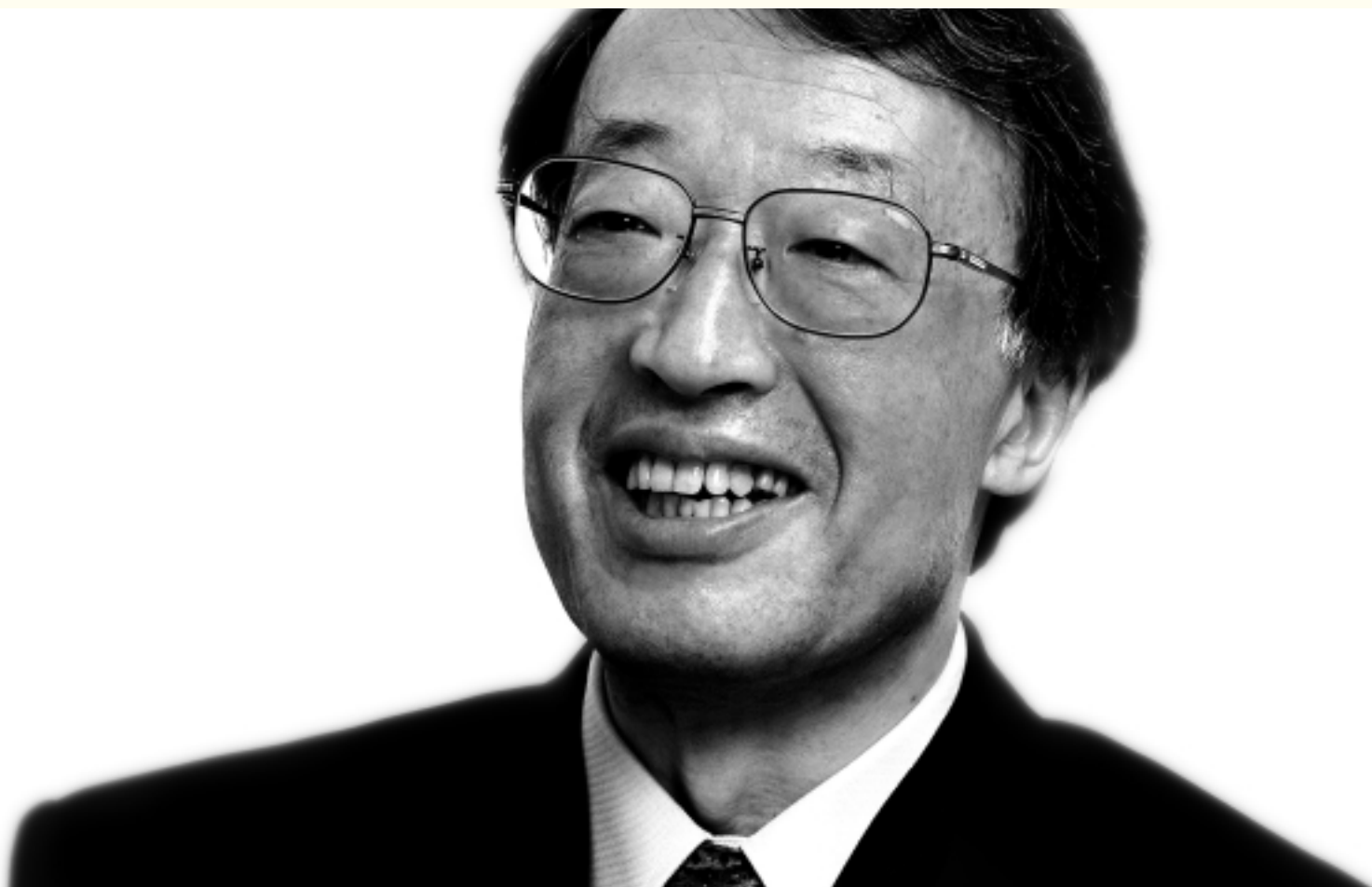


## Leverage R&D Expertise

Interview with Toshiaki Nishihata, Senior Corporate Officer



Toshiaki Nishihata, Ph.D.  
Senior Corporate Officer  
Head of Research and Development Division

## For the Future...

To continuously launch new products, we have set our 2003-2005 Medium-term Management Plan goal of having three compounds in the later stage of Phase II, and we have achieved this goal a year ahead of our initial projections. Even I have been surprised by this accomplishment.



● ● ● ● Please explain the vision and strategy of the Research and Development Division.

Our vision is to continuously discover and develop innovative pharmaceuticals and services that address unmet medical needs and contribute to improving patients' quality of life (QOL). We are realizing this vision as outlined in our Medium-term Management Plan by implementing the following action plan:

1. Redirecting our R&D resources to focus on developing treatments for large unmet medical needs. We continually assess the current benefits of our technology relative to our competitors', and allocate resources to areas where we have a competitive edge.
2. Concentrating our resources on the development of prescrip-

tion ophthalmics, the core business and strength of Santen. We are also enhancing our clinical development pipeline to steadily introduce new products to the market.

3. Increasing the productivity of our R&D investments in the fields of rheumatoid and osteoarthritis by either out-licensing late stage development or seeking co-development arrangements.
4. Beating the competition requires an accelerated R&D process. We aim to complete preclinical studies within eighteen months and clinical trials within five years, for a total of six years and a half years. This is extremely fast-paced compared to our competitors.

● ● ● ● How did you manage to accelerate the R&D process?

To complete clinical trials within five years, it is important to shorten the transition period between phases. To accelerate projects, we first developed a comprehensive plan that identified and defined clinical development processes, benchmarks, and critical steps. We then shifted additional resources to the clinical affairs group and developed parallel contingency plans to minimize areas of risk. One of the top priority action

items resulting from this process was to proactively improve the clinical trial infrastructure in Japan. We have hired Site Management Organizations (SMOs) to improve the ability of independent physicians to conduct clinical trials, supplementing university hospitals. In many cases, we established the clinical trial system in cooperation with independent physicians.

● ● ● ● Please outline the development status of major products in the year ended March 31, 2005.



DE-085(tafluprost) is a novel prostaglandin being studied for the treatment of glaucoma. We are concurrently conducting three Phase III clinical trials for this drug candidate. One pivotal trial will compare tafluprost to the leading drug on the market for glaucoma. The second trial involves clinical data collection from the perspective of evidence-based medicine to address the advantages of our drug and ensure successful application. The third trial is a long-term study required for regulatory approval. We expect to be able to file a New Drug Application (NDA) in Japan two to three months earlier than our initial projections. We are also conducting global Phase III clinical trials of tafluprost and intend to seek regulatory approval in Europe.

DE-092 (olmesartan) is being evaluated in the treatment of glaucoma and ocular hypertension. Olmesartan is currently being studied in a dose-finding Phase II trial in both Japan and the United States. Due to our global approach that emphasizes data sharing between regions, we have been able to accelerate the overall development schedule to start Phase III trials in 2006.

DE-089 (diquafosol tetrasodium) is similarly ahead of the original clinical development schedule by completing the shift from the first half to second stage of Phase II in four months. Diquafosol is being evaluated for the treatment of corneal disorders, including dry eye.

DE-096 is a tumor necrosis factor alpha (TNF- ) inhibitor. We intend to evaluate DE-096 in the treatment of both rheumatoid arthritis and retinal disorders. For this compound, we have already completed early stage Phase II

trials, filed an investigational new drug application (IND) for rheumatoid arthritis and begun administration to patients.

As for the treatment of retinal disorders, we are preparing for early stage Phase II trials.



### Tell us about the globalization of clinical development.

During the past three years, we have conducted several glaucoma clinical trials in Japan, the United States and Europe. The progress made on tafluprost and olmesartan demonstrates that our global approach, initiated several years ago, is now paying dividends. We have made a concerted effort to harmonize clinical protocols across regions whenever possible, thereby allowing us to leverage data obtained in one region of the world to support regulatory approval in another region. Moreover, glob-

al clinical development has reduced costs and accelerated timelines. Over the next several years, we will extend this global approach to several promising retinal compounds that are expected to enter clinical trials.



### Please explain the status of candidate compounds being prepared for clinical trials.

At present, we have three candidates scheduled to begin clinical trials in 2006 or 2007. We will also strive to in-license at least one novel ophthalmic pharmaceutical product within this time period that could begin clinical studies within a year or so after signing the licensing contract.

Looking further ahead, our early stage pipeline appears very promising. There are three compounds in the later phase of drug discovery that could advance to clinical trials in 2007.

Even if we assume the majority of candidate compounds drop out during the development process by 2011, we could potentially introduce one new drug every year.



### Please share your views on the future direction of R&D.

Santen has typically obtained new products from three main sources. The first source is in-house drug discovery. The second source involves the reformulation or adaptation of existing systemic drugs for ophthalmic use, while the third is via in-licensing or acquisition of new products. Currently, there is a 3-to-2 ratio between the compounds we have in-licensed versus those originating from drug discovery. However, due to the strength of our early stage pipeline, we expect to reverse this ratio during the course of our next Medium-term Management Plan.

Many anterior segment conditions such as seasonal allergies or minor eye infections are acute in nature. For these therapeutic areas, we believe that in-licensing new compounds or modifying systemic drugs for ophthalmic use is the most cost-effective strategy, because this practice won't interfere with their major therapeutic domain in many cases. In this regard, we are successfully advancing in-licensing compounds.

In contrast, there are large unmet medical needs in posterior segment vitreoretinal conditions and glaucoma. Concerning their treatments, the market is expanding with a growing number of glaucoma patients partly resulting from aging population, thus making drug development very competitive and

in-licensing more difficult. A superior drug for these conditions could accelerate the market growth on a global scale. Companies are typically not willing to out-license drugs in these therapeutic areas. Since in-licensing is difficult, we have been strengthening our internal drug discovery capability in addition to looking into opportunities for joint efforts.

We also intend to reinforce our genome-related research to seek out new therapeutic drug targets. With better target identification, we hope to increase our probability of success and increase R&D efficiency. We also have an effort underway to identify biomarkers and surrogate endpoints for clinical diseases. By developing biomarkers and incorporating them into early stage screening and testing, we may identify promising compounds earlier and make faster decisions on whether or not to proceed with research.

In summary, we plan on expanding our drug discovery programs, both internally and jointly with other companies. In the years ahead, we will endeavor to gain a competitive edge in drug discovery, while pursuing cross-licensing and other opportunities.

## Prescription Pharmaceuticals in Development

As of July 2005

Generic name	Brand Name/ Development Code	Indication	Region	Phase I	Phase II	Phase III	NDA Filed	Approved	Characteristics
Levofloxacin 1.5%	<i>Iquix</i>	Bacterial corneal ulcer	USA					●	Antibacterial ophthalmic solution containing the active ingredient fluoroquinolone three times higher than current product ( <i>Quixin</i> ). Exhibits potent antibacterial action. Approved in March 2004.
Ciclosporin	DE-076	Vernal keratoconjunctivitis	Japan				●		An orphan drug*2. Expected to treat advanced vernal keratoconjunctivitis for which existing anti-allergy agents are not effective. NDA filed in August 2003.
Tafluprost	DE-085	Glaucoma and ocular hypertension	Japan USA/Europe			● ●			Prostaglandin glaucoma treatment that is expected to have greater efficacy in reducing intraocular pressure than other prostaglandin glaucoma treatments. Can be stored at room temperature.
Olmesartan	DE-092	Glaucoma and ocular hypertension	Japan USA/Europe		● ●				The only angiotensin II receptor antagonist in full-fledged development as a glaucoma treatment. Comparable to prostaglandin products in reducing intraocular pressure.
Lomerizine HCL	DE-090	Glaucoma	Japan		●				A new type of oral glaucoma treatment studied for inhibiting the progression of visual field defects. The only calcium antagonist in full-fledged development as a glaucoma treatment.
Diquafosol tetrasodium	DE-089	Treatment for corneal and conjunctival disorders, including dry eye	Japan		●				A dry eye treatment that stimulates corneal and conjunctival epithelial secretion of tear fluid and moisture.
Levofloxacin and prednisolone A	DE-094	Infectious keratitis	USA		●				Combination of levofloxacin and steroid.
(Undetermined)	DE-096	Rheumatoid arthritis Diabetic macular edema	Japan		● ●*1				An oral TNF inhibitor. Anti-rheumatic effect comparable to injectable biological agents has been observed in basic research. In addition to rheumatoid arthritis, its efficacy against diabetic macular edema was newly confirmed by basic research, and is currently being developed as a treatment for both diseases.
Gefarnate	DE-099	Treatment for corneal and conjunctival disorders, including dry eye	Japan	●					Treats corneal and conjunctival epithelial disorder mostly associated with dry eye by stimulating the secretion of mucin and promoting the corneal epithelial migration. Preservative-free ointment that can be used in combination with existing drugs.

When safety and efficacy of candidate compounds are determined in preclinical studies, they undergo the following clinical trials. After completing the Phase III clinical trials, a new drug application (NDA) is filed for marketing approval.

Phase I: Tests to check drug safety with a small number of healthy volunteers.

Phase II: Tests to determine dosage and administration method with a small number of patients.

Phase III: Tests to confirm safety and efficacy by comparing to existing drugs and placebo with a large number of patients.

\*1 In preparation

\*2 Orphan drug: A drug with an indication for treating a relatively small number of patients. Orphan drug R&D expenses are eligible for government subsidies in Japan.