A protein called bFGF (Trafermin) is a cell growth factor existing in minute quantities in the human body. Using this protein’s function, Kaken developed Fiblast Spray, the world’s first regenerative drug. Fiblast Spray has been shown to stimulate the growth of numerous tissue cells, heal damaged tissue, and boost the formation of new blood vessels. Its effectiveness stems from its power to form new blood vessels, which is garnering widespread recognition. This is due to empirical evidence of Fiblast Spray’s ability to promote the efficient supply of oxygen and nutrients, its effect in the treatment of skin ulcers, and the fact that new skin forms in two to three weeks when applied to bed sores or tissue damaged by burns or ulcers.

The effectiveness of Fiblast Spray was hailed soon after its market launch in June 2001. Today, it is used by all university hospitals, as well as many other hospitals and medical clinics. As a state-of-the-art drug used in regenerative medicine, Fiblast Spray is steadily penetrating the market, and since November 2002 it has held the leading market share among skin ulcer therapeutic agents.

What’s bFGF?

bFGF is stored ubiquitously in extra cellular matrix (ECM) of tissues and released when the tissues undergo some damage like trauma and ischemia, and it works as a potent regeneration agent.

Variety of Cells with FGFR
Epithelial Cell, Vascular Endothelial Cell, Vascular Smooth Muscle Cell, Osteoblast, Chondrocyte, Neuronal Cells etc.

- Neovascularization “Establishment of Lifeline”
- Proliferation
- Tissue Regeneration

Dermal Ulcers, Bone Fractures, Periodontitis, Myocardial Infarction etc.
**Expanding applications for Fiblast Spray**

Fiblast Spray is well recognized as a skin ulcer application that produces new blood vessels containing benign granulations and as a wound-healing agent. We are conducting research and development in anticipation of expanding its application to bone fractures and osteoporosis, periodontitis, diabetic ulcers, and post-operative ulcers.

Clinical trials are being held for its application as a gel for treating bone fractures and osteoporosis, where there is an estimated market worth ¥100 billion for the treatment of two million patients annually (Phase II of clinical trials now in progress).

We are also developing applications in the field of periodontics. Here, Fiblast Spray has enormous market possibilities; if adopted by ordinary dentists it has the potential to reach a patient base consisting of more than 80% of Japanese adults (Phase II of clinical trials now in progress).

Expanding applications of Fiblast Spray to other areas of regenerative medicine has vast hidden potential. This includes vascularization of blood vessels in the areas of peripheral circulation and severe angina, treatment of osteoarthritis, propagation of stem cells, and nerve regeneration.

**Market Expansion**

On the basis of our success in Japan, we have concluded a sales agreement with Hanmi Pharmaceutical Co., Ltd., a South Korean pharmaceutical manufacturer. The market for wound healing agents in South Korea is worth ¥5 billion annually, and we expect to gain a 40% share of that market. We have plans for further expansion and are investigating launching Fiblast Spray onto the Taiwanese and Chinese markets.

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**Increased Production of Mentax, a Kaken Original**

Mentax, a topical antifungal agent, received approval for over-the-counter (OTC) sales in the United States in December 2001. Sales of Mentax have surged as a result. In Japan too, we obtained approval to manufacture Mentax as an alternative OTC remedy for athlete’s foot, and began shipments and sales in January 2003 via other companies. The active ingredient of Mentax is butenafine hydrochloride, which inhibits the reproduction of trichophyton, a fungus that causes athlete’s foot.

**Strengthening Antifungal R&D: Collaboration with Elitra on Genomics Based Drug Discovery**

In February 2003, Kaken concluded a joint research and development agreement with the Elitra Pharmaceuticals, Inc., of the United States, covering R&D on genomic drug discovery for a new wide-spectrum systemic mycosis therapeutic agent. Elitra Pharmaceuticals will conduct screening based on its proprietary vital fungal gene information, while Kaken will undertake pre-clinical trials.

Kaken has obtained exclusive sales rights to sell antifungal agents developed through the joint R&D alliance in Japan and the rest of Asia, as well as Europe.
New Drug Development Pipeline

In new drug development, during the year we applied for approval to manufacture the diagnostic drug KP-102D and the antifungal Mentax Spray (new agent form).

Clinical trials are continuing for KCB-1B, a bFGF-related drug that promotes the healing of bone fractures; KCB-1D, used in the treatment of periodontitis; KP-102LN, used to treat pituitary dwarfism; KN-48, for the treatment of postherpetic neuralgia; and SPK-843, a drug used in the treatment of systemic mycosis. We also began clinical trials for TRK-100STP, a new form of Procylin with added effects for use in treating chronic arterio-occlusive disease. Meanwhile, in the area of drug discovery, we are compiling data with a view to commencing clinical trials in the autumn of 2003 of KP-496, a drug for treating bronchial asthma. Research is also continuing into drugs for treating inflammatory diseases, osteoporosis, and systemic mycosis.

In addition, we have entered into an agreement with Elitra Pharmaceuticals for the collaboration on a drug for treating systemic mycosis using new genomic information.

N.K. Curex Co., an affiliate of Kaken, is developing SNK-860, for treating diabetic neuropathy. In the year under review, we decided to formulate a new development strategy following trials in the United States conducted by Sankyo Co., Ltd.

In other highlights, we are currently in Phase II of clinical trials of KP-102LN, which is used to treat pituitary dwarfism in persons with stunted growth. In the year ending March 2010, we plan to launch on the market a new form of this drug that promotes the release of endogenous growth hormones.

<table>
<thead>
<tr>
<th>Product</th>
<th>Development Stage</th>
<th>Category</th>
<th>Launch</th>
<th>Indication</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>KP-102D (GHRP-2)</td>
<td>NDA</td>
<td>GH secretagogue</td>
<td>2004</td>
<td>Hypothalamo-pituitary function</td>
<td>Developed in-house</td>
</tr>
<tr>
<td>Mentax Spray</td>
<td>NDA</td>
<td>Butenafine</td>
<td>2004</td>
<td>Antifungal</td>
<td>New formulation, jointly developed with Hisamitsu Pharmaceutical Co., Inc.</td>
</tr>
<tr>
<td>KCB-1B</td>
<td>Phase II</td>
<td>bFGF</td>
<td>2009</td>
<td>Intractable bone fractures</td>
<td>New indication</td>
</tr>
<tr>
<td>KCB-1D</td>
<td>Phase II</td>
<td>bFGF</td>
<td>2009</td>
<td>Periodontitis</td>
<td>New indication</td>
</tr>
<tr>
<td>KP-102LN (GHRP-2)</td>
<td>Phases II</td>
<td>GH secretagogue</td>
<td>2009</td>
<td>Short stature</td>
<td>Developed in-house</td>
</tr>
<tr>
<td>TRK-100STP (Procylin)</td>
<td>Phase II</td>
<td>Orally active prostacyclin</td>
<td>2008</td>
<td>ASO</td>
<td>New indication: jointly developed with Toray Industries, Inc.</td>
</tr>
<tr>
<td>KN-48</td>
<td>Phase I</td>
<td>Lidocaine patch</td>
<td>2010</td>
<td>Postherpetic neuralgia</td>
<td>Developed in-house</td>
</tr>
<tr>
<td>SPK-843</td>
<td>Phase I</td>
<td>Polyene antibiotic</td>
<td>2009</td>
<td>Systemic mycosis</td>
<td>Developed in-house</td>
</tr>
<tr>
<td>KP-496</td>
<td>Phase I</td>
<td>LT/TX dual inhibitor</td>
<td>2010</td>
<td>Asthma</td>
<td>Developed in-house</td>
</tr>
<tr>
<td>SNK-860</td>
<td>Under consideration for redevelopment</td>
<td>ARI</td>
<td>2005</td>
<td>Diabetic neuropathy</td>
<td>Jointly developed with N.K. Curex Co., Ltd. and Sanwa Kagaku Kenkyusho Co., Ltd.</td>
</tr>
</tbody>
</table>

N.K. Curex Co., Ltd.