

Development

Key Issues in the 2003–2005 Medium-term Management Plan

- Shorten the time for non-clinical studies to approximately one and a half years
- Shorten the time between Phase I clinical trials and new drug application to approximately five years
- Restructure our R&D organization

Accelerating and Focusing R&D

The ability to create innovative pharmaceuticals and offer them quickly to patients worldwide is essential in order to succeed in the competitive global market. Santen has made accelerating research and development one of its top priorities, and is expediting various initiatives to achieve this goal.

We have narrowed our focus to projects that will provide improvements for patients and allow us to enjoy competitive advantages. Concentrating resources on these priority projects is helping us accelerate product development.

Restructuring Our R&D Organization

Santen reorganized its R&D divisions in December 2002 to enhance planning and leadership capabilities throughout the entire R&D process. The core change in this reorganization was the integration of five former divisions — ophthalmic research, rheumatoid arthritis research, clinical development, pharmaceutical development, and strategy coordination — into a single Research and Development Division. The planning functions that were formerly dispersed among each division are now centered in a single division. Improved decision-making and concentration of the planning functions will lead to accelerated research and development and enhanced operational efficiency.

The reorganization has strengthened the bond that links R&D with sales and marketing. Accordingly, we believe that this closer relationship has improved the quality of new drug development in terms of satisfying therapeutic needs and increasing commercial viability.

Faster Development Time for Non-clinical Studies and Clinical Trials

The 2003-2005 Medium-term Management Plan has set the specific target of reducing the time needed for non-clinical studies to approximately one and a half years from the current three years, and the time needed for clinical trials, between Phase I and new drug application (NDA), to approximately five years from the current seven to eight years.



Clinical development staff discuss the optimal plan for clinical testing of strategic products.

Santen will shorten non-clinical studies by devising new approaches for protocols, including conducting safety studies that focus on starting clinical pharmacology studies at an earlier stage.

To accelerate clinical trials, we will increase the number of staff members involved in clinical development by shifting personnel from research divisions. We will also increase development capacity by effectively utilizing personnel from contract research organizations and site management organizations.

We have reviewed all aspects of our clinical trial operations and have begun to streamline our business processes, including the reorganization of certain functions. In addition, we will further accelerate development by using scientific evidence to optimize clinical trials.

Strong Clinical Development Network in Japan, the U.S. and Europe

Santen has built a strong clinical development network covering Japan, the United States and Europe, and has successfully developed and launched two original drugs in the United States and one in Europe. Non-clinical studies are primarily performed in Japan, while U.S. and European operations will focus on expanding clinical capabilities to support projected growth in tripolar development projects in Japan, the United States and Europe.

Levofloxacin Launched in International Markets

Cravit (levofloxacin ophthalmic solution) is a potent, broad spectrum anti-infective with an excellent ability to penetrate ophthalmic tissue. Santen launched *Cravit* in Japan in April 2000, and then launched the drug under the brand name *Quixin* in the United States in November 2000. In Europe, marketing authorization was granted in the United Kingdom in July 2001, followed by nine other countries during 2002. The drug is now marketed in Germany, Finland, Sweden, Denmark and Iceland under the brand name *Oftaquix*. In Asia, marketing approval was obtained for *Cravit* in six countries, beginning with Hong Kong in November 2000. Sales have already started in Hong Kong, Korea, Thailand, Singapore and Indonesia.

In April 2003, we submitted an NDA to the U.S. Food and Drug Administration (FDA) for levofloxacin 1.5%, a higher concentration formulation of *Quixin*, for the indication of corneal ulcers.

In August 2003, we applied for manufacturing approval in Japan for DE-076 (ciclosporin ophthalmic solution), an orphan drug¹ indicated for an eye allergy known as vernal keratoconjunctivitis². The drug has been studied in patients with advanced vernal keratoconjunctivitis, against which existing anti-allergy drugs are not effective.

Clinical Development Acceleration Centered on Glaucoma Treatments

In the field of glaucoma treatment, which offers the greatest market potential, Santen has three candidate compounds under Phase II clinical trials. We are focusing more resources in this field to accelerate their development.

DE-085, a prostaglandin (PG)-based treatment for glaucoma, is an ophthalmic solution that reduces intraocular pressure by promoting the outflow of fluid in the eye known as aqueous humor. Unlike some PGs that must be refrigerated, DE-085 can be stored at room temperature.



Supervisors of development projects at Santen's tripolar network spanning Japan, the United States and Europe receive joint training at Santen Oy.

Notes

1. Orphan drug: A drug whose labeled indication is for treating a relatively small number of patients. Orphan drug R&D expenses are eligible for government subsidies in Japan.
2. Vernal keratoconjunctivitis: A severe type of eye allergy in which changes in conjunctival cell propagation are evident.

Main Prescription Pharmaceuticals in Pipeline

(As of August 2003)

Generic Name	Brand Name/Development Code	Indication	Original/Licensor	Region	Phase I	Phase II	Phase III	NDA Filed	Approved	Launched	Characteristics of Compound
Levofloxacin 0.5%	<i>Cravit</i> <i>Quixin</i> <i>Oftaquix</i>	Bacterial conjunctivitis	Daiichi Pharmaceutical	Japan						4/2000	New quinolone antibacterial ophthalmic solution. In Europe, the treatment has obtained marketing authorization in 10 countries and has been launched in five countries including Germany.
				USA						11/2000	
				Europe						5/2002	
Levofloxacin 1.5%	(Undetermined)	Bacterial corneal ulcer	Daiichi Pharmaceutical	USA						4/2003	Higher concentration formulation. Stronger antibacterial action expected.
Levofloxacin and prednisolone A	DE-094	Infectious keratitis	Daiichi Pharmaceutical	USA							Combination of levofloxacin and steroid.
Pemirolast potassium	<i>Alegysal</i> <i>Alamast</i> <i>Alamast</i>	Allergic conjunctivitis	Mitsubishi Pharma	Japan						4/1995	A mast cell stabilizer with superior efficacy on allergic conjunctivitis and vernal keratoconjunctivitis.
				USA						7/2000	
				Europe						12/1999	
Sodium hyaluronate	<i>Hyalein</i>	Corneal and conjunctival epithelial disorders Dry eye	Original	Japan						6/1995	Ophthalmic solution containing sodium hyaluronate. Treats corneal and conjunctival epithelial lesions caused by dry eye, contact lenses, etc.
				USA	In preparation						
Ciclosporin	DE-076	Vernal keratoconjunctivitis	Novartis Pharma	Japan						8/2003	An orphan drug. Expected to treat advanced vernal keratoconjunctivitis for which existing anti-allergy drugs are not effective. Because it is an ophthalmic solution, virtually no generalized side effects are noted.
(Undetermined)	DE-085	Glaucoma and ocular hypertension	Co-development with Asahi Glass	USA Japan							Prostaglandin-based treatment for glaucoma. Tripolar development planned in Japan, the United States and Europe. Can be stored at room temperature.
Olmesartan	DE-092	Glaucoma and ocular hypertension	Sankyo	Japan							The only angiotensin II receptor antagonist in full-fledged development as a glaucoma treatment. Comparable to prostaglandin-based treatments in reducing intraocular pressure.
Lomerizine hydrochloride	DE-090	Glaucoma	Nippon Organon	Japan							New type of oral glaucoma treatment studied for inhibiting the progression of visual field defects.
Diquafosol tetrasodium	DE-089	Dry eye	Inspire Pharmaceuticals	Japan							A treatment for dry eye that stimulates the eye surface to secrete tear fluid and moisture. Expected to be used in combination with existing dry eye treatments, and be effective for patients for whom existing treatments are insufficient.
(Undetermined)	DE-096	Rheumatoid arthritis	Original	Japan							An oral TNF inhibitor. Anti-rheumatic effect comparable to injectable biological agents has been observed in basic research.

We are currently conducting Phase II clinical trials for DE-085 in Japan and the United States, and may soon start clinical trials in Europe using the results gained in the United States.

DE-092 (olmesartan ophthalmic solution) is an angiotensin II receptor antagonist that reduces intraocular pressure comparable to PGs in animal models. It is currently under Phase II clinical trials in Japan. Although angiotensin II receptor antagonists enjoy wide use for lowering blood pressure systemically, there is currently no topical solution approved for use in the eye.

DE-090 (lomerizine hydrochloride) is a new type of oral glaucoma treatment that is being studied for inhibiting the progression of visual field defects. It is currently under Phase II clinical trials in Japan, and is expected to be effective for treating glaucoma with normal intraocular pressure.

DE-089 (diquafosol tetrasodium ophthalmic solution) is currently under Phase II clinical trials in Japan as a treatment for dry eye that stimulates the eye surface to secrete tear fluid and moisture. It is expected that the treatment can be used in combination with existing dry eye treatments, and will be effective for patients for whom existing treatments are insufficient.

In Japan, we launched *Hyalein* (sodium hyaluronate ophthalmic solution), a treatment for corneal disorders associated with dry eye and other causes, in June 1995. In Phase III clinical trials conducted in the United States under unique environmental conditions specially designed for the trials, *Hyalein* significantly reduced dry eye symptoms. Unfortunately, the placebo demonstrated an effect that was greater than anticipated. As a result, we are now preparing to restart Phase II clinical trials with a new protocol.

