IRT

the right chemistry

2003

Annual Report

MICHAEL J. ASTRUE
President and Chief Executive Officer

The *right* people, the *right* leadership, the *right* plan, and the *right* culture are all necessary ingredients to build a great company. TKT believes it has the *right chemistry* to put these elements together to become a preeminent rare disease company.

I am proud of the progress we have made at TKT over the past year. We have emerged from challenging times as a tough, resilient company. We expect to build on the progress we made in 2003 to expand our development of protein replacement therapies, primarily for rare genetic diseases which we believe will lead the company to profitability.

In 2004, we are advancing our first generation of products, which primarily target lysosomal storage diseases. We believe with a commercial product for Fabry disease, an ongoing pivotal trial for our Hunter syndrome product, and the initiation of a clinical trial for our Gaucher disease product we are positioned nicely for future growth. We also received a boost by regaining rights to Dynepo™ (epoietin delta), our Gene-Activated® erythropoietin product, outside the United States in March 2004.

Replagal™ (agalsidase alfa), our product to treat Fabry disease, is approved for commercial use in 33 countries. In January 2004, we made the painful decision to end our efforts to obtain United States approval of Replagal because orphan drug exclusivity excludes it from the market until 2010. Nonetheless, we expect Replagal to be an important product outside the United States. Replagal is currently in its third year of sales in Europe, and the patient and physician support has been tremendous. With the success in Europe, the ongoing launch of Replagal in Canada, and the possibility of commercial sales in Australia and Japan later this year, we believe that Replagal could become a $100 million product in two years.

Revenue from Replagal combined with the successful commercialization of our enzyme replacement therapy for Hunter syndrome, Iduronate-2-Sulfatase, or I2S, could take us to breakeven by late 2006. We estimate that there could be an eventual $300 million market opportunity for our Hunter syndrome product with no foreseeable competition. We would expect a fairly rapid uptake to the $75 to $100 million mark following a commercial launch of I2S in the United States and Europe, and then slower but steady expansion of the market year after year.

We expect to build on the progress we made in 2003 to expand our development of protein replacement therapies, primarily for rare genetic diseases.

SHAWN FITZPATRICK,
Manufacturing Supervisor

We are excited about the prospects of our Hunter syndrome program and recently completed patient enrollment in our pivotal trial in approximately six months. We have tried to do everything we can to minimize risk in this study, including selecting clinical endpoints utilized in the recent approval of a product for a similar disease, sizing the trial at 96 patients (the largest trial ever for a lysosomal storage disorder), and running the trial longer than what is typical for trials in this disease class. We are preparing to take the necessary steps to file applications for regulatory approval in both the United States and Europe as early as possible in the second half of 2005.

During the past year, we entered into an important partnership for I2S. Our agreement with Genzyme Corporation to market I2S in Japan and other Pacific Rim markets allows us to draw on their expertise and considerable success in marketing protein products for rare diseases in this region of the world. In addition, we resolved all the legal disputes between our two companies, so that we can focus on drug development instead of litigation.

Hunter syndrome is a horrific disease and we want to see this treatment broadly available to patients as quickly as possible in all markets.

Our GA-GCB program for Gaucher disease entered the clinic in the second quarter of 2004. This trial is similar to, but slightly more robust than, the study the FDA relied upon in approving the existing commercial enzyme replacement therapy. We don't know yet whether additional studies will be required but we intend to explore the possibility that this trial will be enough for approval. We believe we will be the second entrant with an enzyme replacement therapy in the $800 million Gaucher marketplace, and can create the most value from this program through partnering.

ALAN KIMURA,
Executive Director, Clinical Affairs

ANNE MARIE CONWAY,
Program Manager

LEANNE TORRIE,
Manager, Patient Services

Earlier this year we were able to regain the rights outside the United States to Dynepo, our Gene-Activated erythropoietin product, for the treatment of anemia associated with renal disease. We see a significant opportunity for Dynepo, which was approved for commercial use in Europe in 2002, and believe our product may have important advantages over the competition. In order to bring Dynepo to the market as quickly as possible, we are establishing manufacturing in Europe. We are confident we have great choices for marketing Dynepo, and expect to make final decisions on the appropriate pathway by early next year. With Dynepo added to our pipeline, we hope to generate revenue from three products in 2006, a remarkable undertaking for any company - particularly a company of TKT's size.

Beyond our lead programs, TKT has a renewed energy and focus in research. We identified over a dozen potential new research projects and have selected four to bring to a preclinical decision point in the next 12 to 15 months. Most of these diseases represent $200-$500 million market opportunities. By keeping our R&D focused primarily towards protein replacement therapies - the lowest technical risk approach in biotechnology - and non-competitive markets, we believe we can sustain growth.

We continue to make important investments in our business to support our expanding pipeline. We have received regulatory approval to manufacture Replagal at our manufacturing facility, allowing us to move away from contract manufacturing for bulk drug substance of our enzyme replacement products. We have created a subsidiary in Canada to support the Canadian launch of Replagal. We plan to leverage our commercial infrastructure in Europe, Canada and Latin America to support the potential introduction of I2S to the marketplace in 2006.

The remainder of 2004 should be exciting, significant and productive. We believe Replagal will continue to grow in Europe and Latin America, and will succeed in new markets like Canada and Australia. We believe Dynepo will become an important product outside the United States. We believe I2S will become an important therapy for a devastating disease. We believe GA-GCB will provide an important choice to Gaucher patients around the world. We believe our research has identified potential therapies for diseases outside lysosomal storage diseases that will one day represent a second wave of commercial products for TKT.

Our successes have resulted from the creativity and dedication of an extraordinary group of employees at TKT. I thank them for their efforts, and also thank our shareholders for their continued support of TKT.

Sincerely,

Michael J. Astrue
President and Chief Executive Officer

TKT achieved several important milestones during 2003 and early 2004 which we believe have laid the foundation for continued growth. These milestones include:

2003

FEBRUARY – Michael Astrue named President and Chief Executive Officer

MARCH – Focused core business and reduced costs by restructuring organization

MAY – Collaborators successfully identified FGE enzyme, which is essential for catalytic activity of sulfatases

JULY – Alewife manufacturing facility approved by European Commission to manufacture Replagal

SEPTEMBER – Initiated Hunter syndrome pivotal trial – representing largest trial ever for a lysosomal storage disease

OCTOBER – Formed partnership with Genzyme to develop and commercialize I2S in Japan and other Pacific Rim territories

– Federal Circuit Court of Appeals upheld ruling in favor of TKT of non-infringement in Replagal patent litigation brought against TKT by Genzyme and Mount Sinai

– European Patent Office affirmed revocation of a Serono patent which ended litigation against Replagal in Europe

JEANNIE CHIN,
R & D Specialist II

NOVEMBER – Open-label extension study showed I2S treatment improved multiple clinical manifestations of Hunter syndrome at twelve months

DECEMBER – Lydia Villa-Komaroff, Chief Operating Officer of Whitehead Institute and Dennis Langer, President, North America, Dr. Reddy's Laboratories, named to TKT's Board of Directors

– Orphan Australia became marketing and distribution partner for Replagal in Australia and New Zealand

2004

JANUARY – Reallocated resources in Fabry program after ending efforts to seek U.S. approval of Replagal

FEBRUARY – Increased number of countries where Replagal is approved to 28 following Canadian approval

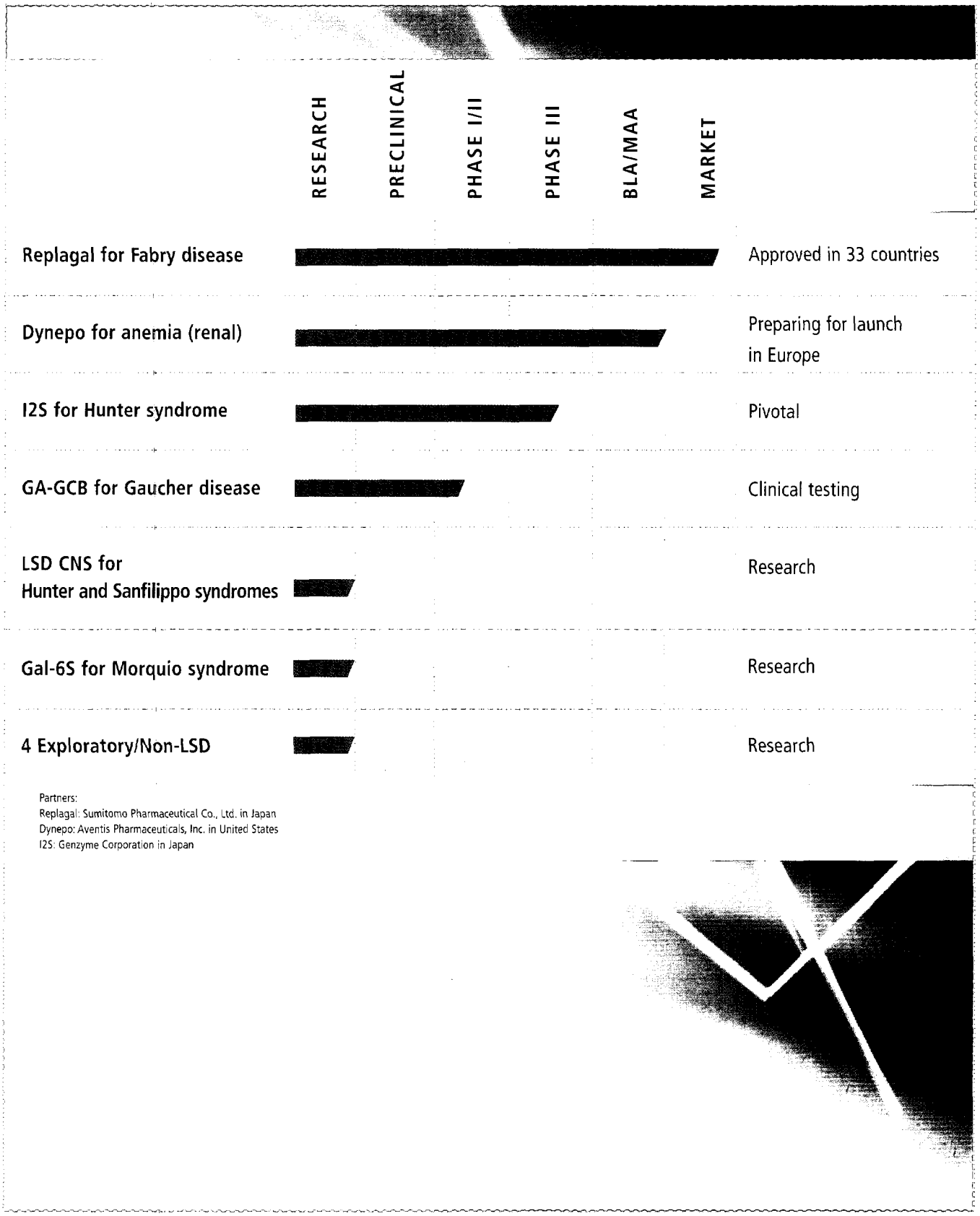
– Paladin Labs became distribution partner for Replagal in Canada

MARCH – Over-enrolled Hunter syndrome pivotal trial, with 96 patients participating from 17 countries

– Regained rights to Dynepo from Aventis outside U.S.

APRIL – Initiated clinical testing of GA-GCB for Gaucher disease

– Sold $90 million principal amount of 1.25% senior convertible notes



Partners:
Replagal: Sumitomo Pharmaceutical Co., Ltd. in Japan
Dynepo: Aventis Pharmaceuticals, Inc. in United States
I2S: Genzyme Corporation in Japan

Form 10-K

2003

Annual Report

UNITED STATES SECURITIES AND EXCHANGE COMMISSION
Washington, D.C. 20549

Form 10-K

FOR ANNUAL AND TRANSITION REPORTS PURSUANT TO SECTIONS 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934

(Mark One)

☑ **ANNUAL REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934**

For the fiscal year ended December 31, 2003

☐ **TRANSITION REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934**

For the transition period from to

Commission File No. 0-21481

Transkaryotic Therapies, Inc.

(Exact name of registrant as specified in its charter)

Delaware	**04-3027191**
(State or other jurisdiction of incorporation or organization)	*(I.R.S. Employer Identification No.)*
700 Main Street **Cambridge, Massachusetts** *(Address of principal executive offices)*	**02139** *(Zip Code)*

Registrant's telephone number, including area code:
(617) 349-0200

Securities registered pursuant to Section 12(b) of the Act:
None

Securities registered pursuant to Section 12(g) of the Act:
Common Stock, $.01 par value
Preferred Stock Purchase Rights
(Title of class)

Indicate by check mark whether the registrant: (1) has filed all reports required to be filed by Section 13 or 15(d) of the Securities Exchange Act of 1934 during the preceding 12 months (or for such shorter period that the registrant was required to file such reports), and (2) has been subject to such filing requirements for the past 90 days. Yes ☑ No ☐

Indicate by check mark if disclosure of delinquent filers pursuant to Item 405 of Regulation S-K is not contained herein, and will not be contained, to the best of registrant's knowledge, in definitive proxy or information statements incorporated by reference in Part III of this Form 10-K or any amendment to this Form 10-K. ☐

Indicate by check mark whether the registrant is an accelerated filer as defined by Rule 12b-2 of the Securities Exchange Act of 1934, as amended. Yes ☑ No ☐

As of June 30, 2003, the approximate aggregate market value of the voting Common Stock held by non-affiliates of the registrant was $398,214,000 based on the last reported sale price of the registrant's voting Common Stock on The Nasdaq National Market as of the close of business on June 30, 2003. There were 34,612,391 shares of Common Stock outstanding as of March 1, 2004.

DOCUMENTS INCORPORATED BY REFERENCE

Document	10-K Part
Specifically Identified Portions of the Registrant's Proxy Statement for the Annual Meeting of Stockholders to be held on June 22, 2004	III

PART I

Item 1. *Business*

Overview

Transkaryotic Therapies, Inc. ("TKT" or the "Company") is a biopharmaceutical company researching, developing and commercializing therapeutics, primarily for the treatment of rare genetic diseases caused by protein deficiencies. TKT has received approval to market and sell Replagal (agalsidase alfa), an enzyme replacement therapy for the long-term treatment of patients with Fabry disease, in 28 countries outside of the United States. Two of the products TKT is developing include iduronate-2-sulfatase ("I2S"), an enzyme replacement therapy for the treatment of Hunter syndrome, and Gene-Activated glucocerebrosidase ("GA-GCB") for the treatment of Gaucher disease. The Company is currently conducting a pivotal clinical trial of I2S and anticipates starting a Phase I/II clinical trial of GA-GCB in the second quarter of 2004. TKT is currently evaluating out-licensing opportunities for GA-GCB as well as a number of other gene-activated and gene therapy products.

Recent Developments

Pivotal Clinical Trial of Iduronate-2-Sulfatase for Hunter Syndrome

In September 2003, TKT began enrolling patients in a randomized, double-blind, placebo-controlled, clinical trial to evaluate the effect of I2S over twelve months in patients with Hunter syndrome. TKT completed enrollment in the pivotal clinical trial in March 2004. The pivotal clinical trial involves the evaluation of I2S in 96 patients with Hunter syndrome at nine sites around the world. If the results of this trial are positive, TKT expects to file applications for marketing approval of I2S in the United States and Europe in the second half of 2005.

Genzyme Distribution Agreement for I2S

In October 2003, TKT and Genzyme Corporation ("Genzyme") entered into an agreement under which Genzyme will develop and commercialize TKT's I2S product in Japan and other Asia/Pacific territories. Under the agreement, Genzyme paid TKT approximately $1.5 million in upfront payments and agreed to pay TKT up to an additional $8.0 million relating to regulatory and commercial milestones, primarily related to a regulatory submission and approval in Japan. TKT will manufacture the I2S bulk drug substance for commercial sale in Genzyme's territories and will receive payments that will equal approximately one-third of net sales in those territories. In addition, Genzyme has options to obtain rights to select other research programs being developed by TKT. TKT has retained all rights in North America, Europe, and Latin America, and intends to commercialize its I2S product directly in those territories.

Regulatory Status of Replagal

In February 2004, TKT received approval to market and sell Replagal in Canada. Including Canada, Replagal is currently approved for commercial sale in a total of 28 countries outside of the United States. In 2003, TKT recorded $57.2 million in product sales, principally in Europe.

TKT has not received approval to market and sell Replagal in the United States. In April 2003, Genzyme received marketing authorization in the United States for Fabrazyme (agalsidase beta), its competing enzyme replacement therapy product for the treatment of Fabry disease. Because Fabrazyme had received orphan drug designation in the United States, Fabrazyme received orphan drug exclusivity upon its marketing approval. Once a product receives orphan drug exclusivity, the United States Food and Drug Administration ("FDA") may not approve another application to market the same drug for the same indication for a period of seven years, except in limited circumstances set forth under the U.S. Food, Drug and Cosmetic Act and its implementing regulations (the "FDA Statute"). Because Fabrazyme received marketing approval in the United States before Replagal and received orphan drug exclusivity, the FDA may not approve Replagal and Replagal will be excluded from the United States market for seven years, until April 2010, unless the

Company receives approval to market and sell Replagal in the United States and the Company can demonstrate that Replagal satisfies the limited criteria for exceptions set forth in the FDA Statute.

In January 2004, the Company determined that it would cease its efforts to seek the approval of Replagal from the FDA for the foreseeable future and withdrew its Biologics License Application ("BLA") for Replagal. TKT intends to continue to market and sell Replagal in countries where it is approved outside the United States and to continue the Company's efforts to introduce Replagal in new markets. TKT also plans to continue to supply Replagal to United States patients in ongoing Replagal clinical trials and investigator sponsored investigational new drug applications ("IND") for the foreseeable future. The Company's decision to cease its efforts to seek FDA approval of Replagal was based in part on the FDA's response to its request for a Special Protocol Assessment. TKT submitted this request to the FDA in November 2003 in an effort to identify a regulatory approach that could lead to United States approval of Replagal. In its response to TKT's request for a Special Protocol Assessment, the FDA indicated that it would expect TKT to conduct a head-to-head trial comparing Replagal to Fabrazyme in patients with Fabry disease as the way to demonstrate either superior safety or efficacy. Based on the limited availability of Fabry patients for clinical trials and the large number of patients necessary to conduct a meaningful head-to-head trial, the Company decided to focus its resources on expansion of the market for Replagal outside the United States and the development of other important programs.

Filing of GA-GCB Investigational New Drug Application

In December 2003, TKT filed an IND with the FDA for human clinical trials of GA-GCB. This IND became effective in January 2004. The Company anticipates starting a Phase I/II clinical trial of GA-GCB in the second quarter of 2004.

Changes in Board of Directors

In November 2003, Dr. Lydia Villa-Komaroff, Chief Operating Officer of Whitehead Institute, and Dr. Dennis Langer, President, North America, of Dr. Reddy's Laboratories, were elected to the Company's board of directors. Also in November 2003, William R. Miller and James E. Thomas resigned from the Company's board of directors.

Products

Therapeutics for the Treatment of Rare Genetic Diseases

Some rare genetic diseases are known to be caused by the deficiency of a single, well-characterized protein. The patient's inability to produce sufficient amounts of the specified protein results in symptoms that can be debilitating and, ultimately, life-threatening. These diseases include lysosomal storage disorders, such as Fabry disease, Gaucher disease, Hunter syndrome, Hurler syndrome, Morquio syndrome, Pompe disease, and Sanfilippo disease. These disorders result from an inherited inability to produce an enzyme responsible for the breakdown of biomolecules such as fats and sugars. The build-up of such biomolecules in lysosomes leads to toxicity, ultimately killing the cells from within. No effective treatment currently exists for most of these rare diseases.

The Company's approach to treat lysosomal storage disorders is to manufacture the missing or deficient protein and deliver it to the patient. The Company's strategy for developing products to treat rare genetic diseases is to build on the Company's core competencies in gene expression, cell culture, and protein purification and characterization to create protein replacement products for diseases which are characterized by the absence of certain metabolic enzymes. In addition to Replagal for Fabry disease, the Company is developing I2S for Hunter syndrome.

Although the primary focus of the Company's research and development efforts in rare genetic diseases has been lysosomal storage disorders, TKT plans to begin development of treatments for other types of rare genetic diseases.

Iduronate-2-Sulfatase (I2S) for Hunter Syndrome

TKT is developing its I2S enzyme replacement therapy for the treatment of Hunter syndrome, also known as mucopolysaccharidosis II ("MPS II"). Hunter syndrome is an inherited lysosomal storage disorder caused by a deficiency of the enzyme iduronate-2-sulfatase. As a result of this deficiency, complex carbohydrates accumulate in cells of the body, causing debilitating symptoms in the patient. Physical manifestations include skeletal deformities, obstructive airway disease, cardiac failure and, in the most severe cases, central nervous system involvement. Many patients die during childhood. The Company believes that I2S enzyme replacement therapy could result in improvements in many of the clinical manifestations associated with Hunter syndrome, other than neurological issues experienced by many patients. Although there is some uncertainty among experts, TKT believes there are up to 2,000 patients worldwide afflicted with Hunter syndrome in jurisdictions where reimbursement may be possible.

The Company's I2S product is a human iduronate-2-sulfatase produced by genetic engineering technology intended for long-term treatment of Hunter syndrome. The rationale for the therapy is that TKT's I2S replaces an enzyme that is deficient in patients with Hunter syndrome, and therefore could potentially either stop or ameliorate the clinical manifestations of the disease. TKT's I2S product has been designated an orphan drug in both the United States and the European Union, and the Company believes that its I2S product is the only known enzyme replacement therapy in development for the treatment of Hunter syndrome. There is currently no effective therapy for Hunter syndrome, and the Company is not aware of any other products being developed to treat this disease.

In March 2002, TKT completed a randomized, double-blind, placebo-controlled, dose-escalating Phase I/II clinical trial to assess the safety, pharmacodynamic and pharmacokinetic profiles, and clinical activity of I2S in 12 patients with Hunter syndrome. In October 2002, at the American Society of Human Genetics Annual Meeting, the principal investigator of the clinical trial reported that, in the study, I2S was generally well-tolerated and demonstrated evidence of clinical activity in several critical areas of Hunter syndrome, including reduction in liver and spleen mass and stabilized pulmonary function. The most common side effects from I2S treatment were infusion reactions characterized by flushing, rigors, dizziness and headaches. Infusion-related reactions occurred in five treated patients and were successfully managed by slowing the infusion rate and using premedications. In addition, one of the nine treated patients developed an IgG antibody to I2S, thereby possibly making the enzyme ineffective in treating the disease in this patient. With only three patients per dose group, the study was not designed to demonstrate statistical significance. All 12 patients are now enrolled in an open label extension study, including nine patients who have received I2S for at least 28 months.

In September 2003, TKT began enrolling patients in a randomized, double-blind, placebo-controlled, clinical trial to evaluate the effect of its iduronate-2-sulfatase product over twelve months in patients with Hunter syndrome. The pivotal clinical trial, entitled "Assessment of Iduronate-2-Sulfatase in MPS II" (or "AIM"), includes 96 patients with Hunter syndrome at nine sites around the world. TKT completed enrollment in the AIM study in March 2004. TKT expects preliminary results from the AIM study in the second quarter of 2005 and, if positive, the Company expects to submit applications for marketing approval in both the United States and Europe in the second half of 2005.

In October 2003, TKT and Genzyme entered into an agreement under which Genzyme will develop and commercialize TKT's I2S product in Japan and other Asia/Pacific territories. Under the terms of the agreement, Genzyme paid TKT approximately $1.5 million in upfront payments. TKT also has the potential to receive up to an additional $8.0 million relating to regulatory and commercial milestones, primarily related to a regulatory submission and approval in Japan. TKT will manufacture the I2S bulk drug substance for commercial sale in Genzyme's territories and will receive payments that will equal approximately one-third of net sales in those territories. In addition, Genzyme has options to obtain rights to select other research programs being developed by TKT. TKT has retained all rights in North America, Europe, and Latin America, and intends to commercialize its I2S product directly in those territories. This agreement has a term of ten years unless terminated earlier by either party.

Replagal for Fabry Disease

Fabry disease is a rare, inherited genetic disorder caused by deficient activity of the lysosomal enzyme alpha-galactosidase A. Patients with Fabry disease show diverse clinical manifestations including severe pain and renal and cardiovascular complications. Some of these clinical manifestations can begin in childhood. It affects both males and females, which results in premature mortality in the fourth or fifth decade of life due to kidney disease, heart disease and stroke. The Company estimates that 5,000 patients worldwide are affected by Fabry disease. However, the number of actual patients is difficult to ascertain because many patients die from kidney or heart disease without the underlying cause of the kidney or heart disease being properly identified as Fabry disease. Due to its rarity and vast array of symptoms diagnosis is often difficult and affected men and woman have a significantly reduced quality of life.

Replagal is a fully human alpha-galactosidase A protein, produced using TKT's proprietary gene activation technology. Replagal therapy replaces the deficient alpha-galactosidase A with active enzyme to stop or ameliorate the clinical manifestations of the disease

In February 2004, TKT received approval to market and sell Replagal in Canada. Including Canada, Replagal is currently approved for commercial sale in a total of 28 countries outside of the United States. In 2003, TKT recorded $57.2 million in product sales, principally in Europe.

In August 2001, the European Commission granted marketing authorization for Replagal in the European Union. Since August 2001, TKT has received approval to market Replagal in a number of other countries. The Company has established pricing and reimbursement for substantially all patients receiving Replagal in the European Union. Country by country pricing was initially established as the local currency equivalent of between approximately $165,000 and $175,000 per patient per year for an average patient weighing 70 kilograms. The price generally remains fixed in the local currencies and varies in United States dollars with exchange rate fluctuations. Both Replagal and Fabrazyme were granted co-exclusive orphan drug status in the European Union for up to 10 years.

As part of its approval of Replagal, the European Commission required the Company to conduct additional clinical trials of Replagal and to provide the European Commission with an annual assessment of Replagal. The Company is currently conducting these trials and expects to submit the results of these trials in accordance with the requirements of the European Commission.

TKT has not received approval to market and sell Replagal in the United States. In April 2003, Genzyme received marketing authorization in the United States for Fabrazyme, its competing enzyme replacement therapy product for the treatment of Fabry disease. Because Fabrazyme had received orphan drug designation in the United States, Fabrazyme received orphan drug exclusivity upon its marketing approval. Once a product receives orphan drug exclusivity, the FDA may not approve another application to market the same drug for the same indication for a period of seven years, except in limited circumstances set forth under the FDA Statute. Because Fabrazyme received marketing approval in the United States before Replagal and received orphan drug exclusivity, the FDA may not approve Replagal and Replagal will be excluded from the United States market for seven years, until April 2010, unless the Company receives approval to market and sell Replagal in the United States and the Company can demonstrate that Replagal satisfies the limited criteria for exceptions set forth in the FDA Statute.

In January 2004, the Company determined that it would cease its efforts to seek the approval of Replagal from the FDA and withdrew its BLA for Replagal. TKT intends to continue to market and sell Replagal in countries where it is approved outside the United States and to continue the Company's efforts to introduce Replagal in new markets. TKT also plans to continue to supply Replagal to United States patients in ongoing Replagal clinical trials and investigator sponsored INDs for the foreseeable future. The Company's decision to cease its efforts to seek FDA approval of Replagal was based in part on the FDA's response to its request for a Special Protocol Assessment. TKT submitted this request to the FDA in November 2003 in an effort to identify a regulatory approach that could lead to United States approval of Replagal. In its response to TKT's request for a Special Protocol Assessment, the FDA indicated that it would expect TKT to conduct a head-to-head trial comparing Replagal to Fabrazyme in patients with Fabry disease as the way to demonstrate either superior safety or efficacy. Based on the limited availability of Fabry patients for clinical trials and the large number of patients necessary to conduct a meaningful head-to-head trial, the Company decided to focus its

resources on expansion of the market for Replagal outside the United States and the development of other important programs.

TKT is a party to a collaboration agreement with Sumitomo Pharmaceutical Co., Ltd. ("Sumitomo"), for the commercialization of Replagal in Japan, Korea, Taiwan, and China. In November 2002, Sumitomo submitted an application for marketing authorization for Replagal in Japan. TKT currently expects a decision on Japanese approval in the second half of 2004.

The Company is a party to a patent litigation with Genzyme and Mount Sinai School of Medicine of New York University ("Mount Sinai") regarding Replagal. In October 2003, pursuant to a global legal settlement, Genzyme agreed to withdraw from this suit and paid the Company approximately $1.6 million. Mount Sinai was not a party to the settlement. Mount Sinai continues to pursue this action. A description of this litigation is set forth in "Item 3. Legal Proceedings — Replagal Litigation."

Gene-Activated Versions of Proteins That Would Compete With Currently Marketed Proteins

TKT's gene activation technology is a proprietary approach to the development and large-scale production of therapeutic protein products. This approach is based on the activation of a human cell's own or endogenous genes encoding therapeutic proteins, as opposed to foreign or exogenous genes. Gene activation does not involve the conventional method of cloning or copying an exogenous gene sequence and inserting the gene sequence into a cell. Under TKT's approach, the endogenous gene encoding a protein, as it naturally exists in the human cell, is activated through the insertion of a segment of DNA into the cell. The Company believes this technology could allow for the development and commercialization of a number of therapeutic proteins, including versions of proteins that would compete with proteins currently being marketed by third parties.

The Company believes that its gene activation technology may be used to express a wide variety of therapeutically valuable proteins at levels suitable for large-scale manufacturing purposes. Since gene activation technology avoids certain technical limitations of conventional recombinant protein production technology and does not rely on manipulation of cloned genes, the Company believes that the gene activation technology is at least as efficient as, and may be more cost-effective than, conventional genetic engineering techniques for protein production.

The Company's Gene-Activated versions of proteins that would compete with proteins currently being marketed by third parties include the Company's GA-GCB, Dynepo, GA-GCSF, GA-FSH, and GA-hGH programs described below. The Company is seeking collaborative partners for all of these products other than Dynepo, which is licensed to Aventis. The Company would consider licensing all of these products to a single collaborative partner or licensing the products on an individual basis to several collaborative partners. The Company also uses its gene activation technology to manufacture some of the Company's therapeutics for the treatment of rare genetic diseases, such as Replagal.

Gene-Activated Glucocerebrosidase (GA-GCB) for Gaucher Disease

TKT is developing a glucocerebrosidase enzyme replacement therapy for the treatment of Gaucher disease. In December 2003, TKT filed an IND with the FDA for a human clinical trial of GA-GCB. This IND became effective in January 2004. The Company anticipates starting a Phase I/II clinical trial of GA-GCB in the second quarter of 2004.

Gaucher disease is the most common of the inherited lysosomal storage diseases and is caused by a deficiency of the enzyme glucocerebrosidase. As a result of this deficiency, certain lipids accumulate in specific cells of the liver, spleen, and bone marrow causing significant clinical symptoms in the patient, including enlargement of the liver and spleen, hematologic abnormalities, and bone disease.

The Company has conducted extensive analytical and animal testing of GA-GCB, which has demonstrated that GA-GCB has the appropriate structural properties and purity, potency, and safety profile required

for initiating human clinical studies. The Company has also conducted manufacturing development work for GA-GCB. TKT uses its proprietary gene activation technology for the manufacture of GA-GCB in a continuous human cell line that is suitable for large-scale manufacturing. TKT is seeking a collaborator for this product.

Genzyme is marketing Cerezyme, its enzyme replacement therapy for Gaucher disease. Cerezyme and its predecessor drug have been on the market worldwide for over a decade, and Genzyme has reported worldwide sales of approximately $739 million for worldwide sales of Cerezyme in 2003. If approved, GA-GCB would face competition from Cerezyme.

Dynepo for Anemia Related to Chronic Renal Failure

In collaboration with Aventis, TKT has developed Dynepo, a fully human erythropoietin for the treatment of anemia related to chronic renal failure. Erythropoietin, a circulating protein hormone that stimulates the differentiation of certain progenitor cells in the bone marrow, is produced in the kidney when the body requires additional red blood cells. When this protein is not produced or not produced in sufficient quantities, anemia develops in the patient.

Aventis is responsible for obtaining regulatory approval and selling and marketing Dynepo throughout the world, except for Japan. In March 2002, the European Commission granted marketing approval of Dynepo in the European Union. Dynepo has not been approved in the United States. In 2000, Aventis submitted a BLA to the FDA seeking marketing authorization for Dynepo in the United States. The FDA did not accept the BLA for filing and requested that Aventis provide additional manufacturing data. Aventis has not yet submitted the requested additional data to the FDA and the Company cannot predict whether or when it will do so.

Aventis has not launched Dynepo in Europe. The Company cannot predict whether or when Aventis will determine to launch Dynepo in Europe.

Dynepo would compete with a multitude of products, including products marketed by Amgen, Johnson & Johnson, F. Hoffmann-La Roche Ltd. (Boehringer Mannheim GmbH), Sankyo Company Ltd., Chugai Pharmaceutical Co., Ltd., and the pharmaceutical division of Kirin Brewery Co., Ltd. in Japan.

The Company and Aventis are parties to patent litigation with Amgen Inc. ("Amgen") in the United States and Kirin-Amgen, Inc. ("Kirin-Amgen") in the United Kingdom with respect to Dynepo. A description of the Dynepo litigation is set forth in "Item 3. Legal Proceedings — Dynepo Patent Litigation".

Gene-Activated Granulocyte Colony Stimulating Factor (GA-GCSF)

TKT has developed a Gene-Activated human granulocyte colony stimulating factor ("GA-GCSF") for the treatment of low white blood cell count, known as neutropenia, which often results from cancer chemotherapy or bone marrow transplantation, and for the treatment of other indications. The Company originally developed GA-GCSF under a collaboration agreement with Aventis. In November 2000, TKT and Aventis terminated their collaboration relating to GA-GCSF, and TKT reacquired the rights to GA-GCSF. The Company has ceased its development of its GA-GCSF product and is seeking collaborative partners for this program.

In 2000, Aventis completed a Phase I clinical trial of GA-GCSF in 32 healthy volunteers. In the study, the volunteers were given equivalent doses of either Neupogen, a commercial product for the treatment of neutropenia marketed by Amgen, or GA-GCSF in a randomized, double blind, multiple dose, dose escalation study. The study was designed to test the safety, tolerability, and preliminary pharmacodynamic and pharmacokinetic behavior of GA-GCSF in these volunteers. The results of this clinical trial suggest that GA-GCSF is well-tolerated and comparable to Neupogen in its pharmacodynamic effects on increasing counts of neutrophils, a type of white blood cell.

GA-GCSF would compete with several treatments for neutropenia currently marketed by Amgen, including Amgen's extended release Neulasta for the treatment of neutropenia associated with myelosuppressive cancer chemotherapy and Amgen's first generation Neupogen.

Gene-Activated Follicle-Stimulating Hormone (GA-FSH)

TKT has developed a Gene-Activated follicle-stimulating hormone ("GA-FSH") to increase ovulation in patients participating in assisted reproductive technology programs and in certain infertile patients. The Company has conducted extensive analytical and animal testing of GA-FSH, which the Company believes has demonstrated that GA-FSH has the appropriate structural properties and the purity, potency, and safety profile required for initiating human clinical studies. The Company has also conducted limited manufacturing development work for GA-FSH. The Company has ceased its development of its GA-FSH product and is seeking collaborative partners for this program.

GA-FSH would compete with several follicle-stimulating hormone products currently marketed in the United States, including products by Organon International, Inc. and Serono International S.A. ("Serono").

Gene-Activated Human Growth Hormone (GA-hGH)

TKT has developed Gene-Activated human growth hormone ("GA-hGH") for the treatment of short stature associated with growth hormone deficiency and other indications. The Company has ceased its development of its GA-hGH product and is seeking collaborative partners for this program.

GA-hGH would compete with several human growth hormones currently marketed in the United States, including products by Pharmacia & Upjohn, Inc., Eli Lilly and Company, Genentech, Inc., and Serono.

Gene Therapy Products

Transkaryotic Therapy, the Company's approach to gene therapy, is based on genetically modifying patients' cells to produce and deliver therapeutic proteins. The Company believes it has developed the basic technologies required for treatment which is safe, cost-effective, and potentially clinically superior to conventional gene therapy approaches that rely on viral-based vectors.

TKT believes its gene therapy system is broadly enabling and, accordingly, may be applicable to the treatment of a wide range of human diseases. For example, TKT believes its gene therapy may be well-suited to allow safe and long-term delivery of therapeutic proteins for the treatment of chronic protein deficiency states, including hemophilia, diabetes, and anemia.

There are a number of technical approaches to gene therapy, but two basic distinctions can be used to characterize the field. The first distinction is viral versus non-viral. Viral-based gene therapy approaches use genetically modified viruses to introduce genes into human cells by infection. Non-viral approaches use noninfectious (chemical or physical) means to introduce the genes. The second distinction is *in vivo* versus *ex vivo*. *In vivo* gene therapies are based on the administration of DNA-based drugs directly to the patient. *Ex vivo* gene therapies are based on removing a small number of cells from a patient, introducing a gene into the cells and implanting the engineered cells into the patient.

TKT's gene therapy technology platform is a non-viral, *ex vivo* system, which the Company believes is significantly different from other approaches to gene therapy. The Company believes that these differences will allow for physiologic levels of protein expression in patients for extended periods and readministration, two goals that historically have represented major obstacles in alternative gene therapy systems.

Transkaryotic Therapy takes advantage of the patient's natural ability to synthesize therapeutic proteins for extended periods. The potential benefits of Transkaryotic Therapy for some indications include:

- improved therapeutic outcome,
- the elimination of frequent painful injections and patient compliance problems,
- a reduction of side effects due to overdosing and underdosing of conventional proteins, and

- significant reductions in cost.

Accordingly, the Company believes that its therapy may be less costly than therapy using conventional protein pharmaceuticals, although for larger indications the cost of the infrastructure necessary to provide Transkaryotic Therapy may be substantial.

The major alternative to TKT's system is based on the use of genetically-modified viruses to infect patients' cells. Transkaryotic Therapy does not use infectious agents such as retroviruses, adenoviruses, or adeno-associated viruses to genetically engineer patients' cells.

The Company has ceased its development efforts in this area and is seeking collaborative partners for all of its gene therapy products.

Factor VIII Gene Therapy for Hemophilia A

The Company developed its Factor VIII gene therapy product pursuant to a collaboration and license agreement with Wyeth, which succeeded Genetics Institute, Inc. ("Wyeth"). In August 2003, the Company reacquired its Factor VIII gene therapy rights from Wyeth and obtained a non-exclusive worldwide license to use Wyeth's intellectual property relating to Factor VIII gene therapy. The Company has ceased its development of its Factor VIII gene therapy program and is seeking collaborative partners for this product.

Hemophilia A is caused by a deficiency or defect in coagulation caused by inadequate amounts of a protein called Factor VIII. Patients with the disease experience acute, debilitating, and often life-threatening bleeding episodes. Depending on the severity of the disease, bleeding may occur spontaneously or after minor trauma. Conventional treatment consists of temporarily increasing the patient's Factor VIII levels through infusions of plasma-derived or recombinantly-produced Factor VIII. The Company estimates that there are approximately 50,000 hemophilia A patients worldwide.

In 2001, TKT completed the treatment phase of a Phase I clinical trial of its Factor VIII gene therapy product in twelve patients with severe hemophilia A. This trial, led by researchers at Beth Israel Deaconess Medical Center in Boston, Massachusetts, was the first clinical trial to evaluate a gene therapy treatment for hemophilia A. The 12 patients in the trial had baseline Factor VIII levels less than 1% of normal. The study involved a one year evaluation phase and a two-year follow-up period. Nine patients received implantation of Factor VIII expressing cells into the greater omentum, an area of the abdomen, and three patients received implantation of Factor VIII expressing cells into the lesser omentum. All twelve patients who received Factor VIII expressing cells were followed for two years to generate long-term data. The study was designed to assess the safety of Factor VIII gene therapy, though clinical activity was also observed.

TKT believes that the results of the study demonstrate that TKT's non-viral, *ex vivo* gene therapy system can be safely administered to patients and may be effective in reducing the occurrence of spontaneous bleeding in patients. Specifically, seven of the nine patients who received Factor VIII expressing cells into the greater omentum had decreased bleeding frequency and/or Factor VIII usage during the first year. Two of these patients had no spontaneous bleeding episodes for nearly one year following implantation of the Factor VIII expressing cells. Clinical changes were not observed in patients who received Factor VIII expressing cells into the lesser omentum. There were no serious adverse events related to the Factor VIII expressing cells or the implantation. No antibodies to Factor VIII were detected in any of the patients.

Collaborations

Genzyme

In October 2003, TKT and Genzyme entered into an agreement under which Genzyme will develop and commercialize TKT's I2S product in Japan and other Asia/Pacific territories. Under the agreement, Genzyme paid TKT approximately $1.5 million in upfront payments and agreed to pay TKT up to an additional $8.0 million relating to regulatory and commercial milestones, primarily related to a regulatory submission and approval in Japan. TKT will manufacture the bulk drug substance for commercial sale in Genzyme's territories and will receive payments that will equal approximately one-third of net sales in those

territories. In addition, Genzyme has options to obtain rights to select other research programs being developed by TKT. TKT has retained all rights in North America, Europe, and Latin America, and intends to commercialize its I2S product directly in those territories. The agreement expires 10 years after Genzyme begins selling I2S, subject to earlier termination by either party under specified circumstances, including a material breach of the agreement by either party.

TKT continues to sell Replagal outside the United States in competition with Genzyme, and is developing a GA-GCB product, which, if approved, will compete with Genzyme's Cerezyme.

Aventis Pharma

TKT entered into an agreement with Aventis in May 1994 focused on the development of Dynepo. Under the agreement, TKT has the potential to receive up to $38.0 million, consisting of license fees, equity investments, milestone payments, and research funding, of which TKT had received $20.0 million at December 31, 2003. The remaining payments are contingent upon the achievement of regulatory and commercial milestones. TKT also is entitled to a low double-digit royalty on net sales of Dynepo by Aventis. Due to the uncertainty involving both the regulatory approval of Dynepo in the United States and ongoing litigation, there can be no assurance that the Company will receive the remaining milestone payments or earn royalties on product sales.

Under the agreement, TKT granted Aventis exclusive worldwide rights to make, use, and sell Dynepo. Aventis is responsible, at its own expense, for development, manufacturing, and marketing activities for the product. The license agreement expires, on a country by country basis, on the later of the date 10 years after the first commercial sale of the covered product in such country and the last to expire of the patents licensed under such agreement with respect to such country, subject to earlier termination by either party under specified circumstances, including a material breach of the agreement by either party. Aventis has relinquished its rights to market and sell Dynepo in Japan to TKT.

The Company and Aventis have been involved in a patent infringement action with Amgen and Kirin-Amgen with respect to Dynepo. The litigation is costly and the Company is required to reimburse Aventis, which is paying the expenses of the Amgen and Kirin-Amgen litigations relating to Dynepo, for 50% of the expenses. Aventis is also entitled to deduct up to 50% of any royalties due to the Company from the sale of Dynepo until Aventis has recouped the full amount of TKT's share of litigation expenses. The Company currently estimates that its share of the expenses associated with the litigation will total between approximately $15.0 million and $20.0 million by the time the matter is finally adjudicated. A description of the Dynepo litigation is set forth in "Item 3. Legal Proceedings — Dynepo Patent Litigation".

Sumitomo Pharmaceutical Co., Ltd.

In July 1998, the Company entered into an exclusive distribution agreement with Sumitomo to commercialize Replagal in Japan, Korea, China and Taiwan. Under the agreement, Sumitomo is responsible, at its own expense, for development and commercialization of Replagal in the territories covered by the agreement. Sumitomo is required to purchase Replagal from the Company for sale in the territories covered by the agreement for a transfer price calculated as a percentage of net sales. Under the agreement, TKT has the potential to receive up to $8.0 million upon the achievement of regulatory milestones, of which TKT had received $3.0 million at December 31, 2003. The Company is entitled to receive the remaining $5.0 million upon Japanese marketing authorization of Replagal. The Company expects that Sumitomo will receive a response from the Japanese authorities in the second half of 2004. The agreement expires on a country-by-country basis 15 years after Sumitomo begins selling Replagal in the respective country, subject to earlier termination by either party under specified circumstances, including a material breach of the agreement by either party.

Research and Development

For the years ended December 31, 2003, 2002 and 2001, the Company spent approximately $74.1 million, $81.3 million, and $65.9 million, respectively, on research and development activities. Collaborative partners

funded $1.7 million, $1.8 million, and $2.7 million of these research and development expenses in 2003, 2002 and 2001, respectively. More information on research and development is set forth under the caption "Results of Operations" in "Item 7. Management's Discussion and Analysis of Financial Condition and Results of Operations."

Sales and Marketing

TKT plans to market and sell the products for which it obtains marketing approval through a combination of establishing its own commercial capabilities and entering into sales, marketing and distribution arrangements with third parties.

TKT Europe

In April 2000, the Company established a subsidiary in Sweden known as TKT Europe-5S AB ("TKT Europe") for the purpose of marketing, selling and distributing Replagal in Europe. The Company owns an 80% equity interest in TKT Europe and a team of European pharmaceutical executives with experience in marketing and selling pharmaceutical products in Europe own the remaining 20% equity interest in TKT Europe. The Company and TKT Europe are parties to a distribution agreement relating to Replagal, and the Company and the European stockholders of TKT Europe are parties to a stockholders' agreement relating to the operation of TKT Europe.

Under the distribution agreement, TKT granted TKT Europe exclusive marketing rights to distribute and market Replagal in all countries in Europe, and TKT Europe agreed to purchase Replagal exclusively from TKT at a negotiated transfer price. TKT is also required to pay TKT Europe a marketing service fee. The distribution agreement continues until December 31, 2010, and is subject to automatic two-year extensions unless a party provides notice of non-renewal at least one year prior to the expiration of the term.

The stockholders' agreement provides for the governance of TKT Europe. Under the agreement, the European stockholders have the right to elect three members of the Board of Directors, and the Company has the right to elect two members of the Board of Directors. Although the consent of TKT is required for various significant matters relating to the operation of TKT Europe, most day-to-day operations of TKT Europe are directed by the European stockholders.

Under the stockholders' agreement for TKT Europe, the Company is entitled to purchase the European stockholders' 20% ownership interest in TKT Europe in September 2004, for a price determined in accordance with a formula. Should the Company not exercise that right, the European stockholders of TKT Europe can require the Company to purchase the European stockholders' ownership interest sixty days thereafter. The buyout price is equal to (a) 20% of the operating profits, as defined in the stockholders' agreement, for the period from September 1, 2003 to August 31, 2004, multiplied by a buyout factor of four, subject to adjustment, plus (b) 20% of the accumulated positive earnings of TKT Europe. As a result, the amount of the buyout price is dependent on the profits of TKT Europe and the commercial success of Replagal in Europe. The Company estimates that the buyout price could be between $55.0 million and $65.0 million based on the Company's current estimates for sales and expenses.

As of March 1, 2004, TKT Europe employed 22 full time employees.

Asia/Pacific

Under the Company's agreement with Sumitomo, Sumitomo is responsible for commercializing Replagal in Japan, Korea, China and Taiwan. Under the Company's agreement with Genzyme, Genzyme is responsible for developing and commercializing TKT's I2S product in Japan and other Asia/Pacific territories.

Canada

In Canada, the Company established TKT Canada Inc. in 2003 for the marketing and sales of Replagal and any future products.

Aventis

Aventis is responsible for obtaining regulatory approval and marketing and selling Dynepo throughout the world except for Japan. Aventis has not launched Dynepo in Europe. The Company cannot predict whether or when Aventis will determine to launch Dynepo in Europe or anywhere else in the world.

United States Commercialization

In the United States, the Company has developed a small commercial infrastructure for the marketing and sale of its products. The Company expects that it will expand its infrastructure in the United States at such time as it anticipates receiving approval to market its products in the United States.

Distributors

TKT uses third party distributors to distribute Replagal in many areas of the world including Australia, Canada, Europe, Israel, and Taiwan.

Customers

The Company had three significant customers, Healthcare at Home Limited, Globopharm AG, and the University of Mainz, who accounted for 18%, 12% and 12%, respectively, of the Company's product sales in 2003. The same customers accounted for 8%, 6% and 22%, respectively, of the Company's product sales in 2002.

Manufacturing

TKT manufactures its therapeutic protein products using its proprietary gene activation technology as well as conventional recombinant protein production technology. TKT currently uses, and expects to continue to use in the future, internal manufacturing and contract manufacturing by third parties to meet its production requirements for preclinical testing, clinical trials, and commercial supply of its products and product candidates.

Prior to July 2003, the Company relied on a contract manufacturing arrangement with a third party for the production of bulk drug substance for Replagal for commercial sale. In January 2003, TKT terminated its arrangements with the contract manufacturer effective in July 2003. In connection with the termination of this arrangement, the Company incurred a termination fee of $2.5 million in 2002. The Company incurred charges of $2.6 million related to excess capacity at the terminated manufacturer's facility during the first half of 2003.

The Company has also manufactured bulk drug substance for Replagal for commercial sale and clinical trials and bulk drug substance for I2S and GA-GCB for clinical trials at its Cambridge, Massachusetts manufacturing facility (the "Alewife Facility"). In July 2003, the European Commission approved the Alewife Facility for the commercial manufacture of bulk drug substance for Replagal.

In October 2003, the Company began significant renovations to the Alewife Facility in order to expand its capacity and configure the facility for the production at a commercial scale of products other than Replagal. In anticipation of these renovations, in the third quarter of 2003 the Company ceased all manufacturing operations at the Alewife Facility. The Company expects to complete these renovations in the first half of 2004 and to recommence manufacturing operations in the second half of 2004. Once the Company completes these renovations, the appropriate regulatory authorities, including the European Commission, will need to re-inspect and re-approve the facility. Following such re-approval, the Company plans to resume manufacture of bulk drug substance for Replagal for commercial sale and clinical trials and of bulk drug substance for I2S and GA-GCB for clinical trials at the Alewife Facility. At the present time, the Company anticipates that existing inventory will be sufficient to fill customer orders for Replagal into 2005. If and when I2S and GA-GCB are approved for commercialization, the Company expects to manufacture bulk drug substance for I2S and GA-GCB for commercial sale at the Alewife Facility. The Company spent approximately $7.1 million for improvements to the Alewife Facility through 2003 and expects to spend an additional $7.0 to $8.0 million related to these renovations during the first half of 2004.

The Company is developing new manufacturing processes to manufacture TKT's bulk drug substance for Replagal and for I2S. Following the development of these new processes, the appropriate regulatory authorities, including the European Commission, will need to approve the new processes.

The Company relies on contract manufacturing arrangements with third parties with respect to the other aspects of the manufacture of Replagal, I2S, and GA-GCB, including the preparation and packaging of TKT-manufactured bulk drug substance into finished product. The Company also relies on third parties for supplies and raw materials used in the manufacture of its products.

Under TKT's collaborative arrangement with Aventis, Aventis is required to manufacture Dynepo for clinical trials and for commercial sales.

Patents, Proprietary Rights, Trade Secrets, and Licenses

Patents and Proprietary Issues

The Company believes that protection of the proprietary nature of its products and technology is important to its business. Accordingly, it has adopted and plans to maintain a vigorous program to secure and maintain such protection. The Company's practice is to file patent applications with respect to technology, inventions, and improvements that are important to its business. The Company also relies upon trade secrets, unpatented know-how, continuing technological innovation, and the pursuit of licensing opportunities to develop and maintain its competitive position.

As of December 31, 2003, TKT owned approximately 32 issued United States patents, approximately 41 pending United States patent applications, approximately 96 corresponding issued foreign patents from third parties, and approximately 230 corresponding pending foreign patent applications. As of December 31, 2003, TKT licensed approximately 18 issued United States patents and additional corresponding foreign patents from third parties. The patents owned or licensed by TKT expire at various dates through 2020 and cover various aspects of TKT's protein products and gene therapy products as well as various methods related to the development and manufacture of such products.

Intellectual Property Relating to Competing Products

For many currently marketed proteins, the product manufactured using conventional genetic engineering techniques does not represent the first time the protein was isolated and purified. As such, it is generally not possible to obtain a broad composition of matter patent for many of the currently marketed proteins. In contrast, the isolated and purified DNA sequences encoding these proteins, various vectors used to insert such DNA sequences into production cell lines, cell lines modified by the insertion of such DNA sequences, and corresponding methods, including methods of producing proteins using this approach, led to issued patents in many cases. While every patent must be analyzed on a claim-by-claim basis, TKT believes that, in many instances, its technology does not infringe claims based on isolated and purified DNA sequences encoding proteins of commercial interest because gene activation technology does not rely on the manipulation of cloned genes. The Company also avoids the use of technologies such as specific protein purification procedures that are the subject of patents that are not limited to protein products manufactured using conventional genetic engineering techniques. The Company, however, is currently involved in litigation with Mount Sinai in the United States relating to Replagal and, along with the Company's collaborative partner, Aventis, is involved in litigation in the United States and the United Kingdom with Amgen and Kirin-Amgen relating to Dynepo. A description of this litigation is set forth in "Item 3. Legal Proceedings."

Trade Secrets

To further protect its trade secrets and other proprietary property, the Company requires all employees, consultants, and collaborators having access to such proprietary property to execute confidentiality and invention rights agreements before beginning their relationship with the Company. While such arrangements are intended to enable the Company to better control the use and disclosure of its proprietary property and provide for the Company's ownership of proprietary technology developed on its behalf, they may not provide

meaningful protection for such property and technology in the event of unauthorized use or disclosure, or in the event that such trade secrets or other proprietary property are independently developed by a third party.

Intellectual Property Licenses

Cell Genesys, Inc.

In June 2002, the Company obtained an exclusive license to certain patents and patent applications from Cell Genesys, Inc. ("Cell Genesys") related to Cell Genesys' approach to gene activation. In consideration for the license, the Company initially paid Cell Genesys $11.0 million in cash and issued to Cell Genesys $15.0 million of shares of the Company's common stock. Under the agreement, Cell Genesys also has the potential to receive certain milestone payments contingent upon the outcome of related patent matters under the license agreement. If all of the milestones occur, the Company will be obligated to pay Cell Genesys an aggregate of $17.0 million payable in part in cash and in part in stock. The Company is not required to make royalty payments to Cell Genesys. The agreement terminates on the termination date of the last-to-expire patent right subject to the agreement, but is subject to earlier termination by either party in the event of a breach of the agreement by the other party. The Company believes the last-to-expire patent expires in 2016.

Under the agreement, the Company agreed that the number of shares of common stock initially issued to Cell Genesys would be adjusted at the time the Company registered such shares for resale under the Securities Act of 1933, if the market value of such shares at that time was greater or less than $15.0 million, as calculated in accordance with a predetermined formula. In January 2003, the Company and Cell Genesys renegotiated the consideration paid for the license, and the Company repurchased the shares of stock issued to Cell Genesys for $15.0 million in cash.

Women's and Children's Hospital, North Adelaide, Australia

The Company has an exclusive worldwide license to pending and issued patents from Women's and Children's Hospital, North Adelaide, Australia related to certain mucopolysaccharidoses diseases, a type of lysosomal storage disorder, including Hurler and Scheie syndromes or MPS I, Hunter syndrome or MPS II, and Sanfilippo syndrome or MPS III. TKT uses these pending and issued patents in the development of I2S. Under this license, TKT is obligated to pay royalties on net sales of products covered by a valid claim of a patent or patent application licensed to TKT. The license also imposes various commercialization, insurance and other obligations on the Company. The Company's failure to comply with these obligations could result in the termination of the license or the conversion of the license from an exclusive license to a non-exclusive license. The license terminates upon the expiration of the last to expire of the patents covered by the license.

Competition

The biotechnology industry is highly competitive and characterized by rapid and significant technological change. The Company believes that the primary competitive factors relating to the products that it is marketing and developing include safety and efficacy compared to competitive products, distribution channels, price and the availability of reimbursement.

Therapeutics for the Treatment of Rare Genetic Diseases

In general, the Company believes that rare genetic diseases have markets that are too small to attract the resources of most larger pharmaceutical and biotechnology companies. As a result, the Company believes that the primary competition with respect to its products for rare genetic diseases is from smaller pharmaceutical and biotechnology companies. For example, competitors for lysosomal storage disorders include BioMarin Pharmaceutical Inc., Actelion Ltd., and Genzyme. Specifically, Replagal competes with Genzyme's Fabrazyme, and any product commercialized by the Company to treat Gaucher disease will compete with Genzyme's Cerezyme. TKT does not know of any party developing an enzyme replacement therapy for the treatment of Hunter syndrome.

The markets for some of the potential products for rare genetic diseases caused by protein deficiencies are quite small. As a result, if competitive products exist, the Company may not be able to successfully commercialize its products. Some jurisdictions, including Europe and the United States, may designate drugs for relatively small patient populations as "orphan drugs". Generally, if a product that has an orphan drug designation subsequently receives the first marketing approval for the indication for which it has such designation, the product is entitled to orphan drug exclusivity. Orphan drug exclusivity means that applications to market the same drug for the same indication may not be approved, except in limited circumstances, for a period of up to 10 years in Europe and for a period of seven years in the United States.

Both Replagal and Fabrazyme were granted co-exclusive orphan drug status in the European Union for up to 10 years. Genzyme has orphan drug exclusivity for Fabrazyme in the United States until April 2010.

Gene-Activated Versions of Proteins That Would Compete With Currently-Marketed Proteins

TKT is developing Gene-Activated protein products that would compete with proteins currently being marketed by third parties. For instance, in the case of Dynepo, competing products are marketed by Amgen, Johnson & Johnson, F. Hoffmann-La Roche Ltd. (Boehringer Mannheim GmbH), Sankyo Company Ltd., Chugai Pharmaceutical Co., Ltd., and the pharmaceutical division of Kirin Brewery Co., Ltd. in Japan.

Many of the protein products against which the Company's Gene-Activated proteins would compete have well-known brand names, have been promoted extensively, and have achieved market acceptance by third-party payors, hospitals, physicians, and patients. In addition, many of the companies that produce these protein products have patents covering techniques used to produce these products, which have served as effective barriers to entry in the therapeutic proteins market. As with Amgen and its erythropoietin product, these companies may seek to block TKT's entry into the market by asserting that the Company's Gene-Activated proteins infringe their patents. Many of these products may be losing most or all of their patent protection in the next few years. As a result, the markets in which these products compete may become genericized. Consequently, some of these companies are also seeking to develop and commercialize new or potentially improved versions of their proteins.

Gene Therapy

The Company's gene therapy system will have to compete with other gene therapy systems, as well as with conventional methods of treating the disease and conditions targeted. Although no gene therapy product is currently marketed, a number of companies, including major biotechnology companies, pharmaceutical companies and development stage companies, are actively involved in this field.

United States Government Regulation

The testing, manufacturing, labeling, advertising, promotion, export, and marketing, among other things, of TKT's products are extensively regulated by governmental authorities in the United States. In the United States, the FDA regulates pharmaceutical products under the FDA Statute, and other laws, including, in the case of biologics, the Public Health Service Act. TKT believes that most of its products will be regulated by the FDA as biologics. TKT cannot market a biologic or drug until it has submitted an application for marketing authorization to the FDA, and the FDA has approved it. Both before and after approval is obtained, violations of regulatory requirements may result in various adverse consequences, including the FDA's delay in approving or refusal to approve a product, suspension or withdrawal of an approved product from the market, operating restrictions, and the imposition of civil or criminal penalties.

The steps required before a product may be approved for marketing in the United States generally include:

- preclinical laboratory tests and animal tests,
- the submission to the FDA of an IND, for human clinical testing, which must become effective before human clinical trials may begin,

- a series of clinical trials to establish the safety and efficacy of the product,
- the submission to the FDA of an application for marketing authorization,
- satisfactory completion of an FDA inspection of the manufacturing facility or facilities at which the product is made to assess compliance with GMP, and
- FDA review and approval of the application for marketing authorization.

Preclinical tests include laboratory evaluation of the product, as well as animal studies to assess the potential safety and efficacy of the product. The results of the preclinical tests, together with chemistry, manufacturing, and control data, are submitted to the FDA as part of an IND, which must become effective before human clinical trials may be commenced. The IND will automatically become effective 30 days after its receipt by the FDA, unless the FDA before that time raises concerns or questions about the conduct of the trials as outlined in the IND. In such a case, the IND sponsor and the FDA must resolve any outstanding concerns before clinical trials can proceed. TKT cannot be sure that a submitted IND will become effective thereby allowing initiation of a clinical trial for the product in question.

Clinical trials typically are conducted in three sequential phases, but the phases may overlap or be combined, and certain phases may not be necessary for a particular product.

- Phase I trials, the initial introduction of the drug into human subjects, usually involve the testing of the drug for safety, adverse effects, dosage tolerance, and pharmacologic action.
- Phase II trials usually involve studies in a limited patient population to: evaluate preliminarily the efficacy of the drug for specific, targeted conditions, determine dosage tolerance and appropriate dosage, and identify possible adverse effects and safety risks.
- Phase III trials generally further evaluate clinical efficacy and test further for safety within an expanded patient population.

The Company or the FDA may suspend clinical trials at any time on various grounds, including a finding that the patients are being exposed to an unacceptable health risk.

The results of the preclinical and clinical studies, together with other detailed information, including information on the manufacture and composition of the product, are submitted to the FDA in the form of an application for marketing authorization. If the application for marketing authorization contains all pertinent information and data, the FDA will formally accept the file for review. The FDA may refuse to file the application for marketing authorization if it does not contain all pertinent information and data. In that case, the applicant may resubmit the application for marketing authorization when it contains the missing information and data. Before approving an application for marketing authorization, the FDA will inspect the facilities at which the product is manufactured, and will not approve the product unless current GMP compliance is satisfactory. The FDA often requests a review of an application for marketing authorization or parts of an application for marketing authorization by an advisory committee of outside experts. The FDA is free to accept or reject the advisory committee's recommendations. The FDA may refuse to approve an application for marketing authorization if applicable regulatory criteria are not satisfied, require additional testing or information, or require post-marketing testing and surveillance to monitor the safety or efficacy of a product. The testing and approval process require substantial time, effort, and financial resources, and TKT cannot be certain that any of its products will be approved on a timely basis, if at all. Also, new federal, state, or local government requirements may be established that could delay or prevent regulatory approval of its products under development.

The FDA sometimes approves biologics and drugs under its accelerated approval regulations. These approvals may be issued when, among other circumstances, clinical studies establish that the biological product has an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit. When approval is granted under the accelerated approval regulations, the holder of the regulatory approval must conduct additional studies after approval to demonstrate the clinical benefit of the product. Failure to conduct

the required studies, or to comply with other accelerated approval requirements, may result in the FDA's withdrawing or modifying the approval.

Once the FDA approves a product, TKT and any third-party manufacturers are required to comply with a number of post-approval requirements. For example, TKT will be required to report certain adverse events to the FDA, and to comply with certain requirements concerning advertising and promotional labeling of the products. Also, quality control and manufacturing procedures must continue to conform to GMP regulations after approval, and the FDA periodically inspects manufacturing facilities to assess compliance with GMP. Accordingly, manufacturers must continue to expend time, monies, and effort in the area of production and quality control to maintain GMP compliance. In addition, discovery of problems may result in restrictions on a product, manufacturer, or holder of marketing approval, including withdrawal of the product from the market.

In addition to regulations enforced by the FDA, TKT is also subject to regulation under the Occupational Safety and Health Act, the Toxic Substances Control Act, the Resource Conservation and Recovery Act, and other present and potential future federal, state, or local regulations. TKT's research and development activities involve the controlled use of hazardous materials, chemicals, biological materials, and various radioactive compounds. Although TKT believes that its safety procedures for handling and disposing of such materials comply with the standards prescribed by state and federal regulations, the risk of accidental contamination or injury from these materials cannot be completely eliminated. In the event of such an accident, TKT could be held liable for any damages that result and any such liability could exceed TKT's resources.

The FDA may grant orphan drug designation to drugs intended to treat a "rare disease or condition" that affects fewer than 200,000 individuals in the United States. Orphan drug designation must be requested before submitting an application for marketing authorization. Orphan drug designation does not convey any advantage in, or shorten the duration of, the regulatory review and approval process. If a product which has an orphan drug designation subsequently receives the first FDA approval for the indication for which it has such designation, the product is entitled to orphan exclusivity, which means the FDA may not approve any other application to market the same drug for the same indication for a period of seven years, except in limited circumstances, such as a showing of clinical superiority to the product with orphan exclusivity. Also, competitors may receive approval of other different drugs or biologics for the indications for which the orphan product has exclusivity.

European Union Government Regulation

In the European Union, TKT's products are subject to extensive regulation by the European Union and the individual member states of the European Union. Preclinical testing must be carried out in accordance with principles of good laboratory practice and is subject to inspections by national authorities. Certification of compliance is required in applications for approval to conduct clinical trials and in marketing authorization applications. Clinical trials are subject to national regulation. At present, the rules are not harmonized, but most member states require some form of notification or approval by government authorities, review and approval by independent ethics committees and other measures to protect the interests of human subjects. Clinical trials are also expected to be carried out in compliance with detailed requirements for good clinical practice. A European Union directive scheduled to take effect in May 2004 will harmonize requirements for regulation of clinical trials but will likely also impose a greater bureaucratic burden on sponsors. Additional requirements include a data-base of trials across the EU, special provisions for notification or approval of trials relating to biotechnology products and inspections by government authorities to insure compliance with good clinical practice. All trials, including those in healthy volunteers, will be regulated in this way. Medicinal products to be used in clinical trials will be required to be manufactured to the same standard as those applicable to commercial products. At the present time the Company does not believe the European Union's new directives will materially affect clinical operations.

Medicinal products intended for commercial distribution in the European Union must be subject to a marketing authorization. For new biotechnology products, marketing authorization applications must be submitted to the European Agency for the Evaluation of Medicinal Products (the "EMEA"). They are

reviewed by scientific experts in the Committee for Proprietary Medicinal Products (the "CPMP"), which issues an opinion that is referred to the Commission of the European Communities for a final decision, taken in conjunction with representatives of the member states. Marketing authorization applications must be supported by technical dossiers containing detailed information (including reports of preclinical studies and clinical trials and manufacturing information) demonstrating that the medicinal product will be safe, effective and of satisfactory quality. In exceptional circumstances for rare diseases, less-than-complete clinical data may be accepted such as when the authorities determine that it would be impractical or unethical to carry out full-scale pivotal clinical trials. Specific obligations are imposed on the granting of such approvals. These obligations form part of the formal marketing authorization issued by the European Commission and must be reviewed at the intervals specified, minimally on an annual basis. The annual review includes a reassessment of the overall benefit/risk ratio. If specific obligations are not fulfilled the marketing authorization can be varied, suspended or withdrawn by the agency. Upon completion of all requirements, these conditions are removed.

The European Union marketing authorization review process is time-consuming, often lasting one to two years or longer. The review process is suspended whenever the applicant is requested to provide additional information; the applicant may be required to withdraw the application and resubmit it at a later date if additional tests are necessary to provide requested information. European Union and national procedures ordinarily make provision for hearings and appeals, but in practice determinations by the authorities on scientific and medical questions relating to the authorization of medicinal products are often conclusive.

All patient information, including the Summary of Product Characteristics, Package Leaflet and label and carton texts must be translated into all the languages of the European Union before approval. Since May 2004, an additional 10 countries have joined the European Union, bringing the number of languages up to 22.

Establishments located within the European Union in which medicinal products are manufactured must be authorized by national authorities and inspected for compliance with good manufacturing practices ("GMP"). European Union authorities also currently inspect establishments in the United States or other non-European Union countries that manufacture medicinal products for European Union markets. Each batch of a medicinal product that is imported to the European Union must be tested for compliance with applicable specifications and certified by a qualified person in the European Union. Although the United States and the European Union have agreed in principle to mutual recognition of GMP inspections, the details have not been worked out in practice, and it is uncertain when, or whether, actual mutual recognition will be achieved.

Advertising and promotion of medicinal products are regulated by national authorities pursuant to broadly harmonized provisions in European Union directives. Interpretation and enforcement vary from country to country, but many European Union member states impose strict requirements concerning inducements and honoraria paid to physicians and other promotional activities. Prescription medicinal products may not be advertised to patients or the general public in the European Union. Some member states restrict or prohibit co-promotion of the same medicinal product by different pharmaceutical companies.

Marketing authorization holders are required to maintain pharmacovigilance systems for collecting and reporting information concerning suspected adverse reactions. In response to pharmacovigilance reports, authorities may initiate proceedings to revise the prescribing information for medicinal products or to suspend or revoke marketing authorizations. Procedural safeguards are often limited, and marketing authorizations can be suspended with little or no advance notice.

Most European Union member states maintain public health systems in which many medicinal products are paid for at least in part by government authorities, insurers or other third parties. Nearly every member state has introduced one or more systems to control the cost of medicines supplied under these programs. Member states fix the prices of medicinal products, impose reimbursement limits, establish positive or negative formularies, encourage prescribing or dispensing of generic substitutes for innovative products, and regulate the profitability of the pharmaceutical industry. Wholesalers often purchase medicinal products in low-price member states and sell them in higher-price member states, so that there is general downward pressure on prices throughout the European Union.

European Union medicines laws establish certain protections in addition to patents that are intended to encourage investment in research and development of medicinal products. European Union law includes special provisions for "orphan medicines" that are intended to treat rare diseases or conditions. Criteria for designation are similar but somewhat different from those in the United States. Orphan medicines are entitled to ten years of market exclusivity except under certain limited circumstances comparable to US law. During this period of market exclusivity, no "similar" product, whether or not supported by full safety and efficacy data, will be approved. This period may also be reduced to six years if the conditions that originally justified orphan designation change or the sponsor makes excessive profits.

Provisions for data and market exclusivity only protect against the grant of marketing authorizations. Many European Union member states maintain alternative procedures that permit commercial distribution of medicinal products without marketing authorizations on a compassionate or "named-patient" basis. Procedures differ from country to country, but all member states forbid advertising of such products and some countries prohibit or discourage named-patient distribution after a suitable licensed product is on the market.

Additional Foreign Regulation

In addition to regulations in the United States and Europe, TKT will be subject to a variety of foreign regulations governing clinical trials and sales of TKT's products, including Replagal and I2S. Whether or not United States or European approval has been obtained, approval of a product by the comparable regulatory authorities of foreign countries must be obtained prior to the commencement of clinical trials and marketing of the product in those countries. The approval process varies from country to country and the time may be longer or shorter than that required for United States or European approval. For marketing outside the United States and Europe, the Company also is subject to foreign regulatory requirements governing human clinical trials and marketing approval for products. The requirements governing the conduct of clinical trials, product licensing, pricing, and reimbursement vary greatly from country to country.

Employees

As of March 1, 2004, TKT had 323 full-time employees and 29 full-time employees at four subsidiaries, TKT Europe, TKT Canada Inc., TKT UK Ltd. and Eminent Biopharmaceutical Services, LLC.

Trademarks

Gene-Activated®, and TKT® are registered trademarks and Replagal™, and Transkaryotic Therapy™ are trademarks of TKT. Dynepo™ is a trademark of Aventis. All other trademarks, service marks or trade names referenced in this annual report are the property of their respective owners.

Available Information

TKT maintains a website with the address www.tktx.com. TKT's website includes links to its Corporate Governance Guidelines, Code of Business Conduct, Audit Committee Charter, Compensation Committee Charter, and Nominating and Corporate Governance Committee Charter. TKT is not including the information contained in its website as part of, or incorporating it by reference into, this annual report on Form 10-K. TKT makes available, free of charge, through its website its annual reports on Form 10-K, quarterly reports on Form 10-Q and current reports on Form 8-K, and amendments to these reports, as soon as reasonably practicable after TKT electronically files these materials with, or otherwise furnishes them to, the Securities and Exchange Commission.

Item 2. *Properties*

TKT owns or leases a total of approximately 400,000 square feet of office, manufacturing and laboratory space in Massachusetts. The Company occupies the material properties set forth in the table below:

Property Location	Square Feet	Use	Owned/Leased	Lease Expiration Date
Cambridge, Massachusetts	182,000	Corporate Headquarters Office Laboratory	Leased	2012
Cambridge, Massachusetts	34,000	Manufacturing Office Laboratory	Leased	2004-2008
Belmont, Massachusetts	16,000	Warehouse	Leased	2008

In addition to the properties the Company currently occupies, the Company is seeking to sell or sublease the material properties set forth in the table below:

Property Location	Square Feet	Use	Owned/Leased	Lease Expiration Date
Cambridge, Massachusetts	55,000	Office Laboratory	Leased	2004-2008
Cambridge, Massachusetts	25,000	Office	Leased	2012
Randolph, Massachusetts	40,000	Manufacturing	Owned	N/A
Randolph, Massachusetts	48,000	Manufacturing	Leased	2011

Item 3. *Legal Proceedings*

The Company is a party to a number of legal proceedings. The Company can provide no assurance as to the outcome of any of these proceedings. A decision by a court in the United States or in any other jurisdiction in a manner adverse to the Company could have a material adverse effect on the Company's business, financial condition and results of operations.

Replagal Patent Litigation

In July 2000, Genzyme and Mount Sinai filed a patent infringement action against the Company in the United States District Court of Delaware. The complaint alleges that the Company's activities relating to Replagal infringe a patent licensed by Genzyme from Mount Sinai. In January 2002, the United States District Court of Delaware dismissed this patent litigation granting the Company's motion for summary judgment of non-infringement and denying Genzyme and Mount Sinai's motion for summary judgment of infringement. Genzyme and Mount Sinai sought monetary damages and injunctive relief.

In March 2002, Genzyme and Mount Sinai appealed the United States District Court of Delaware's ruling to the United States Court of Appeals for the Federal Circuit, and in January 2003 the United States Court of Appeals for the Federal Circuit heard oral arguments on the appeal. In October 2003, pursuant to a global legal settlement, Genzyme agreed to withdraw from this suit and paid the Company $1,555,000. Mount Sinai is not a party to the settlement. In October 2003, the United States Court of Appeals for the Federal Circuit affirmed a finding of non-infringement by the Company. In January 2004, the Federal Circuit denied Mount Sinai's petition for a rehearing en banc. The Company believes it is possible, but unlikely, that Mount Sinai will obtain further appellate review of this decision by the United States Supreme Court.

Dynepo Patent Litigation

In April 1997, Amgen commenced a patent infringement action against the Company and Aventis in the United States District Court of Massachusetts. In January 2001, the United States District Court of Massachusetts concluded that Dynepo infringed eight of the 18 claims of five patents that Amgen had asserted. Amgen did not seek and was not awarded monetary damages.

In January 2003, the United States Court of Appeals for the Federal Circuit issued a decision affirming in part and reversing in part the decision of the United States District Court of Massachusetts and remanded the action to the United States District Court of Massachusetts for further proceedings. In particular, the United States Court of Appeals for the Federal Circuit:

- upheld the United States District Court of Massachusetts' determination of invalidity of one of Amgen's patents;
- upheld the United States District Court of Massachusetts' determination that some claims of two other Amgen patents were infringed, but vacated the United States District Court of Massachusetts' determination that those patents were not invalid; and
- vacated the United States District Court of Massachusetts' determination that Dynepo infringed some claims of the two remaining Amgen patents, and vacated the United States District Court of Massachusetts' determination that one of these patents was not invalid.

As part of the United States Court of Appeals for the Federal Circuit's ruling, it remanded the case to the United States District Court of Massachusetts and instructed it to reconsider the validity of Amgen's patents in light of potentially invalidating prior art. The United States District Court of Massachusetts has recently concluded the remand proceedings and heard oral argument on some of these issues in July 2003. The Company expects that the United States District Court of Massachusetts will enter a decision on the remanded issues at some point during the first half of 2004. The United States District Court of Massachusetts also recently issued a decision upholding its earlier findings that Amgen successfully rebutted the presumption of prosecution history estoppel with respect to certain patents, and therefore, the Company and Aventis infringe such patents in light of recent Supreme Court precedents. On remand, the Company and Aventis presented affirmative defenses with respect to such patents. Both Amgen and Aventis, together with the Company, will have the right to appeal the decision of the United States District Court of Massachusetts to the United States Court of Appeals for the Federal Circuit.

In addition, in July 1999, the Company commenced legal proceedings with Aventis in the United Kingdom against Kirin-Amgen, which sought a declaration that a European patent held by Kirin-Amgen will not be infringed by the Company's activities relating to Dynepo and that certain claims of Kirin-Amgen's U.K. patent are invalid. In April 2001, the High Court of Justice in the United Kingdom ruled that Dynepo infringed one of four claims of the patent asserted by Kirin-Amgen. In July 2002, the Court of Appeals in the United Kingdom reversed the High Court of Justice and ruled that Dynepo did not infringe Kirin-Amgen's patent. Kirin-Amgen petitioned the House of Lords to hear an appeal from the decision of the Court of Appeals. The House of Lords agreed to hear this appeal during the summer of 2004.

The Company can provide no assurance as to the outcome of either litigation. If the Company and its collaborator, Aventis, are not successful in the Dynepo litigation, the Company and Aventis would be precluded from making, using and selling Dynepo in the United States and/or in the United Kingdom. The Company is required to reimburse Aventis, which is paying the litigation expenses, for 50% of the expenses. Aventis is entitled to deduct up to 50% of any royalties due to the Company from it with respect to the sale of Dynepo until Aventis has recouped the full amount of the Company's share of litigation expenses.

Purported Class Action Shareholder Suit

In January and February 2003, various parties filed purported class action lawsuits against the Company and Richard Selden, its then Chief Executive Officer, in the United States District Court for the District of Massachusetts. The complaints generally allege securities fraud during the period from January 2001 through January 2003. Each of the complaints asserts claims under Section 10(b) of the Securities Exchange Act of 1934, Rule 10b-5 promulgated thereunder, and Section 20(a) of the Exchange Act, and alleges that the Company and its officers made false and misleading statements and failed to disclose material information concerning the status and progress for obtaining United States marketing approval of its Replagal product to treat Fabry disease during that period.

In March 2003, various plaintiffs filed motions to consolidate, to appoint lead plaintiff, and to approve plaintiff's selections of lead plaintiffs' counsel. In April 2003, various plaintiffs filed a Joint Stipulation and Proposed Order of Lead Plaintiff Applicants to Consolidate Actions, To Appoint Lead Plaintiffs and to Approve Lead Plaintiffs' Selection of Lead Counsel, Executive Committee and Liaison Counsel. In April 2003, the Court endorsed the Proposed Order, thereby consolidating the various matters under one matter: *In re Transkaryotic Therapies, Inc., Securities Litigation, C.A. No. 03-10165-RWZ.*

In July 2003, the plaintiffs filed a Consolidated and Amended Class Action Complaint (the "Amended Complaint"), against the Company; Dr. Selden; Daniel Geffken, the Company's former Chief Financial Officer; Walter Gilbert, Jonathan S. Leff, Rodman W. Moorhead, III, and Wayne P. Yetter, members of the Company's Board of Directors; William R. Miller and James E. Thomas, former members of the Company's Board of Directors; SG Cowen Securities Corporation; Deutsche Bank Securities; Pacific Growth Equities, Inc.; and Leerink Swann & Company.

The Amended Complaint alleges securities fraud during the period from January 4, 2001 through January 10, 2003. The Amended Complaint alleges that the defendants made false and misleading statements and failed to disclose material information concerning the status and progress for obtaining United States marketing approval of Replagal during that period. The Amended Complaint asserts claims against each of the defendants under Section 11 of the Securities Act and against Dr. Selden under Section 15 of the Securities Act; against SG Cowen Securities Corporation, Deutsche Bank Securities, Pacific Growth Equities, Inc., and Leerink Swann & Company under Section 12(a)(2) of the Securities Act; against Dr. Selden and the Company under Section 10(b) of the Exchange Act and Rule 10b-5 promulgated thereunder; and against Dr. Selden under Section 20(a) of the Exchange Act. The plaintiffs seek equitable and monetary relief, an unspecified amount of damages, with interest, and attorney's fees and costs.

In September 2003, the Company filed a motion to dismiss the Amended Complaint. A hearing of the motion occurred in December 2003. A class has not been certified.

Derivative Suit

In April 2003, South Shore Gastrointerology UA 6/6/1980 FBO Harold Jacob, and Nancy R. Jacob Ttee filed a Shareholder Derivative Complaint against Dr. Selden; against the following members of the Company's board of directors: Jonathan S. Leff, Walter Gilbert, Wayne P. Yetter, Rodman W. Moorhead III; against the following former members of the Company's Board of Directors: James E. Thomas, and William Miller; and against the Company as nominal defendant, in Middlesex Superior Court in the Commonwealth of Massachusetts, Civil Action No. 03-1669. On May 29, 2003, the parties moved to transfer venue to the Business Litigation Session in Suffolk Superior Court in the Commonwealth of Massachusetts. The parties' motion was allowed, and in June 2003 the matter was accepted into the Business Litigation Session as Civil Action No. 03-02630-BLS.

The complaint alleges that the individual defendants breached fiduciary duties owed to the Company and its shareholders by disseminating materially false and misleading statements to the market and causing or allowing the Company to conduct its business in an unsafe, imprudent and unlawful manner. The complaint purports to assert derivative claims against the individual defendants for breach of fiduciary duty, and to assert a claim for contribution and indemnification on behalf of the Company for any liability the Company incurs as a result of the individual defendants' alleged misconduct. The complaint seeks declaratory, equitable and monetary relief, an unspecified amount of damages, with interest, and attorney's fees and costs.

In August 2003, the plaintiff filed its Verified Amended Derivative Complaint (the "Amended Derivative Complaint"). The Amended Derivative Complaint alleges that the individual defendants breached fiduciary duties owed to the Company and its stockholders by causing the Company to issue materially false and misleading statements to the public, by signing its Form 10-Ks for the years 2000 and 2001 and by signing a registration statement. The Amended Derivative Complaint also alleges that defendant Dr. Selden sold the Company's stock while in possession of material non-public information. The plaintiffs seek declaratory, equitable and monetary relief, an unspecified amount of damages, with interest, and attorney's fees and costs.

In September 2003, the Company served a motion to dismiss the Amended Derivative Complaint. A hearing of the motion was held in January 2004.

SEC Investigation

In May 2003, the Company received a copy of a formal order of investigation by the SEC. The order of investigation relates to the Company's disclosures and public filings with regard to Replagal and the status of the FDA's approval process for Replagal, as well as transactions in the Company's securities. The Company is cooperating fully and will continue to cooperate fully with the SEC in the investigation.

Item 4. ***Submission of Matters to a Vote of Security Holders***

No matters were submitted to a vote of security holders during the fourth quarter of the fiscal year covered by this report.

Executive Officers

As of March 1, 2004, the executive officers of the Company are as follows:

Name	Age	Position held with the Company
Michael J. Astrue	47	President and Chief Executive Officer
David D. Pendergast, Ph.D.	55	Executive Vice President and Chief Operating Officer
Renato Fuchs, Ph.D.	61	Senior Vice President, Manufacturing and Operations
Gregory D. Perry	43	Vice President, Finance, and Chief Financial Officer

Each officer's term of office extends until the first meeting of the Board of Directors following the next annual meeting of stockholders and until a successor is elected and qualified.

Michael J. Astrue joined the Company as President and Chief Executive Officer in February 2003. Prior to rejoining TKT, Mr. Astrue served as TKT's Senior Vice President and General Counsel from April 2000 to January 2003, after which he served briefly as a Visiting Fellow at the Hudson Institute, a research organization. From 1993 to 1999, he served as Vice President, Secretary and General Counsel of Biogen, Inc., a biotechnology company. Mr. Astrue received a B.A. from Yale University and a J.D. from Harvard Law School.

David D. Pendergast, Ph.D., has served as Executive Vice President and Chief Operating Officer since October 2003. Prior to October 2003 and since joining TKT in December 2001, Dr. Pendergast served in a number of senior quality and operations roles at TKT, including Executive Vice President, Operations. Prior to joining TKT, Dr. Pendergast was employed by Biogen from April 1996 through August 2001, most recently serving as Vice President, Product Development and Quality Assurance. Dr. Pendergast received a B.S. in Chemistry from Western Michigan University and a Ph.D. in Pharmaceutics from the University of Wisconsin.

Renato Fuchs, Ph.D., joined the Company as Senior Vice President, Manufacturing and Operations, in March 2002. Prior to joining TKT, Dr. Fuchs was employed by Chiron Corporation, a pharmaceutical company, from 1993 through February 2002, most recently serving as Senior Vice President, BioPharmaceuticals. Dr. Fuchs received a B.S. in Chemical Engineering from University of Valle and a Ph.D. in Biochemical Engineering from the Massachusetts Institute of Technology.

Gregory D. Perry joined the Company as Vice President, Finance, and Chief Financial Officer in May 2003. From September 1998 to November 2002, Mr. Perry was employed by PerkinElmer, Inc. where he most recently served as Senior Vice President, Finance and Business Development, Life Sciences. Prior to joining PerkinElmer, Mr. Perry was Chief Financial Officer of the Automotive Aftermarket Products Group at Honeywell International Incorporated from March 1997 to September 1998. Mr. Perry also held numerous positions of increasing responsibility in finance and business development at General Electric Company,

including Chief Financial Officer of GE Medical Systems, Europe, headquartered in Paris, France. Mr. Perry received a B.A. from Amherst College.

PART II

Item 5. *Market for the Registrant's Common Stock and Related Stockholder Matters*

The Company was incorporated in Delaware in 1988 and the Company's Common Stock commenced trading on October 17, 1996 on The Nasdaq National Market under the symbol "TKTX." As of March 1, 2004, there were 115 holders of record of the Company's Common Stock.

The following table sets forth for the fiscal periods indicated the range of high and low bid prices for the Company's Common Stock on The Nasdaq National Market. These prices reflect inter-dealer prices, without retail mark-up, mark-down or commission and may not represent actual transactions.

	High	Low
2003		
Quarter Ended:		
December 31	$16.23	$10.34
September 30	13.73	10.22
June 30	11.82	5.25
March 31	10.20	3.74
2002		
Quarter Ended:		
December 31	$34.10	$ 8.41
September 30	42.00	28.21
June 30	43.17	31.02
March 31	46.50	31.97

The Company has never declared or paid any cash dividends on its capital stock. The Company currently anticipates that it will retain all future earnings, if any, to fund the development and growth of its business and does not anticipate paying any cash dividends on its Common Stock in the foreseeable future.

Item 6. *Selected Financial Data*

The following selected consolidated financial data of the Company for the five years ended December 31, 2003 are derived from the consolidated financial statements of the Company. The information set forth below should be read in conjunction with "Management's Discussion and Analysis of Financial Condition and

Results of Operations" included as Item 7 and the consolidated financial statements and related footnotes included as Item 8 in this Form 10-K.

Statement of Operations Data

	Year Ended December 31,				
	2003	2002	2001	2000	1999
	(In thousands, except per share amounts)				
Revenues	$ 58,889	$ 36,500	$ 6,188	$ 7,247	$ 3,870
Cost of goods sold	12,484	10,511	185	—	—
Research and development expenses	74,062	81,309	65,921	56,440	43,946
Intellectual property license expense	1,350	34,660	—	—	—
Restructuring charges	12,461	—	—	—	—
Impairment charge	—	16,069	—	—	—
Net loss	$(75,234)	$(129,762)	$(70,243)	$(51,021)	$(44,456)
Basic and diluted net loss per share	$ (2.18)	$ (3.75)	$ (2.78)	$ (2.25)	$ (2.25)

Balance Sheet Data

	December 31,				
	2003	2002	2001	2000	1999
	(In thousands)				
Cash, cash equivalents and marketable securities	$180,947	$256,708	$399,754	$245,456	$192,495
Other current assets	44,392	41,784	14,141	1,842	2,054
Property and equipment, net	61,908	59,372	41,587	23,597	20,384
Total assets	289,169	359,806	457,707	272,393	215,291
Total stockholders' equity	258,322	323,867	436,163	247,857	195,782

Item 7. *Management's Discussion and Analysis of Financial Condition and Results of Operations*

Overview

TKT is a biopharmaceutical company researching, developing and commercializing therapeutics, primarily for the treatment of rare genetic diseases caused by protein deficiencies. TKT has received approval to market and sell Replagal (agalsidase alfa), an enzyme replacement therapy for the long-term treatment of patients with Fabry disease, in 28 countries outside of the United States. Two of the products TKT is developing include I2S, an enzyme replacement therapy for the treatment of Hunter syndrome, and GA-GCB for the treatment of Gaucher disease. The Company is currently conducting a pivotal clinical trial of I2S and anticipates starting a Phase I/II clinical trial of GA-GCB in the second quarter of 2004. TKT is currently evaluating out-licensing opportunities for GA-GCB as well as a number of other gene-activated and gene therapy products.

With the exception of 1995, the Company has incurred substantial annual operating losses since inception. The Company expects to incur significant operating losses until substantial product sales are generated. Until such time, the Company is dependent upon product sales, collections of accounts receivable, existing cash resources, interest income, external financing from equity offerings, debt financings, and collaborative research and development alliances to finance its operations. At December 31, 2003, the Company's accumulated deficit was $440,668,000. The Company expects that its existing capital resources, together with anticipated proceeds from collections on existing and future accounts receivable on product sales, anticipated cash payments under collaborative agreements, and interest income, will be sufficient to fund its operations into 2005.

The Company's results of operations may vary significantly from period to period depending on, among other factors:

- the timing and amount of Replagal product sales, as well as the collection of receivables;
- continued progress in its research and development programs, particularly I2S;
- the scope and results of its clinical trials;
- the timing of, and the costs involved in, obtaining regulatory approvals;
- the cost of expansion of TKT's internal manufacturing facilities;
- the inherent variability of biological manufacturing activities;
- fluctuations in foreign exchange rates for sales denominated in currencies other than the United States dollar;
- the quality and timeliness of the performance of third party suppliers;
- the cost of commercialization activities, including product marketing, sales and distribution;
- the costs involved in preparing, filing, prosecuting, maintaining, and enforcing patent claims and other patent-related costs, including litigation costs and the results of such litigation;
- the outcome of pending purported class action and other related, or potentially related, actions and the litigation costs with respect to such actions;
- the timing and cost of the Company's purchase of the minority interest in TKT Europe;
- the outcome of the SEC investigation; and
- TKT's ability to establish and maintain collaborative arrangements.

Critical Accounting Policies and Significant Judgments and Estimates

The Company's discussion and analysis of its financial condition and results of operations are based on the Company's consolidated financial statements, which have been prepared in accordance with accounting principles generally accepted in the United States. The preparation of these financial statements requires TKT to make estimates and assumptions that affect the reported amounts of assets and liabilities and the disclosure of contingent assets and liabilities at the date of the financial statements as well as the reported revenues and expenses during the reporting periods. TKT bases its estimates on historical experience and on various other factors that are believed to be reasonable under the circumstances. On an ongoing basis, TKT evaluates these estimates and judgments. Actual results may differ from these estimates under different assumptions or conditions.

The Company regards an accounting estimate underlying its financial statements as a "critical accounting estimate" if the nature of the estimate or assumption is material due to level of subjectivity and judgment involved or the susceptibility of such matter to change and if the impact of the estimate or assumption on financial condition or operating performance is material.

While TKT's significant accounting policies are more fully described in Note 2 to TKT's consolidated financial statements included in this annual report, TKT regards the following accounting policies as critical accounting estimates.

Revenue Recognition

Product Sales. The Company recognizes revenue from product sales in accordance with Staff Accounting Bulletin 104 (SAB 104), *Revenue Recognition*, when there is persuasive evidence that an arrangement exists, delivery has occurred, the price is fixed or determinable, and collection is reasonably assured. The Company determines that collection is reasonably assured in Europe and in some other countries outside of the United States, once reimbursement agreements and pricing arrangements are established and formalized,

as these agreements establish the relevant governmental agency's intent to pay, or once there are legally binding purchase agreements between a hospital and the Company, or once approval has been granted for the reimbursement of cost for individual patients. The Company only records revenues in those countries for which one of the conditions set forth in the previous sentence has been met. If any of the above circumstances were to change, it could affect the Company's revenue recognition in future periods.

In the European pharmaceutical industry, it is common practice that customers, principally hospitals, have a general right of return on purchases of product. To date, the Company has not had any sales returns. The Company generally ships small quantities of Replagal to customers on the basis of firm purchase orders. The customers generally order Replagal for specific patients, and the drug is typically utilized within one month of receipt. In part due to the expensive price of the drug, customers maintain small inventories of it, typically less than a one month supply. Because of these circumstances, the Company expects that it will have no or minimal returns in the future and, accordingly, has not recorded a reserve for sales returns and allowances in accordance with SFAS No. 48, *Revenue Recognition When Right-of-Return Exists.* If any product is returned, the Company may need to begin to record reserves for sales returns and allowances and incur charges to revenues in future periods.

License and Research Revenues. The Company records contract revenue for research and development as it is earned based on the performance requirements of the contract. Nonrefundable contract fees for which no further performance obligations exist, and there are no continuing involvement by the Company, are recognized on the earlier of when the payments are received or when collection is assured. The Company recognizes revenue from non-refundable up-front license fees and milestone payments where there is continual involvement through development collaboration or an obligation to supply product, as the obligation is fulfilled or ratably over the development period or the period of the manufacturing obligation, as appropriate. The Company recognizes revenue associated with substantive performance milestones based upon the achievement of the milestones, as defined in the respective agreements. Advance payments received in excess of amounts earned are classified as deferred revenue. The Company has estimated the term of the Genzyme distribution agreement to be 13 years, which represents the period under which the Company will supply bulk drug substance to Genzyme. If this estimate changes, the Company may need to adjust revenue recognition in future periods.

Accounts Receivable

In certain European countries, such as Italy and Belgium, customary payment terms on accounts receivable are significantly longer than in the United States, particularly for products treating orphan drug indications. In these countries, the Company historically has received and expects to continue to receive, payments approximately one year from the invoice date. Accounts receivable balances for Italy and Belgium were 56% and 49% of total accounts receivable at December 31, 2003 and 2002, respectively. The Company monitors its days' sales outstanding and collections in these countries. To date, customers in these countries have been paying within the customary payment terms. If collections and days' sales outstanding in these countries deteriorate in the future, the Company may need to discount those receivables.

Inventories

Inventories are stated at the lower of cost or market, with cost determined under the first-in, first-out (FIFO) method. Inventories are reviewed periodically for slow-moving or obsolete status based on sales activity, both projected and historical.

Replagal inventory balances as of December 31, 2003 consist of raw materials, work in process and finished goods. In general, the Company's manufacturing process for Replagal consists of two distinct phases: the manufacture of bulk drug substance and the preparation and packaging of bulk drug substance into finished product. Bulk drug substance has a shelf life of up to 12 months before the product is prepared and packaged into finished goods vials, and an additional two years upon packaging of finished goods in vials. The Company's estimates relating to the current demand for Replagal and future sales projections indicate that all of the inventory will be utilized within the designated shelf lives of both bulk drug substance and finished

goods vials. If actual product sales differ from the Company's projections, inventory may not be fully utilized. As a result, the Company would need to write-down the value of such inventory to its net realizable value. This write down would be recorded as additional cost of goods sold.

Asset Impairment

The Company reviews its long-lived assets for impairment indicators at each reporting period in accordance with SFAS No. 144, *Accounting for the Impairment or Disposal of Long-Lived Assets.* In the fourth quarter of 2002, the Company concluded that an impairment indicator existed with respect to a manufacturing facility. An undiscounted cash flow analysis confirmed the impairment, and the Company obtained an appraisal of the manufacturing facility to determine its fair market value. Accordingly, the Company recorded an impairment charge of $16,069,000 at December 31, 2002, based upon the difference between the fair market value of the facility and its carrying value at such date. The Company is actively seeking a buyer for this facility. Upon a sale of the facility, any difference between the sales price and the carrying value of the facility will be recognized as an impairment charge, or credit, in the period of the sale.

Restructuring Charges

In February 2003, TKT announced a major reorganization in an effort to reduce costs and narrow the scope of the Company's research initiatives. The reorganization included reduction in workforce, consolidation of facilities and disposal of certain assets. These restructuring charges were accounted for in accordance with SFAS No. 146, *Accounting for Costs Associated with Exit or Disposal Activities*, and included a net facilities charge. In determining the net facilities charge, various assumptions were made, with respect to sublease terms and expected sublease rates. These estimates were made based on a periodic review of current sublease environment and acquired market quotes. Should operating lease rental rates decline or should it take longer than expected to find suitable tenants to sublease the facilities, adjustments to the net present value of remaining lease obligations may be necessary in future periods based upon the future events and circumstances. See "Results of Operations" below and Note 5 to the Condensed Consolidated Financial Statements for further discussion of the Company's restructuring actions.

Results of Operations

The following discussion of the financial condition and results of operations of the Company should be read in conjunction with the accompanying consolidated financial statements and the related footnotes thereto.

Revenues

Revenues for 2003, 2002 and 2001 were:

	Year Ended December 31,			2003 vs. 2002		2002 vs. 2001	
	2003	2002	2001	$ Change	% Change	$ Change	% Change
	(In thousands, except percentages)						
Product sales	$57,225	$34,682	$3,535	$22,543	65%	$31,147	881%
License and research revenues	1,664	1,818	2,653	(154)	(8%)	(835)	(31%)
	$58,889	$36,500	$6,188	$22,389	61%	30,312	490%

Product Sales

Since 2001, substantially all Replagal product sales have been in Europe. Prior to product approval in August 2001, product sales were made in Europe under compassionate use programs. Compassionate use programs in certain countries in Europe allow limited sales of products that have not yet been approved by the appropriate regulatory agency. The increase in product sales in 2003 reflects an overall increase in unit sales over 2002. The increase in Replagal product sales in 2002 was a result of the launch of Replagal, the availability of Replagal for sale in additional countries for the entire year, the receipt of pricing and reimbursement in additional countries, and additional patients commencing therapy.

The Company prices Replagal in the functional currency of the country into which it is sold. While overall price levels in local currencies have generally remained consistent since 2001, foreign exchange fluctuations caused an increase in the United States dollar denominated average selling prices. Substantially all of the Company's manufacturing costs are in United States dollars. Therefore, any fluctuation in the value of the payment currencies relative to the United States dollar is likely to impact gross margins since the Company's manufacturing costs would remain approximately the same while its revenue in terms of United States dollars would change.

Foreign currency fluctuations increased sales and gross margins by approximately $9,443,000, or 27%, in 2003 and $2,558,000, or 72%, in 2002. In 2001, these currency fluctuations were immaterial to gross margin. The Company's gross margin will continue to be affected by currency fluctuations in the future. Product sales and gross margins will be negatively affected if the U.S. dollar strengthens against currencies in which the Company sells Replagal. The Company currently does not engage in foreign currency hedging activities.

The Company expects continued growth in European sales in 2004 and a significant percentage growth of sales from the rest of the world, excluding the United States, as additional countries approve Replagal and reimbursement is established.

License and Research Revenues

The Company earned substantially all of its license and research revenues in 2003, 2002, and 2001 under its collaborative agreements with Genzyme, Sumitomo and Wyeth. The decrease in license and research revenues in 2003 primarily reflects a decrease in revenues from Wyeth due to the termination of research and development fees from Wyeth in 2003, which was offset by a $500,000 fee that Wyeth paid to TKT in connection with the termination of the collaboration agreement in August 2003. The decrease in license and research revenue in 2002 from 2001 was due to the timing of completion of obligations under each collaborative agreement.

Cost of Goods Sold

Components of cost of goods sold for 2003, 2002 and 2001 are as follows:

	Year Ended December 31,			2003 vs. 2002		2002 vs. 2001	
	2003	2002	2001	$ Change	% Change	$ Change	% Change
	(In thousands, except percentages)						
Cost of product sales	$ 9,894	$ 8,011	$185	$1,883	24%	$ 7,826	4230%
Termination of contract manufacturing agreement and related charges	2,590	2,500	—	90	4%	2,500	—
Cost of goods sold	$12,484	$10,511	$185	$1,973	19%	$10,326	5582%
Cost of goods sold as a percentage of product sales	22%	30%	5%				

For the years ended December 31, 2003, 2002 and 2001, cost of goods sold was $12,484,000, $10,511,000 and $185,000, respectively. The increase of $1,973,000, or 19%, in 2003 was due primarily to increased product sales volume. For the year ended December 31, 2003, the decrease in cost of goods sold as a percentage of sales reflected continuing improvements in manufacturing and production efficiencies and the sale of Replagal inventory that had been produced at the Company's Alewife Facility. In July 2003, the Alewife Facility was approved by the European Commission to manufacture bulk drug substance for Replagal. The costs to manufacture Replagal at the Alewife Facility prior to approval were expensed as research and development costs. These factors reduced cost of goods sold by $1,252,000 in 2003. The Company incurred additional charges amounting to $2,590,000, or 5% of product sales, in 2003 related to excess capacity at the terminated contract manufacturer of bulk drug substance of Replagal.

The increase of cost of goods sold in 2002 as compared to 2001 was primarily due to full year Replagal sales in 2002. The increase also reflects that the Company sold units of Replagal containing expensed bulk drug substance in 2001 and in the first half of 2002. As a result of the sale of these units, cost of goods sold as a percentage of sales did not begin to reflect all production costs until the second half of 2002. In 2002, the Company also incurred a charge of $2,500,000, or 7% of 2002 product sales, related to the termination of the contract manufacturer of bulk drug substance of Replagal.

The Company has historically relied on contract manufacturing arrangements with third parties for the production of Replagal bulk drug substance for commercial sale, as well as contract packaging and labeling services. In January 2003, the Company terminated its agreement with a third party manufacturer of the bulk drug substance of Replagal, effective in July 2003. In October 2003, the Company began significant renovations to the Alewife Facility in order to expand its capacity and configure the facility for the production on a commercial scale of products other than Replagal. In anticipation of these renovations, in the third quarter of 2003, the Company ceased all manufacturing operations at the Alewife Facility. Production at the Alewife Facility is scheduled to recommence in the second half of 2004. At the present time, the Company anticipates that existing inventory will be sufficient to fill customer orders for Replagal into 2005. The Company will continue to rely on third party manufacturers for preparation and packaging services.

The Company expects that Replagal inventory produced both at the contract manufacturer and at the Alewife Facility will be sold in 2004. Cost of goods sold will reflect a mix of full production costs with respect to inventory produced at the contract manufacturer, and partial production costs with respect to inventory manufactured at the Alewife Facility as the majority of such costs were previously expensed. The Company expects the cost of goods sold percentage for 2004 will be approximately 20% of product sales.

Research and Development Expenses

Research and development expenses totaled $74,062,000 in 2003, as compared to $81,309,000 in 2002 and $65,921,000 in 2001. The decrease in 2003 of $7,247,000, or 9%, was primarily due to decreases in research and development staffing and in outside testing and supplies costs in connection with the Company's restructuring plan. This decrease also reflected $5,500,000 in non-recurring expenditures related to set-up and technology transfer fees paid to the contract manufacturer of Replagal bulk drug substance in 2002. In addition, in 2003, the overall decrease in research and development costs was partially offset by increases in both clinical trial costs associated with the commencement of the I2S pivotal clinical trial of $1,478,000, and research and development occupancy costs of $3,264,000 primarily related to the Company's occupancy of its new corporate headquarters for a full year in 2003.

The increase in 2002 of $15,388,000, or 23%, was primarily due to increases in research and development staffing and manufacturing development costs. In addition, in November 2002, the Company occupied a new combined headquarters and research and development facility for two months, which increased its research and development occupancy costs in 2002. The increase in 2002 was partially due to the Company's incurrence of expenditures totaling $5,500,000 related to set-up and technology transfer fees paid to a contract manufacturer of Replagal bulk drug substance.

The Company does not intend to engage in any further product development activities related to its Gene-Activated protein products, which are versions of proteins that would compete with proteins currently being marketed by third parties, except with respect to GA-GCB. The Company is seeking collaborative partners for all of these Gene-Activated protein products other than Dynepo. The Company also does not intend to engage in further product development activities related to its gene therapy programs unless those activities are funded under a collaboration agreement with a third party. The Company expects its research and development expenses in 2004 to increase compared to 2003 primarily because of expenses that it expects to incur for the Company's pivotal clinical trial for I2S and the Phase I/II clinical trial for GA-GCB, including costs to manufacture clinical supplies.

The Company's two largest research and development programs, Replagal and I2S, represent the majority of the Company's total research and development spending. The expenses associated with these

programs totaled approximately 75% in 2003 as compared to 74% in 2002 and 72% in 2001 of total research and development expenses.

Research and development expenses for the Replagal program totaled $27,222,000, $40,320,000, and $36,151,000 for the years ended December 31, 2003, 2002 and 2001, respectively. The decrease of $13,098,000, or 32%, in 2003 was primarily the result of the conclusion of certain Replagal clinical trials prior to the beginning of the 2003 periods as well as decreased expenses incurred in connection with producing clinical materials and set up and technology transfer fees totaling $5,500,000 paid to the contract manufacturer of Replagal bulk drug substance. The increase of $4,169,000, or 12%, in 2002 was due primarily to an increase in expenditures related to the continued development of internal manufacturing capability.

TKT has ceased efforts to seek the approval of Replagal from the FDA. As a result of this decision, the Company expects the amount of future Replagal-related research and development expenses will decrease significantly. The Company will continue to incur expenses related to the conditions associated with the Company's European approval of Replagal, including an obligation to conduct additional clinical trials and an obligation to submit an annual assessment of Replagal for review by regulatory authorities. Future Replagal-related expenditures are principally dependent upon those regulatory requirements.

Research and development expenses for the I2S program equaled $28,144,000 in 2003 as compared to, $19,959,000 in 2002, and $11,405,000 in 2001. The increases of $8,185,000, or 41%, and $8,554,000, or 75%, for 2003 and 2002, respectively, reflect increases in allocated employee costs associated with I2S research and development activities and expenses incurred in connection with the Company's ongoing clinical trials of I2S in 2003 and 2002, including the phase I/II study in 2002, ongoing maintenance studies in 2002 and 2003 and the double-blind, placebo-controlled pivotal clinical trial of I2S which commenced in the fourth quarter of 2003. In addition, expenditures for the manufacture of I2S for use in these studies and clinical trials contributed to the increase in expenses period over period.

Future research and development costs for the I2S program are not reasonably certain because such costs are dependent on a number of variables, including the cost and design of any additional clinical trials, uncertainties in the timing of the regulatory process, and the costs associated with large-scale manufacture of I2S. The Company estimates that the cost of its pivotal clinical trial of I2S may aggregate approximately $10,000,000 to $15,000,000 in 2004. The Company expects that expenses related to I2S will be significant in 2004 as the Company intends to prepare applications for marketing approval of I2S.

Intellectual Property License Expense

In June 2002, the Company obtained an exclusive license to certain patents and patent applications from Cell Genesys, Inc. ("Cell Genesys") related to Cell Genesys' approach to gene activation. In consideration for the license, the Company initially paid Cell Genesys $11,000,000 in cash and issued to Cell Genesys shares of the Company's common stock worth $15,000,000 as of the date of the agreement.

Under the license agreement, the Company agreed that the number of shares of common stock initially issued to Cell Genesys would be adjusted at the time the Company registered such shares for resale under the Securities Act of 1933, as amended, if the market value of such shares at that time was greater or less than $15,000,000. Pursuant to the agreed upon formula, at December 31, 2002, with the closing price of the Company's common stock at $9.90 per share, the Company would have been required to issue to Cell Genesys an additional 1,148,000 shares of common stock. As a result, the Company recorded an additional non-cash license fee expense of $8,660,000 in the fourth quarter of 2002.

On January 15, 2003, the Company and Cell Genesys renegotiated the consideration paid for the license, and the Company repurchased the shares of stock issued to Cell Genesys for $15,000,000 in cash. The Company incurred an additional license expense in the first quarter of 2003 of $1,350,000, which represents the further decline in the market value of the Company's common stock from December 31, 2002 to January 15, 2003. The repurchased shares have been recorded as treasury stock.

Under the license agreement, Cell Genesys also has the potential to receive certain milestone payments from the Company contingent upon the outcome of related patent matters under the license agreement. If all

of the milestones are achieved, the Company will be obligated to pay Cell Genesys an aggregate of $17,000,000 payable in part in cash and in part in stock. The Company cannot predict when those milestones will become due, if ever. The Company is not required to make royalty payments to Cell Genesys.

Selling, General and Administrative Expenses

The Company's components for selling, general and administrative expenses for 2003, 2002, and 2001 were as follows:

	Year Ended December 31,			2003 vs. 2002		2002 vs. 2001	
	2003	2002	2001	$ Change	% Change	$ Change	% Change
	(In thousands, except percentages)						
General and administrative	$19,677	$14,608	$14,390	$5,069	35%	$ 218	2%
Selling and marketing	16,880	16,621	10,433	259	2%	6,188	59%
Selling, general and administrative expenses	$36,557	$31,229	$24,823	$5,328	17%	$6,406	26%

Selling, general and administrative expenses increased 17% in 2003. Contributing to this increase were legal costs incurred in connection with the Company's shareholder lawsuits and SEC investigation which amounted to $2,400,000, ongoing Replagal sales and marketing initiatives in Europe and other countries, executive severance charges of $1,104,000, and occupancy costs related to the Company's new corporate headquarters of $1,184,000. The increase of $6,406,000, or 26%, for 2002 reflect costs incurred in preparation for the launch of Replagal in Europe and other countries and the creation of a sales and marketing infrastructure including sales, marketing and distribution capabilities.

Selling, general and administrative expenses related to selling and marketing activities increased by 2% in 2003 and 59% in 2002. In general, these increases year over year were due to increased European Replagal sales and marketing efforts by TKT Europe, the Company's majority owned subsidiary. The Company expects selling and marketing expenses to increase in 2004 as the Company's establishes infrastructure and distribution capabilities to support commencement of Replagal product sales in additional countries outside of the European Union. In addition, the Company expect to incur transition costs related to the buyout of its minority interest in TKT Europe.

Restructuring Charges

In February 2003, TKT announced a major reorganization in an effort to reduce costs and narrow the scope of the Company's research initiatives. As part of this restructuring, during the first quarter of 2003, TKT reduced its United States headcount by approximately 100 positions. TKT has further reduced its headcount through attrition. As of December 31, 2003, TKT had 321 full-time United States employees. TKT has also consolidated its facilities as part of the restructuring.

The Company recorded charges of $12,461,000 in 2003, in accordance with SFAS No. 146, *Accounting for Costs Associated with Exit or Disposal Activities.* Included in the charges are $1,319,000 of employee severance and outplacement services costs for 74 employees, primarily in research and development, $10,544,000, representing the net present value of remaining lease obligations and sublease income estimates for four facilities that the Company no longer occupies, and a write-down of $598,000 of leasehold improvements in facilities that were vacated. The Company's employee-related and facility consolidation restructuring actions were completed as of December 31, 2003. The Company will continue to record restructuring charges primarily related to vacated facility expenses during the remainder of the lease terms until such facilities are sublet.

Impairment Charge

In January 2001, the Company purchased a manufacturing facility, which it intended to use to manufacture one or more of its potential products. In the fourth quarter of 2002, the Company concluded that an impairment indicator existed in regard to the facility, in accordance with SFAS No. 144, "Accounting for

the Impairment or Disposal of Long-Lived Assets", and thus evaluated the asset for impairment. An undiscounted cash flow analysis confirmed the impairment, and the Company obtained an appraisal of the manufacturing facility to determine its fair market value, which indicated that the fair value of the facility was substantially lower than its carrying value. Accordingly, the Company recorded an impairment charge of $16,069,000 at December 31, 2002, based upon the difference between the fair market value of the facility and its carrying value at such date. The facility is classified as a held-for-sale asset in accordance with SFAS No. 144.

Other income:

Net Interest Income

Net interest income was $2,704,000 in 2003 as compared to $7,516,000 in 2002 and $11,274,000 in 2001. The average cash and marketable securities balances were $203,876,000 in 2003 compared to $328,940,000 in 2002 and $261,940,000 in 2001. Decrease in net interest income in 2003 from 2002 and 2001 was primarily due to the decrease in cash and marketable securities balances and lower rates of return. Average cash and marketable securities increased in 2002 from 2001 due to proceeds from equity financing, which resulted in net proceeds of $257,867,000. The Company expects rates of return to remain low, and average cash and marketable securities balance to decrease based on normal operations and buyout of minority interest in TKT Europe during the second half of 2004.

Other Income

In October 2003, the Company received $500,000 from Bain & Company in connection with a legal settlement. TKT recorded the $500,000 settlement as other income during the fourth quarter of 2003.

Minority Interest

For the year ended December 31, 2003, the Company recorded a minority interest amounting to $413,000 related to the Company's 80% interest in the cumulative net income of TKT Europe. The Company consolidated 100% of TKT Europe's losses in 2002 and 2001.

Gain on Sale of Investment

In 1996, TKT made a strategic equity investment of $300,000 in a European biotechnology company, which was sold in 2001, resulting in a realized gain of $3,224,000.

Net Loss

The Company had net losses of $75,234,000 in 2003 as compared to $129,762,000 in 2002 and $70,243,000 in 2001. Basic and diluted net loss per share was $2.18 for the year ended December 31, 2003, as compared to a basic and diluted net loss per share of $3.75 for 2002 and $2.78 for 2001. Included in the loss for the year ended December 31, 2003 are restructuring charges of $12,461,000 and intellectual property license fee expense of $1,350,000, which contributed $0.36 and $0.04, respectively, to basic and diluted net loss per share. Included in the loss for the year ended December 31, 2002 is an intellectual property license fee expense of $34,660,000 and an asset impairment charge of $16,069,000, which contributed $1.00 and $0.46, respectively, to basic and diluted net loss per share.

For the years ended December 31, 2003, 2002 and 2001, weighted average shares outstanding were 34,559,000, 34,616,000 and 25,228,000, respectively. The increase in weighted average shares outstanding reflects the sale of 7,785,000 common shares from the Company's public offerings of Common Stock in June and December 2001 and the issuance of 3,571,000 shares of Common Stock upon the conversion of all of the then outstanding Series A Convertible Preferred Stock in November 2001.

Liquidity And Sources Of Capital

Since its inception, TKT has financed its operations through:

- the sale of common and preferred stock,
- borrowings under debt agreements,
- revenues from collaborative agreements,
- interest income and,
- more recently, with collections from accounts receivable.

In the near term, TKT expects to finance its operations principally from existing cash and cash equivalents and from collections of accounts receivable related to sales of Replagal. The Company expects that its existing capital resources, together with anticipated collections on existing and future accounts receivable on product sales, anticipated cash payments under collaborative agreements, and interest income, will be sufficient to fund its operations into 2005.

Cash Flows

The Company had cash, cash equivalents and marketable securities totaling $180,947,000 at December 31, 2003, including restricted marketable securities collateralizing letters of credit totaling $7,993,000. At December 31, 2003, the Company's 80%-owned subsidiary, TKT Europe, held $64,508,000 of the $180,947,000 primarily denominated in Swedish Krona, British Pound, and Euro. Cash equivalents and marketable securities are invested in United States government and agency obligations and money market funds.

The Company used net cash of $66,826,000 for operating activities for the year ended December 31, 2003. Major cash flow changes consisted of a net loss of $75,234,000, an increase in accounts receivable of $3,662,000, an increase in accrued restructuring of $8,041,000, a decrease in accrued expenses of $12,531,000, and a decrease of inventory of $4,909,000. Net cash usage decreased in 2003 from 2002 primarily due to cost savings associated with the Company's restructuring efforts, growth in Replagal sales, increased accounts receivable collections, and a decrease in inventories.

Working capital at December 31, 2003 was $204,190,000 compared to $262,553,000 at December 31, 2002. Significant changes in working capital during 2003 included a $12,531,000 decrease in accrued expenses, primarily related to intellectual property license expense related to Cell Genesys. Accounts receivable increased by $3,662,000 in 2003 due to growth of Replagal sales in Europe. Inventory decreased by $4,909,000 in 2003 due to increases in Replagal sales and a reduction in manufacturing activity at the terminated contract manufacturer and the Company's Alewife Facility.

In certain European countries, such as Italy and Belgium, customary payment terms on accounts receivable are significantly longer than in the United States, particularly for products treating orphan drug indications. In these countries, the Company historically has received, and expects to continue to receive, payments approximately one year from the invoice date. Accounts receivable balances for Italy and Belgium were 56% and 49% of total accounts receivable at December 31, 2003 and 2002, respectively. The Company monitors its days' sales outstanding and collections in these countries. To date, these customers have been paying within the customary payment terms. If collections and days' sales outstanding in these countries deteriorate in the future, the Company's liquidity will be adversely affected.

Net cash provided by investing activities was $79,175,000 for the year ended December 31, 2003. Net maturities and sales of marketable securities contributed $93,842,000 to net cash provided by investing activities. The Company used net cash of $14,774,000 during 2003 for property and equipment purchases related to leasehold improvements and equipment for the Company's manufacturing facility. The Company expects to spend a total of approximately $14,000,000 for purchases of property and equipment in 2004, principally for expanding its internal manufacturing capabilities.

The $8,007,000 effect of exchange rate changes on cash and cash equivalents is primarily due to the weakening United States dollar relative to the Swedish Krona, Euro, British Pounds and the translation of our foreign subsidiaries' cash and accounts receivable balances, which are primarily denominated in the Euro currency.

The Company's cash requirements for operating activities and investment activities have significantly exceeded its internally generated funds. The Company expects that its cash requirements for such activities will continue to exceed its internally generated funds until it is able to generate substantially greater product sales.

The Company expects that it will require substantial additional funds to support its research and development programs, obligations under license agreements, acquisition of technologies, preclinical and clinical testing of its products, pursuit of regulatory approvals, acquisition of capital equipment, expansion of internal manufacturing capabilities, selling, general and administrative expenses, and the buyout of the minority interests in TKT Europe.

The Company plans to meet its long-term cash requirements through proceeds from product sales and revenues from collaborative agreements. In December 2000 the Company filed a shelf registration statement on Form S-3 with the SEC, which became effective in December 2000. This shelf registration statement permits the Company to offer, from time to time, any combination of common stock, preferred stock, debt securities and warrants of up to an aggregate of $500,000,000. The Company currently has approximately $232,000,000 available under this shelf registration statement. The Company may also pursue opportunities to obtain additional external financing in the future through debt financing, lease arrangements related to facilities and capital equipment, and collaborative research and development agreements.

If the Company is unable to obtain additional financing, the Company may be required to reduce the scope of its planned research, development, sales and marketing efforts, which could harm the Company's business, financial condition and operating results. The source, timing and availability of any future financing will depend principally upon equity and debt market conditions, interest rates and, more specifically, on the Company's continued progress in its preclinical and clinical development programs, and the extent of its commercial success. There can be no assurance that external funds will be available on favorable terms, if at all.

Contractual Obligations

The following table summarizes the Company's estimated significant contractual obligations at December 31, 2003:

	Payments Due by Period				
	Less than 1 Year	1-3 Years	4-5 Years	After 5 Years	Total
Non-cancelable operating leases	$11,388	$22,461	$23,700	$26,760	$ 84,309
Estimate of TKT Europe buyout price	55,000	—	—	—	55,000
Estimate of clinical trial commitments	5,497	3,973	—	—	9,470
Purchase commitments	750	—	—	—	750
Total contractual cash obligations	$72,635	$26,434	$23,700	$26,760	$149,529

In April 2000, the Company established TKT Europe for the purpose of marketing, selling and distributing Replagal in Europe. Under the stockholders' agreement for TKT Europe, the Company is entitled to purchase the European stockholders' 20% ownership interest in TKT Europe in September 2004, for a price determined in accordance with a formula. Should the Company not exercise that right, the European stockholders of TKT Europe can require the Company to purchase the European stockholders' ownership interest sixty days thereafter. The buyout price is equal to (a) 20% of the operating profits, as defined in the stockholders' agreement, for the period from September 1, 2003 to August 31, 2004, multiplied by a buyout factor of four, subject to adjustment, plus (b) 20% of the accumulated positive earnings of TKT Europe. As a result, the amount of the buyout price is dependent on the profits of TKT Europe and the commercial success

of Replagal in Europe. The Company estimates that the buyout price could be between $55,000,000 and $65,000,000 based on the Company's current estimates for sales and expenses.

As of December 31, 2003, the Company had committed to pay approximately $9,470,000 to various contract vendors for administering and executing clinical trials. The timing of payments is not reasonably certain as payments are dependent upon actual services performed by the organizations as determined by patient enrollment levels and related activities. However, the Company does expect to pay for these commitments throughout 2004 and into 2005 as ongoing trials are completed.

The Company also is subject to the potential commitments discussed in the following paragraph that is not included in the above table:

In June 2002, the Company obtained an exclusive license to certain patent and patent applications from Cell Genesys related to Cell Genesys' approach to gene activation. In consideration for the license, the Company paid $11,000,000 cash in June 2002 and an additional $15,000,000 in January 2003. If Cell Genesys achieves all the milestones related to patent matters under the license agreement, the Company will be obligated to pay Cell Genesys an aggregate of $17,000,000 payable in part in cash and in part in stock. The Company cannot predict when these milestones will become due, if ever. The Company is not required to make royalty payments to Cell Genesys.

Net Operating Loss Carryforwards

At December 31, 2003, the Company had net operating loss carryforwards of approximately $298,410,000, which expire at various times through 2023. Due to the degree of uncertainty related to the ultimate use of loss carryforwards and tax credits, the Company has fully reserved against any potential tax benefit. The future utilization of net operating loss carryforwards and tax credits may be subject to limitation under the changes in stock ownership rules of the Internal Revenue Code. Because of this limitation, it is possible that taxable income in future years, which would otherwise be offset by net operating losses, will not be offset and, therefore, will be subject to tax.

Litigation Expenses

The Company is a party to the legal proceedings listed below which are described in greater detail under Item 3. Legal Proceedings. The costs related to these proceedings have been significant and the Company expects that these costs will continue to be significant. The Company can provide no assurance as to the outcome of any of these proceedings. A decision by a court in the United States or in any other jurisdiction in a manner adverse to the Company could have a material adverse effect on the Company's business, financial condition and results of operations.

- The Company has been engaged in patent litigation with Genzyme and Mount Sinai with respect to Replagal. In October 2003, pursuant to a global legal settlement, Genzyme agreed to withdraw from this patent litigation and paid the Company $1,555,000. Mt. Sinai is not a party to the settlement. As of December 31, 2003, the Company had incurred approximately $4,687,000 in litigation expenses associated with the Replagal litigation.
- The Company and Aventis have been involved in patent infringement actions with Amgen and Kirin-Amgen with respect to Dynepo. The litigation is costly and the Company is required to reimburse Aventis, which is paying the litigation expenses, for 50% of the expenses. Aventis is entitled to deduct up to 50% of any royalties due to the Company from the sale of Dynepo until Aventis has recouped the full amount of TKT's share of litigation expenses. The Company currently estimates that its share of the expenses associated with the litigation will total between approximately $15,000,000 and $20,000,000 by the time the matter is finally adjudicated.
- In 2003 various parties filed purported class action lawsuits against the Company, its former CEO, former CFO, the members of the Company's Board of Directors and other parties. In April 2003 a derivative law suit was filed against the Company's former CEO, the members of the Company's Board of Directors and the Company as a nominal defendant, alleging that the individual defendants breached fiduciary duties

owed to the Company and its shareholders. As of December 31, 2003, the Company had incurred approximately $1,000,000 related to the shareholders law suit and derivative law suit.

- In May 2003 the Company received a copy of a formal order of investigation by the SEC. As of December 31, 2003, the Company had incurred approximately $1,400,000 related to this matter.

Recent Accounting Pronouncements

In January 2003, the FASB issued Interpretation No. 46, *Consolidation of Variable Interest Entities* (FIN 46) and in December 2003, issued a revision to FIN 46 (FIN 46R). This interpretation addresses the requirements for business enterprises to consolidate related entities in which they are determined to be the primary beneficiary as a result of their variable economic interest. The interpretation is intended to provide guidance in judging multiple economic interests in an entity and in determining the primary beneficiary. The interpretation outlines disclosure requirements for Variable Interest Entities in existence prior to January 31, 2003, and outlines consolidation requirements for Variable Interest Entities created after January 31, 2003. The Company will adopt the provisions of FIN 46 in the first quarter of 2004 and the interpretation is not expected to have an impact on the Company's consolidated financial statements.

The Emerging Issues Task Force ("EITF") recently reached a consensus on its tentative conclusions for EITF 00-21, *Revenue Arrangements with Multiple Deliverables*. EITF 00-21 provides accounting guidance for customer solutions where delivery or performance of products, services and/or performance may occur at different points in time or over different periods of time. Companies are required to adopt this consensus for fiscal periods beginning after June 15, 2003. The Company applied EIFT 00-21 to the distribution agreement and legal settlement with Genzyme as discussed in footnote 14 to the consolidated financial statements.

In May 2003, the FASB issued Statement 150, *Accounting for Certain Financial Instruments with Characteristics of both Liabilities and Equity*. Statement 150 establishes standards for classifying and measuring certain financial instruments with characteristics of both liabilities and equity. Statement 150 requires that an issuer classify a financial instrument that is within its scope as a liability (or an asset in some circumstances) because that financial instrument embodies an obligation of the issuer. Statement 150 is effective for financial instruments entered into or modified after May 31, 2003, and otherwise is effective for public companies during the first interim period beginning after June 15, 2003. The adoption of this pronouncement did not have a material impact on the Company's financial position, results of operations or liquidity.

Forward-Looking Statements

This annual report contains forward-looking statements within the meaning of Section 27A of the Securities Act of 1933, as amended, and Section 21E of the Securities and Exchange Act of 1934, as amended, that involve risks and uncertainties. The Company may, in some cases, use words such as "project," "believe," "anticipate," "plan," "expect," "estimate," "intend," "should," "would," "could," "will," or "may," or other words that convey uncertainty of future events or outcomes to identify these forward-looking statements. There are a number of important factors that could cause actual results to differ materially from the results anticipated by these forward-looking statements. These important factors include those set forth below under "Certain Factors That May Affect Future Results." These factors and the other cautionary statements made in this annual report should be read as being applicable to all related forward-looking statements wherever they appear in this annual report. If one or more of these factors materialize, or if any underlying assumptions prove incorrect, the Company's actual results, performance or achievements may vary materially from any future results, performance or achievements expressed or implied by these forward-looking statements. In addition, any forward-looking statements represent the Company's estimates only as of the date this annual report was filed with the Securities and Exchange Commission and should not be relied upon as representing the Company's estimates as of any subsequent date. While the Company may elect to update forward-looking statements at some point in the future, the Company specifically disclaims any obligation to do so, even if its estimates change.

Certain Factors That May Affect Future Results

The following important factors could cause actual results to differ from those indicated by forward-looking statements made by the Company in this annual report and elsewhere from time to time.

Development, Clinical and Regulatory Risks

If our clinical trials are not successful, we may not be able to develop and commercialize our products, including I2S.

In order to obtain regulatory approvals for the commercial sale of our potential products, we and our collaborators will be required to complete extensive clinical trials in humans to demonstrate the safety and efficacy of our products. However, we may not be able to commence or complete these clinical trials in any specified time period, or at all, either because the FDA or other regulatory agencies object, because we are unable to attract or retain clinical trial participants, or for other reasons. Even if we complete a clinical trial of one of our potential products, the data collected from the clinical trial may not indicate that our product is safe or efficacious to the extent required by the FDA, the European Commission, or other regulatory agencies to approve the potential product.

For example, we are currently conducting a pivotal clinical trial of I2S in 96 patients with Hunter syndrome at nine sites around the world. If the results are positive, we expect to file applications for marketing approval in the United States and Europe in the second half of 2005. However, even if we file such applications, the FDA, the European Commission and other regulatory agencies with which we file applications may not agree that our product is safe and efficacious and may not approve our product.

The results from preclinical testing of a product that is under development may not be predictive of results that will be obtained in human clinical trials. In addition, the results of early human clinical trials may not be predictive of results that will be obtained in larger scale, advanced stage clinical trials. Furthermore, we, one of our collaborators, or a regulatory agency with jurisdiction over the trials may suspend clinical trials at any time if the patients participating in such trials are being exposed to unacceptable health risks, or for other reasons.

The rate of completion of clinical trials is dependent in part upon the rate of enrollment of patients. Patient accrual is a function of many factors, including the size of the patient population, the proximity of patients to clinical sites, the eligibility criteria for the study, the existence of competitive clinical trials, and the availability of alternative treatments. Delays in planned patient enrollment may result in increased costs and prolonged clinical development. In addition, patients may withdraw from a clinical trial for a variety of reasons. If we fail to accrue and maintain the number of patients into one of our clinical trials for which the clinical trial was designed, the statistical power of the clinical trial may be reduced which would make it harder to demonstrate that our products are safe and efficacious.

Regulatory authorities, clinical investigators, institutional review boards, data safety monitoring boards and the hospitals at which our clinical trials are conducted all have the power to stop our clinical trials prior to completion. If our studies are not completed, we would be unable to show the safety an efficacy required to obtain marketing authorization for our product.

We may not be able to obtain marketing approvals for our products.

We are not able to market any of our products in the United States, Europe or in any other jurisdiction without marketing approval from the FDA, the European Commission, or any equivalent foreign regulatory agency. The regulatory process to obtain marketing approval for a new drug or biologic takes many years and requires the expenditure of substantial resources.

In August 2001, the European Commission granted marketing authorization of Replagal in the European Union, approximately one year after we submitted our Marketing Authorization Application to the European Agency for the Evaluation of Medicinal Products, or EMEA, and approximately five years after we filed our

Investigational New Drug Application, or IND, with the FDA. We are continuing to seek marketing approval for Replagal in a number of other countries in the world.

If the results from the pivotal trial of our I2S product are positive, we expect to file applications for marketing approval of our I2S product in the United States and Europe in the second half of 2005.

Although the European Commission has granted marketing approval of Dynepo, a fully human erythropoietin for the treatment of anemia related to chronic renal failure, in the European Union, Dynepo has not been approved in the United States. In 2000, our collaborator on the development of Dynepo, Aventis, submitted a Biologics License Application, or BLA to the FDA seeking marketing authorization for Dynepo in the United States. The FDA did not accept the BLA for filing, and requested that Aventis provide additional manufacturing data. Aventis has not yet submitted the requested additional data to the FDA, and we cannot predict whether or when Aventis will do so. In addition, Aventis has not launched Dynepo in Europe.

There can be no assurance as to whether or when any of our applications for marketing authorization relating to any of our products, including Replagal, I2S, and Dynepo, or additional applications for marketing authorization that we may make in the future as to these or other products, will be approved by the relevant regulatory authorities. Among other things, we have had only limited experience in preparing applications and obtaining regulatory approvals. If approval is granted, it may be subject to limitations on the indicated uses for which the product may be marketed or contain requirements for costly post-marketing testing and surveillance to monitor safety or efficacy of the product. For example, there are conditions associated with our European approval of Replagal, including an obligation to conduct additional clinical trials and an obligation to submit an annual assessment of Replagal for review by the European Commission. If we do not complete these clinical trials on a timely basis or the results of these trials are not satisfactory to the European Commission, the European Commission may withdraw or suspend Replagal approval. If approval of an application to market a product is not granted on a timely basis or at all, or we are unable to maintain our approval, our business may be materially harmed.

We have developed several Gene-Activated protein products that would compete with proteins that are currently being marketed by third parties. The FDA and European regulatory authorities may consider our gene activated protein products to be "follow-on" biologics. The FDA and European regulatory authorities are re-evaluating their respective approval processes with respect to "follow-on" biologics. Therefore, the process for approval, and timing of approval, for our Gene-Activated products may be heavily influenced by United States and European decisions regarding "follow-on" biologics. The timing and content of these decisions, if any, is highly unpredictable. If the process ultimately adopted for approval, or the timing of approval, for "follow-on" biologics is cumbersome or lengthy, we may not be able to realize much, if any, value from our Gene-Activated products, or we may not be able to partner with third parties to continue developing or marketing such products.

We may not be able to obtain orphan drug exclusivity for our products for the treatment of rare genetic diseases.

Some jurisdictions, including Europe and the United States, may designate drugs for relatively small patient populations as "orphan drugs." Orphan drug designation must be requested before submitting an application for marketing authorization. Orphan drug designation does not convey any advantage in, or shorten the duration of, the regulatory review and approval process, but does make the product eligible for orphan drug exclusivity and certain tax credits in the United States. Generally, if a product with an orphan drug designation subsequently receives the first marketing approval for the indication for which it has such designation, the product is entitled to orphan drug exclusivity. Orphan drug exclusivity means that another application to market the same drug for the same indication may not be approved, except in limited circumstances set forth in the FDA Statute, for a period of up to ten years in Europe and for a period of seven years in the United States. Obtaining orphan drug designations and orphan drug exclusivity for our products for the treatment of rare genetic diseases may be critical to the success of these products. Our competitors may obtain orphan drug exclusivity for products competitive with our products before we do as Genzyme did with Fabrazyme in the United States. Even if we obtain orphan drug exclusivity for any of our potential

products, we may not be able to maintain it. For example, if a competitive product is shown to be clinically superior to our product, any orphan drug exclusivity we have obtained will not block the approval of such competitive product.

In August 2001, the European Commission granted marketing authorization of Replagal in the European Union. The European Commission also granted marketing authorization of Genzyme's Fabrazyme in the European Union in August 2001. In connection with these approvals, the European Commission granted Replagal and Fabrazyme co-exclusive orphan drug status in the European Union for up to 10 years.

In April 2003, Genzyme received marketing authorization in the United States for Fabrazyme. Because Fabrazyme had received orphan drug designation in the United States, upon its marketing approval, Fabrazyme received orphan drug exclusivity. Because Fabrazyme received marketing approval in the United States before Replagal and received orphan drug exclusivity, the FDA may not approve Replagal and Replagal will be excluded from the United States market for seven years, until April 2010, unless we receive approval to market and sell Replagal in the United States and we can demonstrate that Replagal satisfies the limited criteria for exceptions set forth in the FDA Statute.

In November 2001, our I2S product for the treatment of Hunter syndrome was designated an "orphan drug" in the United States and in Europe. If our I2S product receives the first marketing approval for Hunter syndrome, then our I2S product will be entitled to orphan drug exclusivity and no other application to market the same drug for the same indication may be approved, except in limited circumstances, for a period of up to 10 years in Europe and for a period of seven years in the United States.

If we fail to comply with the extensive regulatory requirements to which our products are subject, we could be subject to adverse consequences and penalties.

The testing, manufacturing, labeling, advertising, promotion, export, and marketing, among other things, of our products are subject to extensive regulation by governmental authorities in Europe, the United States, and elsewhere throughout the world.

If one of our products is approved by the European Commission, the FDA or another regulatory agency, we and any third party manufacturers we use will be required to comply with a number of post-approval requirements. In each case, the product, the facilities at which the product is manufactured, any post-approval clinical data and our promotional activities will be subject to continual review and periodic inspections by the EMEA, the FDA and other regulatory authorities.

For example, Replagal was granted approval in "exceptional circumstances" by the European Commission. In exceptional circumstances for rare diseases, less-than-complete clinical data may be accepted such as when the authorities determine that it would be impractical or unethical to carry out full-scale pivotal clinical trials. Specific obligations are imposed on the granting of such approvals. These obligations form part of the formal marketing authorization issued by the European Commission and must be reviewed at the intervals specified, minimally on an annual basis. The annual review includes a reassessment of the overall benefit/risk ratio. If specific obligations are not fulfilled the marketing authorization can be varied, suspended or withdrawn by the agency. Upon completion of all requirements, these conditions are removed. The European Commission required us as part of its post-approval requirements to conduct additional clinical trials of Replagal. If we do not complete these clinical trials on a timely basis or the results of these studies are not satisfactory to the European Commission or we otherwise fail to comply with the conditions imposed on us pursuant to approval in exceptional circumstances, the approval of Replagal by the European Commission could be withdrawn or suspended. In addition, in the United States we will be required to report certain adverse events to the FDA and to comply with certain requirements concerning advertising and promotional labeling of the products.

We are required to maintain pharmacovigilance systems for collecting and reporting information concerning suspected adverse reactions to our products. In response to pharmacovigilance reports, regulatory authorities may initiate proceedings to revise the prescribing information for our products or to suspend or

revoke our marketing authorizations. Procedural safeguards are often limited, and marketing authorizations can be suspended with little or no advance notice.

Quality control and manufacturing procedures must continue to conform to current Good Manufacturing Practice regulations, or GMP, after approval. Regulatory authorities, including the EMEA and the FDA, periodically inspect manufacturing facilities to assess compliance with GMP. Accordingly, we and our contract manufacturers will need to continue to expend time, monies, and effort in the area of production and quality control to maintain GMP compliance. In addition, discovery of problems may result in financial penalties, suspension or withdrawal of an approved product from the market, operating restrictions, and the imposition of criminal penalties.

In addition to regulations adopted by the EMEA, the FDA, and other foreign regulatory authorities, we are also subject to regulation under the Occupational Safety and Health Act, the Toxic Substances Control Act, the Resource Conservation and Recovery Act, and other federal, state, and local regulations.

Our research and development efforts may not result in products appropriate for testing in human clinical trials.

We expend significant resources on research and development and preclinical studies of product candidates. However, these efforts may not result in the development of products appropriate for testing in human clinical trials. For example, our research may result in product candidates that are not expected to be efficacious in treating disease or that reveal safety concerns. We may postpone or terminate research and development of a product candidate or a program at any time for any reason such as the safety or efficacy of the potential product, allocation of resources or unavailability of qualified research and development personnel.

Adverse events in the field of gene therapy may impair our ability to obtain collaborative partners for our gene therapy programs.

We have terminated internal development of our gene therapy programs and are seeking collaborative partners with which to continue to develop these programs. Adverse events in the field of gene therapy, although not occurring in our clinical trials, may impair our ability to enter into collaborations for our programs. In particular, in November 1999, a patient with a rare metabolic disorder died in a gene therapy trial conducted at the University of Pennsylvania. In addition, in October 2002, a French boy developed a leukemia-like disease nearly three years after participating in a gene therapy study as a baby. As a result of these and other events, a number of gene therapy clinical trials have been terminated or suspended in the United States and in other countries, and regulatory authorities have grown increasingly concerned about the safety of gene therapy.

Litigation and Intellectual Property Risks

We are a party to patent litigation involving Replagal which could preclude us from manufacturing or selling Replagal.

In July 2000, Genzyme and Mount Sinai School of Medicine of New York University filed a patent infringement action against us in the United States District Court of Delaware. The complaint alleges that our activities relating to Replagal infringe a patent licensed by Genzyme from Mount Sinai. In January 2002, the United States District Court of Delaware dismissed this patent litigation granting our motion for summary judgment of non-infringement and denying Genzyme and Mount Sinai's motion for summary judgment of infringement. Genzyme and Mount Sinai sought monetary damages and injunctive relief.

In March 2002, Genzyme and Mount Sinai appealed the United States District Court of Delaware's ruling to the United States Court of Appeals for the Federal Circuit, and in January 2003 the United States Court of Appeals for the Federal Circuit heard oral arguments on the appeal. In October 2003, pursuant to a global legal settlement, Genzyme agreed to withdraw from this suit and paid us approximately $1.6 million. Mount Sinai is not a party to the settlement. In October 2003, the United States Court of Appeals for the

Federal Circuit affirmed a finding of non-infringement by us. In January 2004, the Federal Circuit denied Mount Sinai's petition for a rehearing en banc. We believe it is possible, but unlikely, that Mount Sinai will obtain further appellate review of this decision by the United States Supreme Court.

We are a party to litigation with Amgen, Inc. and Kirin-Amgen, Inc. involving Dynepo which could preclude us from manufacturing or selling Dynepo.

In April 1997, Amgen commenced a patent infringement action against us and Aventis in the United States United States District Court of Massachusetts. In January 2001, the United States District Court of Massachusetts concluded that Dynepo infringed eight of the 18 claims of five patents that Amgen had asserted. Amgen did not seek and was not awarded monetary damages.

In January 2003, the United States Court of Appeals for the Federal Circuit issued a decision affirming in part and reversing in part the decision of the United States District Court of Massachusetts and remanded the action to the United States District Court of Massachusetts for further proceedings. In particular, the United States Court of Appeals for the Federal Circuit:

- upheld the United States District Court of Massachusetts' determination of invalidity of one of Amgen's patents;
- upheld the United States District Court of Massachusetts' determination that some claims of two other Amgen patents were infringed, but vacated the United States District Court of Massachusetts' determination that those patents were not invalid; and
- vacated the United States District Court of Massachusetts' determination that Dynepo infringed some claims of the two remaining Amgen patents, and vacated the United States District Court of Massachusetts' determination that one of these patents was not invalid.

As part of the United States Court of Appeals for the Federal Circuit's ruling, it remanded the case to the United States District Court of Massachusetts and instructed it to reconsider the validity of Amgen's patents in light of potentially invalidating prior art. The United States District Court of Massachusetts has recently concluded the remand proceedings and heard oral argument on some of these issues in July 2003. We expect that the United States District Court of Massachusetts will enter a decision on the remanded issues at some point during the first half of 2004. The United States District Court of Massachusetts also recently issued a decision upholding its earlier findings that Amgen successfully rebutted the presumption of prosecution history estoppel with respect to certain patents, and therefore, we and Aventis infringe such patents in light of recent Supreme Court precedents. On remand, we and Aventis presented affirmative defenses with respect to such patents. Both Amgen and Aventis, together with us, will have the right to appeal the decision of the United States District Court of Massachusetts to the United States Court of Appeals for the Federal Circuit.

In addition, in July 1999, we commenced legal proceedings with Aventis in the United Kingdom against Kirin-Amgen, which sought a declaration that a European patent held by Kirin-Amgen will not be infringed by our activities relating to Dynepo and that certain claims of Kirin-Amgen's U.K. patent are invalid. In April 2001, the High Court of Justice in the United Kingdom ruled that Dynepo infringed one of four claims of the patent asserted by Kirin-Amgen. In July 2002, the Court of Appeals in the United Kingdom reversed the High Court of Justice and ruled that Dynepo did not infringe Kirin-Amgen's patent. Kirin-Amgen petitioned the House of Lords to hear an appeal from the decision of the Court of Appeals. The House of Lords agreed to hear this appeal during the summer of 2004.

We can provide no assurance as to the outcome of either litigation. If we and our collaborator, Aventis, are not successful in the Dynepo litigation, we and Aventis would be precluded from making, using and selling Dynepo in the United States and/or in the United Kingdom. We are required to reimburse Aventis, which is paying the litigation expenses, for 50% of the expenses. Aventis is entitled to deduct up to 50% of any royalties due to us from it with respect to the sale of Dynepo until Aventis has recouped the full amount of our share of litigation expenses. We currently estimate that our share of the expenses associated with the litigation will total between approximately $15.0 million and $20.0 million by the time the matter is finally adjudicated.

We are a party to shareholder lawsuits and a derivative action regarding the adequacy of our public disclosure which could have a material adverse affect on our financial condition.

In January and February 2003, various parties filed purported class action lawsuits against us and Richard Selden, our then Chief Executive Officer, in the United States District Court for the District of Massachusetts. The complaints generally allege securities fraud during the period from January 2001 through January 2003. Each of the complaints asserts claims under Section 10(b) of the Securities Exchange Act of 1934, Rule 10b-5 promulgated thereunder, and Section 20(a) of the Exchange Act, and alleges that we and our officers made false and misleading statements and failed to disclose material information concerning the status and progress for obtaining United States marketing approval of our Replagal product to treat Fabry disease during that period.

In March 2003, various plaintiffs filed motions to consolidate, to appoint lead plaintiff, and to approve plaintiff's selections of lead plaintiffs' counsel. In April 2003, various plaintiffs filed a Joint Stipulation and Proposed Order of Lead Plaintiff Applicants to Consolidate Actions, To Appoint Lead Plaintiffs and to Approve Lead Plaintiffs' Selection of Lead Counsel, Executive Committee and Liaison Counsel. In April 2003, the Court endorsed the Proposed Order, thereby consolidating the various matters under one matter: *In re Transkaryotic Therapies, Inc., Securities Litigation, C.A. No. 03-10165-RWZ.*

In July 2003, the plaintiffs filed a Consolidated and Amended Class Action Complaint, which we refer to as the Amended Complaint, against us; Dr. Selden; Daniel Geffken, our former Chief Financial Officer; Walter Gilbert, Jonathan S. Leff, Rodman W. Moorhead, III, and Wayne P. Yetter, members of our Board of Directors; William R. Miller and James E. Thomas, former members of our Board of Directors; SG Cowen Securities Corporation; Deutsche Bank Securities; Pacific Growth Equities, Inc.; and Leerink Swann & Company.

The Amended Complaint alleges securities fraud during the period from January 4, 2001 through January 10, 2003. The Amended Complaint alleges that the defendants made false and misleading statements and failed to disclose material information concerning the status and progress for obtaining United States marketing approval of Replagal during that period. The Amended Complaint asserts claims against each of the defendants under Section 11 of the Securities Act and against Dr. Selden under Section 15 of the Securities Act; against SG Cowen Securities Corporation, Deutsche Bank Securities, Pacific Growth Equities, Inc., and Leerink Swann & Company under Section 12(a)(2) of the Securities Act; against Dr. Selden and us under Section 10(b) of the Exchange Act and Rule 10b-5 promulgated thereunder; and against Dr. Selden under Section 20(a) of the Exchange Act. The plaintiffs seek equitable and monetary relief, an unspecified amount of damages, with interest, and attorney's fees and costs.

In September 2003, we filed a motion to dismiss the Amended Complaint. A hearing of the motion occurred in December 2003. A class has not been certified.

In April 2003, South Shore Gastrointerology UA 6/6/1980 FBO Harold Jacob, and Nancy R. Jacob Ttee filed a Shareholder Derivative Complaint against Dr. Selden; against the following members of our board of directors: Jonathan S. Leff, Walter Gilbert, Wayne P. Yetter, Rodman W. Moorhead III; against the following former members of our Board of Directors: James E. Thomas, and William Miller; and against us as nominal defendant, in Middlesex Superior Court in the Commonwealth of Massachusetts, Civil Action No. 03-1669. On May 29, 2003, the parties moved to transfer venue to the Business Litigation Session in Suffolk Superior Court in the Commonwealth of Massachusetts. The parties' motion was allowed, and in June 2003 the matter was accepted into the Business Litigation Session as Civil Action No. 03-02630-BLS.

The complaint alleges that the individual defendants breached fiduciary duties owed to us and our shareholders by disseminating materially false and misleading statements to the market and causing or allowing us to conduct our business in an unsafe, imprudent and unlawful manner. The complaint purports to assert derivative claims against the individual defendants for breach of fiduciary duty, and to assert a claim for contribution and indemnification on behalf of us for any liability we incur as a result of the individual defendants' alleged misconduct. The complaint seeks declaratory, equitable and monetary relief, an unspecified amount of damages, with interest, and attorney's fees and costs.

In August 2003, the plaintiff filed its Verified Amended Derivative Complaint, which we refer to as the Amended Derivative Complaint. The Amended Derivative Complaint alleges that the individual defendants breached fiduciary duties owed to us and our stockholders by causing us to issue materially false and misleading statements to the public, by signing our Form 10-Ks for the years 2000 and 2001 and by signing a registration statement. The Amended Derivative Complaint also alleges that defendant Dr. Selden sold our stock while in possession of material non-public information. The plaintiffs seek declaratory, equitable and monetary relief, an unspecified amount of damages, with interest, and attorney's fees and costs.

In September 2003, we served a motion to dismiss the Amended Derivative Complaint. A hearing of the motion was held in January 2004.

As of December 31, 2003, we had spent approximately $1.0 million related to these lawsuits. We expect that the costs related to these suits will be significant. We can provide no assurance as to the outcome of any of these suits. If we are not successful in defending these actions, our business, results of operations and financial condition could be adversely affected. In addition, even if we are successful, the defense of these actions may divert the attention of our management and other resources that would otherwise be engaged in running our business.

The SEC is investigating us regarding our public disclosures and filings, as well as transactions in our securities, which could have a material adverse effect on our financial condition.

In May 2003, we received a copy of a formal order of investigation by the SEC. The order of investigation relates to our disclosures and public filings with regard to Replagal and the status of the FDA's approval process for Replagal, as well as transactions in our securities. We are cooperating fully and will continue to cooperate fully with the SEC in the investigation. As of December 31, 2003, we had spent approximately $1.4 million related to this matter.

If this investigation results in a determination that we have failed to properly disclose information relating to Replagal and the status of the FDA's approval process for Replagal or that there were improper transactions in our securities, we could be subject to substantial fines or penalties and other sanctions. An adverse determination could have a material effect on our financial position and results of operations. However, at this time, we cannot accurately predict the outcome of this proceeding. In addition, even if we are successful, this investigation may divert the attention of our management and other resources that would otherwise be engaged in running our business.

We may become involved in additional and expensive patent litigation or other proceedings.

The biotechnology industry has been characterized by significant litigation, and other proceedings regarding patents, patent applications, and other intellectual property rights. We may become a party to additional patent litigation and other proceedings with respect to our proteins or other technologies. Such litigation could result in liability for damages, prevent our development and commercialization efforts, and divert management's attention and resources.

An adverse outcome in any patent litigation or other proceeding involving patents could subject us to significant liabilities to third parties and require us to cease using the technology or product that is at issue or to license the technology or product from third parties. We may not be able to obtain any required licenses on commercially acceptable terms, or at all.

The cost to us of any patent litigation or other proceeding, even if resolved in our favor, could be substantial. Some of our competitors may be able to sustain these costs more effectively than we can because of their substantially greater financial resources. Uncertainties resulting from the initiation and continuation of patent litigation or other proceedings could have a material adverse effect on our ability to develop, manufacture, and market products, form strategic alliances, and compete in the marketplace.

If we are unable to obtain patent protection for our discoveries, the value of our technology and products may be adversely affected.

Our success will depend in large part on our ability to obtain patent protection for our processes and products in the United States and other countries. The patent situation in the field of biotechnology generally is highly uncertain and involves complex legal, scientific and factual questions. We may not be issued patents relating to our technology. Even if issued, patents may be challenged, invalidated, or circumvented. Our patents also may not afford us protection against competitors with similar technology. Because some patent applications in the United States are maintained in secrecy until patents issue, third parties may have filed or maintained patent applications for technology used by us or covered by our pending patent applications without our being aware of these applications. As a result, third parties could assert claims against us concerning our gene activation or other technology.

We may not hold proprietary rights to certain product patents, process patents, and use patents related to our products or their methods of manufacture. In some cases, these patents may be owned or controlled by third parties. As a result, we may be required to obtain licenses under third party patents to market certain of our potential products. If licenses are not available to us on acceptable terms, we may not be able to market these products.

If we are unable to protect the confidentiality of our proprietary information and know-how, the value of our technology and products will be adversely affected.

We rely upon unpatented proprietary technology, processes, and know-how. We seek to protect this information in part by confidentiality agreements with our employees, consultants, and other third party contractors. These agreements may be breached, and we may not have adequate remedies for any such breach. In addition, our trade secrets may otherwise become known or be independently developed by competitors.

If we fail to comply with our obligations under the agreements under which we license commercialization rights to products or technology from third parties, we could lose license rights.

We are a party to over 20 patent licenses under which we have acquired rights to proprietary technology of third parties, including a license to patents related to I2S, and expect to enter into additional patent licenses in the future. These licenses impose various commercialization, sublicensing, royalty, insurance, and other obligations on us. If we fail to comply with these obligations, the licensor may have the right to terminate the license and we could lose our license to use the acquired rights. If these rights are lost, we may not be able to market products that were covered by the license.

Business Risks

Our revenue from product sales is dependent on the commercial success of Replagal.

Replagal is our only commercial product. We expect that Replagal will account for all of our product sales into at least 2005. The commercial success of Replagal will depend on its acceptance by physicians, patients and other key decision-makers for the treatment of Fabry disease. The commercial success of Replagal will also depend in part upon Replagal receiving marketing approval in Japan and other countries. As noted above, we have ceased our efforts to seek the approval of Replagal in the United States.

Our revenue from sales of Replagal and our cash held by TKT Europe are subject to foreign currency fluctuations.

We have exposure to currency risk for Replagal sales in Europe. Country by country pricing of Replagal was initially established as the local currency equivalent of between approximately $165,000 and $175,000 per patient per year for an average patient weighing 70 kilograms. The price generally remains fixed in the local currencies and varies in United States dollars with exchange rate fluctuations. Since the approval of Replagal in August 2001, the United States dollar has weakened substantially versus most European currencies, including the Euro, which has resulted in increased revenues for us from sales of Replagal. If the United

States dollar were to strengthen versus these currencies, this currency fluctuation would adversely impact our Replagal product sales. Foreign currency fluctuations favorably contributed $9.4 million to product sales for the year ended December 31, 2003 as compared to the same period of 2002.

We also have exposure to currency risk for cash and cash equivalents held by TKT Europe, which are primarily denominated in Swedish Krona, British Pound and Euro. Any change in the value of the U.S. dollar as compared to these foreign currencies may have an adverse effect on our liquidity. For example, a hypothetical 10 percent increase in currency rates relative to the U.S. dollar would result in an approximate $5.9 million decrease in our cash and cash equivalents held by TKT Europe as of December 31, 2003.

The continuity of our sales of Replagal in Europe may be affected by our expected purchase of the holdings of the minority stockholders of our majority-owned sales and marketing subsidiary in Europe.

In April 2000, we established an 80%-owned subsidiary, TKT Europe, for the purpose of marketing, selling and distributing Replagal in Europe. Under the stockholders' agreement for TKT Europe, we agreed that the holders of the remaining 20% interest in TKT Europe would, with specified exceptions, manage the day-to-day operations of TKT Europe. As a result, our ability to successfully market and sell Replagal in Europe has been dependent on the efforts of the minority stockholders of TKT Europe.

Under the stockholders' agreement for TKT Europe, we are entitled to purchase the European stockholders' 20% ownership interest in TKT Europe in September 2004 for a price determined in accordance with a formula. Should we not exercise that right, the European stockholders of TKT Europe can require us to purchase the European stockholders' ownership interest sixty days thereafter. We currently expect that we will purchase the European stockholders' interest in TKT Europe for between $55 million and $65 million based on our current estimates for sales and expenses.

If we purchase the European stockholders' interest in TKT Europe or if the European stockholders exercise their contractual right to require us to purchase their interest, our ability to successfully market and sell Replagal in Europe would be dependent on our ability to integrate the functions of TKT Europe into our infrastructure. In addition, if we cannot retain existing marketing and sales personnel of TKT Europe, it is likely that the current relationships that TKT Europe maintains with patients, physicians and other key decision-makers for the treatment of Fabry disease would be affected, and any such changes could adversely affect our results of operations in Europe, including our sales of Replagal, and could result in the loss of market share in Europe.

We face significant competition, which may result in others discovering, developing or commercializing products before, or more successfully, than we do.

The biotechnology industry is highly competitive and characterized by rapid and significant technological change. Our competitors include pharmaceutical companies, biotechnology firms, universities, and other research institutions. Many of these competitors have substantially greater financial and other resources than we do and are conducting extensive research and development activities on technologies and products similar to, or competitive with, ours.

We may be unable to develop technologies and products that are more clinically efficacious or cost-effective than products developed by our competitors. Even if we obtain marketing approval for our product candidates, many of our competitors have more extensive and established sales, marketing, and distribution capabilities than we do. Litigation with third parties, such as our litigation with Amgen, could delay our time to market or preclude us from reaching the market for certain products and enable our competitors to more quickly and effectively penetrate certain markets.

Therapeutics for the Treatment of Rare Genetic Diseases

We believe that the primary competition with respect to our products for the treatment of rare genetic diseases is from biotechnology and smaller pharmaceutical companies. Competitors include BioMarin Pharmaceutical Inc., Actelion Ltd., and Genzyme. The markets for some of the potential therapeutics for rare

genetic diseases caused by protein deficiencies are quite small. As a result, if competitive products exist, we may not be able to successfully commercialize our products.

We believe that our primary competition with respect to Replagal is Genzyme. Replagal and Fabrazyme were each granted marketing authorization in the European Union and were also granted co-exclusive orphan drug status in the European Union for up to 10 years. Fabrazyme has received marketing authorization and orphan drug exclusivity in the United States.

We believe that our primary competition with respect to our GA-GCB product for the treatment of Gaucher disease will be Genzyme's product Cerezyme.

Gene-Activated Versions of Proteins That Would Compete With Currently-Marketed Proteins

We have developed several Gene-Activated protein products that would compete with proteins that are currently being marketed by third parties. For instance, in the case of Dynepo, competing products are marketed by Amgen, Johnson & Johnson, F. Hoffmann-La Roche Ltd. (Boehringer Mannheim GmbH), Sankyo Company Ltd., Chugai Pharmaceutical Co., Ltd., and the pharmaceutical division of Kirin Brewery Co., Ltd. in Japan.

Many of the products against which our Gene-Activated proteins would compete have well-known brand names, have been promoted extensively, and have achieved market acceptance by third-party payors, hospitals, physicians, and patients. In addition, many of the companies that produce these protein products have patents covering techniques used to produce these products, which have often served as effective barriers to entry in the therapeutic proteins market. As with Amgen and its erythropoietin product, these companies may seek to block our entry into the market by asserting that our Gene-Activated proteins infringe their patents. Many of these companies are also seeking to develop and commercialize new or potentially improved versions of their proteins.

Gene Therapy

Our gene therapy system will have to compete with other gene therapy systems, as well as with conventional methods of treating the disease and conditions targeted. Although no gene therapy product is currently marketed, a number of companies, including major biotechnology companies, pharmaceutical companies and development stage companies, are actively involved in this field.

The market may not be receptive to our products upon introduction.

The commercial success of any of our products for which we obtain marketing approval from the European Commission, the FDA, and other regulatory authorities will depend upon their acceptance by patients, the medical community and third party payors as clinically effective, safe and cost-effective. It may be difficult for us to achieve market acceptance of our products.

Other factors that we believe will materially affect market acceptance of our products include:

- the timing of the receipt of marketing approvals;
- the countries in which such approvals are obtained; and
- the safety, efficacy, convenience, and cost-effectiveness of the product as compared to competitive products.

We have limited manufacturing experience and may not be able to develop the experience and capabilities needed to manufacture our products in compliance with regulatory requirements.

The manufacture of proteins is complicated and technical. We have limited manufacturing experience. In order to continue to develop products, apply for regulatory approvals, and commercialize our products, we will need to develop, contract for, or otherwise arrange for the necessary manufacturing capabilities. We have

manufactured, and plan to continue in the future to manufacture, the bulk drug substance for our products for preclinical testing, clinical trials, and commercial sale.

Any manufacturing of our products must comply with GMP as required by the countries in which we intend to sell our products. Before approving an application for marketing authorization for a product, the FDA, the European Commission, or any other equivalent foreign regulatory agency will inspect the facilities at which the product is manufactured. If we or our third party manufacturers do not comply with applicable GMP, such regulatory agency may refuse to approve our application for marketing authorization. Once the regulatory agency approves a product, we or our third party manufacturers must continue to comply with GMP. If we or our third party manufacturers fail to maintain compliance with GMP, adverse consequences can result, including suspension or withdrawal of an approved product from the market, operating restrictions, and the imposition of civil and criminal penalties.

We are developing new manufacturing processes to manufacture bulk drug substance for Replagal and for I2S. Following the development of these new processes, we will need to obtain regulatory approval of these new processes before we may manufacture our products using these new processes.

In some of our manufacturing processes, we use bovine-derived serum sourced from Canada and the United States. The discovery of cattle in both Canada and the United States with bovine spongiform encephalopathy, or mad cow disease, could cause the regulatory agencies in some countries to impose restrictions on our products, or prohibit us from using our products at all in such countries.

We are incurring significant costs to expand our manufacturing facility. Any delays in completing the renovations to our facility or obtaining re-approval of our facility following completion of the renovations could adversely affect our ability to supply the bulk drug substance needed to manufacture our products.

We are investing substantial funds to expand the capacity of our Alewife manufacturing facility in Cambridge, Massachusetts and to configure the facility for the production at a commercial scale of products other than Replagal. In anticipation of these renovations, in the third quarter of 2003, we ceased all manufacturing operations at our Alewife facility. We expect to complete these renovations in the first half of 2004 and recommence manufacturing operations in the second half of 2004. Following completion of these renovations, the appropriate regulatory authorities, including the European Commission, will need to re-inspect and re-approve the Alewife facility before we can produce bulk drug substance at the Alewife facility for commercial sale and clinical trials. If we are unable to successfully complete our renovations in a timely manner or to obtain regulatory approval of the Alewife facility, our ability to supply our products for commercial sale and clinical use, including Replagal, I2S and GA-GCB, could be interrupted and our sales of Replagal and the timing of our I2S or GA-GCB clinical trials could be adversely affected.

We also plan to use the Alewife facility to manufacture I2S and GA-GCB for commercial use if and when such products are approved for commercialization. If we are unable to successfully manufacture these products in our Alewife facility, we may not be able to supply patients with I2S or GA-GACB or complete our clinical trials.

We depend on third party contract manufacturers for various aspects of the manufacture of our products, including the preparation and packaging of TKT-manufactured bulk drug substance into finished product. If these manufactures fail to meet our requirements, our product development and commercialization efforts may be materially harmed.

To the extent that we are a party to manufacturing arrangements with third parties, we are dependent upon these third parties to perform their obligations in a timely manner and in accordance with applicable government regulations. For instance, we rely on contract manufacturing arrangements with third parties with respect to various aspects of the manufacture of Replagal, I2S, and GA-GCB, other than the manufacture of the bulk drug substance for such products, including the preparation and packaging of TKT-manufactured bulk drug substance into finished product. Each of these manufacturing arrangements relates to only some aspects of the manufacturing process. In the event that any one of these manufacturers fails to or is unable to

comply with its obligations under its manufacturing agreement with us, and if the manufacturer's failure materially delays the ultimate production of Replagal, I2S, or GA-GCB and adversely affects our inventory levels, our sales of Replagal or the timing of our I2S or GA-GCB clinical trials could be adversely affected.

In addition, the value of the inventory under the control of these third party contract manufacturers far exceeds the amount of liability such third parties are willing to assume for their negligence. In the event that inventory in the possession of one of these third party manufacturers is damaged, we could face significant financial losses and we could also experience an interruption in supply which could have a significant long-term affect on our sales.

Under our collaborative agreement with Aventis, Aventis is responsible for the manufacture of Dynepo for clinical trials and commercial sales and is also responsible for conducting future clinical trials and commercial sales. We are not a party to any other arrangements relating to the manufacture of Dynepo and, as a result, we are dependent on Aventis and its third party manufacturer for the manufacture of Dynepo.

There are a limited number of third-party manufacturers capable of manufacturing our protein products with a limited amount of production capacity. As a result, we may experience difficulty in obtaining adequate manufacturing capacity for our needs. If we are unable to obtain or maintain contract manufacturing of these products, or to do so on commercially reasonable terms, we may not be able to complete development of these products or market them.

If we fail to manage our inventory correctly, we could experience supply shortages or a significant build-up of high-cost products and raw materials.

Manufacture of proteins, including our products and potential products, is expensive and requires lengthy production cycle times. We build inventory of both bulk drug substance and of finished product in order to ensure the adequate supply to patients of our products and potential products, including Replagal and I2S. Accordingly, we have significant capital invested in inventory because of the high cost of manufacturing protein products, including Replagal and I2S. Furthermore, much of our inventory is stored in a single facility. However, we have limited experience in managing our supply for Replagal and our other potential products. If we fail to keep an adequate inventory of our products, it is possible that patients could miss treatments, which could have an adverse effect on our ability to sell our products and on our clinical trials. Conversely, if we are unable to sell our high-cost inventory in a timely manner, or if our high-cost inventory were to be destroyed or expire, we could experience cash flow difficulties as well as losses.

Some of the raw materials used to manufacture our products are expensive and are available from a small number of suppliers. If we fail to keep an adequate inventory of our raw materials, it is possible that we would be unable to manufacture our products in a timely manner. Conversely, if we are unable to use our high cost raw materials, or if our high-cost raw materials were to be destroyed or expire, we could experience cash flow difficulties as well as losses.

If we fail to obtain reimbursement, or an adequate level of reimbursement, by third party payors in a timely manner for our products, or if we are unable to collect payment in a timely manner, we may not have commercially viable markets for our products.

In certain countries, particularly the countries of the European Union, the pricing of prescription pharmaceuticals and the level of reimbursement are subject to governmental control. In some countries, it can take an extended period of time to establish and obtain reimbursement, and reimbursement approval may be required at the individual patient level, which can lead to further delays. In addition, in some countries such as Italy, Spain and Belgium, it can take an extended period of time to collect payment even after reimbursement has been established.

In the United States and elsewhere, the availability of reimbursement by governmental and other third party payors affects the market for any pharmaceutical product. These third party payors continually attempt to contain or reduce the costs of health care by challenging the prices charged for medical products and services. For example, in Germany, the reimbursement authority unilaterally reduced the price that it would

reimburse for pharmaceutical products, including Replagal, by six percent in 2003 and an additional ten percent in 2004. Governmental and reimbursement authorities or third party payors in other countries may attempt to control costs by limiting access to pharmaceutical products such as Replagal or by narrowing the class of patients for which a pharmaceutical product such as Replagal may be prescribed. If we are not able to obtain pricing and reimbursement at satisfactory levels for our products that receive marketing approval, our revenues and results of operations will be adversely affected, possibly materially.

We expect that the prices for many of our products, when commercialized, including in particular our products for the treatment of rare genetic diseases, may be high compared to other pharmaceutical products. For example, we have established pricing and reimbursement for substantially all patients receiving Replagal in the European Union. Country by country pricing was initially established as the local currency equivalent of between approximately $165,000 and $175,000 per patient per year for an average patient weighing 70 kilograms. The price generally remains fixed in the local currencies and varies in United States dollars with exchange rate fluctuations. We may encounter particular difficulty in obtaining satisfactory pricing and reimbursement for products for which we seek a high price.

The Centers for Medicare and Medicaid Services of the United States Department of Health and Human Services has considered proposals from time to time to reduce the reimbursement rate with respect to erythropoietin. If Dynepo is approved and commercialized, adoption by the Centers for Medicare and Medicaid Services of any such proposal might have an adverse effect on the pricing of Dynepo.

We also may experience pricing pressure with respect to Replagal and other products for which we may obtain marketing approval due to the trend toward managed health care, the increasing influence of health maintenance organizations and legislative proposals. We may not be able to sell our products profitably if reimbursement is unavailable or limited in scope or amount.

We have limited sales and marketing experience and capabilities and will need to develop this expertise or depend on third parties to successfully sell and market our products on our behalf.

Except for TKT Europe with respect to the marketing and selling of Replagal, we have limited sales and marketing experience and capabilities, and limited resources to devote to sales and marketing activities. In order to market our products, including Replagal, we will need to develop this experience and these capabilities or rely upon third parties, such as our collaborators, to perform these functions. If we rely on third parties to sell, market, or distribute our products, our success will be dependent upon the efforts of these third parties in performing these functions. In many instances, we may have little or no control over the activities of these third parties in selling, marketing, and distributing our products. If we choose to conduct these activities directly, as we plan to do with respect to some of our potential products and with Replagal following our expected purchase of the European stockholders' interests in TKT Europe, we may not be able to recruit and maintain an effective sales force.

Competition for technical, commercial and administrative personnel is intense in our industry and we may not be able to sustain our operations or grow if we are unable to attract and retain qualified personnel.

While we do not feel that any single individual is indispensable, our success is highly dependent on the retention of principal members of our technical, commercial, and administrative staff.

Our future growth will require hiring a significant number of qualified technical, commercial and administrative personnel. Accordingly, recruiting and retaining such personnel in the future will be critical to our success. There is intense competition from other companies and research and academic institutions for qualified personnel in the areas of our activities. If we are not able to continue to attract and retain, on acceptable terms, the qualified personnel necessary for the continued development of our business, we may not be able to sustain our operations or grow.

We depend on our collaborators to develop, conduct clinical trials of, obtain regulatory approvals for, and manufacture, distribute, market and sell products on our behalf and their efforts may not be scientifically or commercially successful.

We are parties to collaborative agreements with third parties relating to certain of our principal products. We are relying on Genzyme to develop and commercialize I2S in Japan and certain other countries in Asia; on Aventis to develop, conduct clinical trials of, obtain regulatory approvals for, and manufacture, market, and sell Dynepo in the United States and Europe; and Sumitomo to develop and commercialize Replagal in Japan, Korea, China and Taiwan. We also use third party distributors to distribute our products in many areas of the world including Australia, Canada, Europe, and Israel. Our collaborators may not devote the resources necessary or may otherwise be unable or unwilling to complete development and commercialization of these potential products. Our existing collaborations are subject to termination without cause on short notice under specified circumstances. In some cases, we may not receive payments contemplated in the agreements with our collaborators if our collaborators fail to achieve certain regulatory and commercial milestones.

Our existing collaborations and any future collaborative arrangements with third parties may not be scientifically or commercially successful. Factors that may affect the success of our collaborations include the following:

- our collaborators may be pursuing alternative technologies or developing alternative products, either on their own or in collaboration with others, that may be competitive with the product as to which they are collaborating with us or that could affect our collaborative partners' commitment to the collaboration with us;
- reductions in marketing or sales efforts or a discontinuation of marketing or sales of our products by our collaborators would reduce our revenues, which will be based on a percentage of net sales by the collaborator;
- under our collaboration agreements, we cannot conduct specified types of research and development in the field that is the subject of the collaboration. These agreements have the effect of limiting the areas of research and development that we may pursue, either alone or in cooperation with third parties;
- our collaborators may underfund or not commit sufficient resources to the testing, marketing, distribution or other development of our products;
- our collaborators may not properly maintain or defend our intellectual property rights or they may utilize our proprietary information in such a way as to invite litigation that could jeopardize or invalidate our proprietary information or expose us to potential liability;
- our collaborators may terminate their collaborations with us, as Aventis has done with respect to our GA-GCSF product, which could make it difficult for us to attract new collaborators or adversely affect the perception of us in the business and financial communities; and
- our collaborators may pursue higher priority programs or change the focus of their development programs, which could affect the collaborator's commitment to us.

If third parties on whom we rely for clinical trials do not perform as contractually required or as we expect, we may not be able to obtain regulatory approval for or commercialize our product candidates, and our business may suffer.

We do not have the ability to independently conduct the clinical trials required to obtain regulatory approval for our products. We depend on independent clinical investigators, contract research organizations and other third party service providers in the conduct of the clinical trials of our product candidates and expect to continue to do so. We rely heavily on these parties for successful execution of our clinical trials, but do not control many aspects of their activities. For example, the investigators are not our employees. However, we are responsible for ensuring that each of our clinical trials is conducted in accordance with the general investigational plan and protocols for the trial. Third parties may not complete activities on schedule, or may not conduct our clinical trials in accordance with regulatory requirements or our stated protocols. The failure

of these third parties to carry out their obligations could delay or prevent the development, approval and commercialization of our product candidates.

We may be exposed to product liability claims and may not be able to obtain adequate product liability insurance.

Our business exposes us to the risk of product liability claims that is inherent in the manufacturing, testing, and marketing of human therapeutic products. We maintain clinical trial liability insurance and product liability insurance in amounts that we believe to be reasonable. This insurance is subject to deductibles and coverage limitations. We may not be able to obtain additional insurance or maintain insurance on acceptable terms or at all. Moreover, any insurance that we do obtain may not provide adequate protection against potential liabilities. If we are unable to obtain insurance at acceptable cost or otherwise protect against potential product liability claims, we will be exposed to significant liabilities, which may materially and adversely affect our business and financial position. These liabilities could prevent or interfere with our product commercialization efforts.

If we fail to obtain marketing authorizations in a timely manner, our costs associated with clinical trials will increase.

After completion of a clinical trial designed to show safety or efficacy, we often enroll patients taking our products in maintenance clinical trials in which these patients continue to receive treatment with our products pending approval for marketing authorization in the relevant jurisdiction. The costs associated with maintaining open-ended maintenance clinical trials can be significant, and if we fail to obtain marketing authorizations in a timely manner for the product being tested in such trials, our costs associated with these maintenance clinical trials could increase.

Financing Risks

We have not been profitable and expect to continue to incur substantial losses.

We have experienced significant operating losses since our inception in 1988. As of December 31, 2003, our accumulated deficit was $440.7 million. We had net losses of $75.2 million, $129.8 million and $70.2 million in 2003, 2002 and 2001, respectively.

We expect that we will continue to incur substantial losses and that, until we have substantial product sales, our cumulative losses will continue to increase. We recorded $57.2 million in product sales for the year ended December 31, 2003 and $34.7 million in product sales in 2002. We expect that the losses that we incur will fluctuate from quarter to quarter and that these fluctuations may be substantial.

We will need additional financing, which may be difficult to obtain. If we do not obtain additional financing, our financial condition will be adversely affected.

We expect that our existing capital resources, together with anticipated proceeds from collections on existing and future accounts receivable on product sales, anticipated cash payments under collaborative agreements, and interest income, will be sufficient to fund our operations into 2005 and our expected buyout of the European stockholders' interest in TKT Europe for between $55 million and $65 million. Our cash requirements for operating activities, financing activities and investment activities have exceeded our internally generated funds. We expect that our cash requirements for such activities will continue to exceed our internally generated funds until we are able to generate substantial product sales.

Our future capital requirements will depend on many factors, including the following:

- the timing and amount of Replagal product sales, as well as the cash collections on receivables;
- continued progress in our research and development programs, particularly I2S;
- the scope and results of our clinical trials;

- the timing of, and the costs involved in, obtaining regulatory approvals;
- the cost of expansion of TKT's internal manufacturing facilities;
- the inherent variability of biological manufacturing activities;
- fluctuations in foreign exchange rates for sales denominated in currencies other than the United States dollar;
- the quality and timeliness of the performance of third party suppliers;
- the cost of commercialization activities, including product marketing, sales and distribution;
- the costs involved in preparing, filing, prosecuting, maintaining, and enforcing patent claims and other patent-related costs, including litigation costs and the results of such litigation;
- the outcome of pending purported class action and other related, or potentially related, actions and the litigation costs with respect to such actions;
- the timing and cost of TKT's purchase of the minority interest in TKT Europe;
- the outcome of the SEC investigation; and
- TKT's ability to establish and maintain collaborative arrangements.

Because we do not expect to reach profitability until the end of 2006, at the earliest, if at all, we will need to seek additional funding to fund our operations. We may do so through collaborative arrangements and public or private financings. Additional financing may not be available to us on acceptable terms, if at all. If we do not obtain additional financing, our financial condition will be adversely affected.

If we raise additional funds by issuing equity securities, further dilution to our then existing stockholders will result. In addition, the terms of the financing may adversely affect the holdings or the rights of such stockholders. If we are unable to obtain funding on a timely basis, we may be required to significantly curtail one or more of our research or development programs. We also could be required to seek funds through arrangements with collaborators or others that may require us to relinquish rights to certain of our technologies, product candidates, or products which we would otherwise pursue on our own.

Our stock price has been and may in the future be volatile, which could lead to losses by investors.

Our stock has been and in the future may be subject to substantial price volatility, which may prevent you from reselling our common stock at or above the price you paid for it. The value of your investment could decline due to the effect of any of the following factors upon the market price of our common stock:

- announcements of technological innovations or new commercial products by our competitors;
- disclosure of results of clinical testing or regulatory proceedings by us or our competitors;
- results of litigation;
- the timing, amount and receipt of revenue from sales of our products and margins on sales of our products;
- governmental regulation and approvals;
- developments in patent or other proprietary rights;
- public concerns as to the safety of products developed by us or the fields of study in which we work; and
- general market conditions.

In addition, the stock market has experienced significant price and volume fluctuations, and the market prices of biotechnology companies have been highly volatile. Moreover, broad market and industry fluctuations that are not within our control may adversely affect the trading price of our common stock. During the period from January 1, 2002 to December 31, 2003, the closing sale price of our common stock ranged from a low of $3.74 per share to a high of $46.50 per share. You must be willing to bear the risk of fluctuations in the price of our common stock and the risk that the value of your investment in our stock could decline.

Our corporate governance structure, including provisions in our certificate of incorporation and by-laws, our stockholder rights plan and Delaware law, may prevent a change in control or management that stockholders may consider desirable.

Section 203 of the Delaware General Corporation Law and our certificate of incorporation, by-laws and stockholder rights plan contain provisions that might enable our management to resist a takeover of our company or discourage a third party from attempting to take over our company These provisions include the inability of stockholders to act by written consent or to call special meetings, and the ability of our board of directors to designate the terms of and issue new series of preferred stock without stockholder approval.

These provisions could have the effect of delaying, deferring, or preventing a change in control of us or a change in our management that stockholders may consider favorable or beneficial. These provisions could also discourage proxy contests and make it more difficult for you and other stockholders to elect directors and take other corporate actions. These provisions could also limit the price that investors might be willing to pay in the future for shares of our common stock.

Item 7A. ***Quantitative and Qualitative Disclosures About Market Risk***

The Company maintains its investment portfolio consistent with its Investment Policy, which has been approved by the Board of Directors. The Company's investment portfolio principally consists of investments in United States government and agency obligations. The Company's investments also are subject to interest rate risk and will decrease in value if market interest rates increase. However, due to the relatively short duration of the Company's investments, interest rate risk is mitigated. The Company does not own derivative financial instruments in its investment portfolio.

Accordingly, the Company does not believe that there is any material market risk exposure with respect to derivative or other financial instruments which would require disclosure under this item.

As of December 31, 2003, the Company did not have any off-balance sheet arrangements.

The Company has exposure to currency risk for Replagal sales in Europe. Country by country pricing was initially established as the local currency equivalent of between approximately $165,000 and $175,000 per patient per year for an average patient weighing 70 kilograms. The price generally remains fixed in the local currencies and varies in United States dollars with exchange rate fluctuations. Foreign currency fluctuations increased sales and gross margins by approximately $9,443,000 in 2003.

The Company has exposure to currency risk for cash and cash equivalent balances in Europe. As of December 31, 2003, the Company had approximately $64,500,000 denominated principally in Euro, British Pounds and Swedish Krona. A hypothetical 10 percent increase in currency rates relative to the United States dollar would result in an approximate $5,900,000 decrease in the fair value of the Company's cash and cash equivalents balances denominated in Swedish Krona, British Pound, and Euro as of December 31, 2003. The Company currently does not hedge its cash currency exposure.

Item 8. ***Financial Statements and Supplementary Data***

The following financial statements and supplementary data are included as part of this Annual Report on Form 10-K:

- Report of Independent Auditors
- Consolidated Balance Sheets as of December 31, 2003 and 2002
- Consolidated Statements of Operations for the years ended December 31, 2003, 2002 and 2001
- Consolidated Statement of Stockholders' Equity for the years ended December 31, 2003, 2002 and 2001
- Consolidated Statements of Cash Flows for the years ended December 31, 2003, 2002 and 2001

REPORT OF INDEPENDENT AUDITORS

Board of Directors and Stockholders
Transkaryotic Therapies, Inc.

We have audited the accompanying consolidated balance sheets of Transkaryotic Therapies, Inc. (the "Company") as of December 31, 2003 and 2002, and the related consolidated statements of operations, stockholders' equity, and cash flows for each of the three years in the period ended December 31, 2003. These financial statements are the responsibility of the Company's management. Our responsibility is to express an opinion on these financial statements based on our audits.

We conducted our audits in accordance with auditing standards generally accepted in the United States. Those standards require that we plan and perform the audit to obtain reasonable assurance about whether the financial statements are free of material misstatement. An audit includes examining, on a test basis, evidence supporting the amounts and disclosures in the financial statements. An audit also includes assessing the accounting principles used and significant estimates made by management, as well as evaluating the overall financial statement presentation. We believe that our audits provide a reasonable basis for our opinion.

In our opinion, the financial statements referred to above present fairly, in all material respects, the consolidated financial position of Transkaryotic Therapies, Inc. at December 31, 2003 and 2002, and the consolidated results of its operations and its cash flows for each of the three years in the period ended December 31, 2003, in conformity with accounting principles generally accepted in the United States.

/s/ ERNST & YOUNG LLP

Boston, Massachusetts
March 4, 2004

TRANSKARYOTIC THERAPIES, INC.
CONSOLIDATED BALANCE SHEETS

	December 31, 2003	December 31, 2002
	(in thousands, except par values)	
ASSETS		
Current assets:		
Cash and cash equivalents	$172,954	$154,604
Marketable securities	7,993	102,104
Accounts receivable	23,064	15,684
Inventories	16,741	21,650
Prepaid expenses and other current assets	4,587	4,450
Total current assets	225,339	298,492
Property and equipment, net	61,908	59,372
Other assets	1,922	1,942
Total assets	$289,169	$359,806
LIABILITIES AND STOCKHOLDERS' EQUITY		
Current liabilities:		
Accounts payable	$ 7,466	$ 11,804
Accrued expenses	11,925	12,767
Current portion of accrued restructuring charges	1,523	—
Current portion of deferred revenue	235	—
Accrued intellectual property license expense	—	11,368
Total current liabilities	21,149	35,939
Long-term portion of accrued restructuring charges	6,518	—
Long-term portion of deferred revenue	2,767	
Minority interest	413	—
Stockholders' equity:		
Series B preferred stock, $.01 par value, 1,000 shares authorized; no shares issued and outstanding at December 31, 2003 and December 31, 2002, respectively	—	—
Common stock, $.01 par value; 100,000 shares authorized; 34,974 and 34,845 shares issued, and 34,607 and 34,845 outstanding, at December 31, 2003 and December 31, 2002, respectively	350	348
Additional paid-in capital	686,545	685,566
Accumulated deficit	(440,668)	(365,434)
Accumulated other comprehensive income	14,377	3,387
Less treasury stock, at cost; 367 shares at December 31, 2003	(2,282)	—
Total stockholders' equity	258,322	323,867
Total liabilities and stockholders' equity	$289,169	$359,806

See accompanying Notes to Consolidated Financial Statements.

TRANSKARYOTIC THERAPIES, INC.
CONSOLIDATED STATEMENTS OF OPERATIONS

	Year Ended December 31,		
	2003	2002	2001
	(in thousands, except per share amounts)		
Revenues:			
Product sales	$ 57,225	$ 34,682	$ 3,535
License and research revenues	1,664	1,818	2,653
	58,889	36,500	6,188
Operating expenses:			
Cost of goods sold	12,484	10,511	185
Research and development	74,062	81,309	65,921
Intellectual property license expense	1,350	34,660	—
Selling, general and administrative	36,557	31,229	24,823
Restructuring charges	12,461	—	—
Impairment charge	—	16,069	—
	136,914	173,778	90,929
Loss from operations before minority interest	(78,025)	(137,278)	(84,741)
Minority interest	(413)	—	—
Loss from operations after minority interest	(78,438)	(137,278)	(84,741)
Other income:			
Interest income, net	2,704	7,516	11,274
Other income	500	—	—
Gain on sale of investment	—	—	3,224
	3,204	7,516	14,498
Net loss	$(75,234)	$(129,762)	$(70,243)
Basic and diluted net loss per share	$ (2.18)	$ (3.75)	$ (2.78)
Shares used to compute basic and diluted net loss per share	34,559	34,616	25,228

See accompanying Notes to Consolidated Financial Statements.

TRANSKARYOTIC THERAPIES, INC.
CONSOLIDATED STATEMENTS OF STOCKHOLDERS' EQUITY

	Convertible Preferred Stock		Common Stock		Treasury Stock		Additional Paid-In	Accumulated	Deferred	Other Comprehensive	Total Stockholders'
	Shares	Amount	Shares	Amount	Shares	Amount	Capital	Deficit	Compensation	Income(Loss)	Equity
							(in thousands)				
Balance at December 31, 2000	10	$1	22,700	$227	—	—	$413,242	$(165,429)	$(860)	$ 676	$247,857
Issuances of common stock, net	—	—	8,031	80	—	—	257,787	—	—	—	257,867
Conversion of convertible preferred stock, net	(10)	(1)	3,571	36	—	—	(35)	—	—	—	—
Compensation expense related to equity issuances	—	—	—	—	—	—	54	—	657	—	711
Reversal of deferred compensation related to forfeited restricted stock and stock options granted	—	—	—	—	—	—	(89)	—	89	—	—
Unrealized gain on marketable securities	—	—	—	—	—	—	—	—	—	7	7
Foreign currency translation adjustment	—	—	—	—	—	—	—	—	—	(36)	(36)
Net loss	—	—	—	—	—	—	—	(70,243)	—	—	(70,243)
Comprehensive loss	—	—	—	—	—	—	—	—	—	—	(70,272)
Balance at December 31, 2001	—	—	34,302	343	—	—	670,959	(235,672)	(114)	647	436,163
Issuances of common stock, net	—	—	176	1	—	—	2,319	—	—	—	2,320
Issuance of common stock related to license expense	—	—	367	4	—	—	12,288	—	—	—	12,292
Compensation expense related to equity issuances	—	—	—	—	—	—	—	—	114	—	114
Unrealized loss on marketable securities	—	—	—	—	—	—	—	—	—	(309)	(309)
Foreign currency translation adjustment	—	—	—	—	—	—	—	—	—	3,049	3,049
Net loss	—	—	—	—	—	—	—	(129,762)	—	—	(129,762)
Comprehensive loss	—	—	—	—	—	—	—	—	—	—	(127,022)
Balance at December 31, 2002	—	—	34,845	348	—	—	685,566	(365,434)	—	3,387	323,867
Issuances of common stock, net	—	—	129	2	—	—	275	—	—	—	277
Repurchase of common stock	—	—	—	—	(367)	(2,282)	—	—	—	—	(2,282)
Compensation expense related to equity issuances	—	—	—	—	—	—	704	—	—	—	704
Unrealized loss on marketable securities	—	—	—	—	—	—	—	—	—	(269)	(269)
Foreign currency translation adjustment	—	—	—	—	—	—	—	—	—	11,259	11,259
Net loss	—	—	—	—	—	—	—	(75,234)	—	—	(75,234)
Comprehensive loss	—	—	—	—	—	—	—	—	—	—	(64,244)
Balance at December 31, 2003	—	—	34,974	$350	(367)	$(2,282)	$686,545	$(440,668)	$ —	$14,377	$258,322

See accompanying Notes to Consolidated Financial Statements.

TRANSKARYOTIC THERAPIES, INC.
CONSOLIDATED STATEMENTS OF CASH FLOWS

	Year Ended December 31, 2003	2002	2001
		(in thousands)	
OPERATING ACTIVITIES:			
Net loss	$(75,234)	$(129,762)	$(70,243)
Adjustments to reconcile net loss to net cash used for operating activities:			
Intellectual property license expense	—	23,660	—
Impairment charge	—	16,069	—
Depreciation and amortization	11,554	7,935	5,886
Gain on sale of investment	—	—	(3,224)
Loss on fixed asset disposal	606	—	—
Compensation expense related to equity issuances	704	114	711
Minority interest	413	—	—
Changes in operating assets and liabilities:			
Increase in accounts receivable	(3,662)	(11,472)	(2,401)
Decrease (increase) in inventory	4,909	(14,503)	(7,147)
Decrease (increase) in prepaid expenses and other current assets	86	412	(2,807)
(Decrease) increase in accounts payable	(4,714)	2,201	5,432
(Decrease) increase in accrued expenses	(12,531)	425	3,610
Increase in accrued restructuring expenses	8,041	—	—
Increase in deferred revenue	3,002	—	—
Net cash used for operating activities	(66,826)	(104,921)	(70,183)
INVESTING ACTIVITIES:			
Proceeds from sales and maturities of marketable securities	117,764	221,039	198,263
Purchases of marketable securities	(23,922)	(247,571)	(74,898)
Purchases of property and equipment	(14,774)	(41,789)	(23,876)
Proceeds from disposal of property and equipment	85	—	—
Decrease (increase) in other assets	22	283	(727)
Net cash provided by (used for) investing activities	79,175	(68,038)	98,762
FINANCING ACTIVITIES:			
Issuances of common stock, net	276	2,320	257,867
Principal payments of long-term debt	—	—	(12,000)
Repurchase of treasury stock	(2,282)	—	—
Net cash provided by (used for) financing activities	(2,006)	2,320	245,867
Effect of exchange rate changes on cash and cash equivalents	8,007	1,366	(14)
Net increase (decrease) in cash and cash equivalents	18,350	(169,273)	274,432
Cash and cash equivalents at January 1	154,604	323,877	49,445
Cash and cash equivalents at December 31	$172,954	$ 154,604	$323,877
Supplemental disclosure of non-cash financing activity:			
Issuance of common stock as consideration for intellectual property license	$ —	$ 12,292	$ —

See accompanying Notes to Consolidated Financial Statements.

1. Nature of Business and Basis of Presentation

Transkaryotic Therapies, Inc. ("TKT" or the "Company") is a biopharmaceutical company researching, developing and commercializing therapeutics, primarily for the treatment of rare genetic diseases caused by protein deficiencies. TKT has received approval to market and sell Replagal (agalsidase alfa), an enzyme replacement therapy for the long-term treatment of patients with Fabry disease, in 28 countries outside of the United States. Two of the products that TKT is currently developing include iduronate-2-sulfatase ("I2S"), an enzyme replacement therapy for the treatment of Hunter syndrome, and Gene-Activated glucocerebrosidase ("GA-GCB") for the treatment of Gaucher disease. The Company is currently conducting a pivotal clinical trial of I2S and anticipates starting a Phase I/II clinical trial of GA-GCB in the second quarter of 2004. TKT is currently evaluating out-licensing opportunities for GA-GCB as well as a number of other gene-activated and gene therapy products.

With the exception of 1995, the Company has incurred substantial annual operating losses since inception. The Company expects to incur significant operating losses until substantial product sales are generated. Until such time, the Company is dependent upon product sales, collections of accounts receivable, existing cash resources, interest income, external financing from equity offerings, debt financings, and collaborative research and development alliances to finance its operations. At December 31, 2003, the Company's accumulated deficit was $440,668,000. The Company expects that its existing capital resources, together with anticipated proceeds from collections on existing and future accounts receivable on product sales, anticipated cash payments under collaborative agreements, and interest income, will be sufficient to fund its operations into 2005.

2. Significant Accounting Policies

Principles of Consolidation

The consolidated financial statements include the accounts of the Company and its wholly-owned and majority-owned subsidiaries. All significant intercompany transactions have been eliminated.

Foreign Currency Translation

The financial statements of the Company's foreign subsidiaries are measured using the local currency as the functional currency. Assets and liabilities are translated at exchange rates in effect as of the balance sheet date. Income and expense accounts are translated at the average monthly exchange rates during the year. Resulting translation adjustments are recorded as a separate component of accumulated other comprehensive income. Foreign currency transaction gains included in the Company's results of operations were $943,000 in 2003. In 2002 and 2001, foreign currency transaction gains and losses were not material to the consolidated financial statements. Currently, the Company does not hedge its foreign currency exposure.

The majority of product sales since 2001 have been in Europe. The Company prices Replagal in the functional currency of the country into which it is sold. While overall price levels in local currencies have generally remained consistent since 2001, foreign exchange fluctuations caused an increase in the United States dollar denominated average selling prices. Substantially all of the Company's manufacturing costs are in United States dollars. Therefore, any fluctuation in the value of the payment currencies relative to the United States dollar is likely to impact gross margins since the Company's manufacturing costs would remain approximately the same while its revenue in terms of United States dollars would change. The Company's gross margin will continue to be affected by currency fluctuations in the future. Foreign currency fluctuations increased sales and gross margins by approximately $9,443,000 and $2,558,000 in 2003 and 2002, respectively. In 2001, these currency fluctuations were immaterial to gross margin.

Comprehensive Loss

Comprehensive loss comprises net loss, unrealized gains and losses on marketable securities and cumulative foreign currency translation adjustments. Unrealized gains on marketable securities of $0 and $269,000 were included in accumulated other comprehensive income at December 31, 2003 and 2002, respectively. Accumulated other comprehensive income also included $14,377,000 and $3,118,000 of cumulative foreign currency translation adjustments at December 31, 2003 and 2002, respectively.

Use of Estimates

The preparation of financial statements in conformity with accounting principles generally accepted in the United States requires management to make estimates and assumptions that affect the amounts reported in the financial statements and accompanying notes. Actual results could differ from those estimates.

Revenue Recognition

The Company recognizes revenue from product sales in accordance with Staff Accounting Bulletin 104 (SAB 104), *Revenue Recognition*, when there is persuasive evidence that an arrangement exists, delivery has occurred, the price is fixed or determinable, and collection is reasonably assured. The Company determines that collection is reasonably assured in Europe and in some other countries outside of the United States, once reimbursement agreements and pricing arrangements are established and formalized, as these agreements establish the relevant governmental agency's intent to pay, or once there are legally binding purchase agreements between a hospital and the Company, or once approval has been granted for the reimbursement of cost for individual patients. The Company only records revenues in those countries for which one of the conditions set forth in the previous sentence has been met.

In the European pharmaceutical industry, it is common practice that customers, principally hospitals, have a general right of return on purchases of product. To date, the Company has not had any sales returns. The Company generally ships small quantities of Replagal to customers on the basis of firm purchase orders. The customers generally order Replagal for specific patients, and the drug is typically utilized within one month of receipt. In part due to the expensive price of the drug, customers maintain small inventories of it, typically less than a one month supply. Because of these circumstances, the Company expects that it will have no or minimal returns in the future and, accordingly, has not recorded a reserve for sales returns and allowances in accordance with Statement of Financial Accounting Standards ("SFAS") No. 48, *Revenue Recognition When Right-of-Return Exists.*

For multiple-deliverable arrangements entered into after July 1, 2003, the Company applies EITF 00-21, *Revenue Arrangements with Multiple Deliverables.* The Company evaluates such arrangements to determine if the deliverables are separable into units of accounting and then applies applicable revenue recognition criteria to each unit of accounting. The Company applied EITF 00-21 to the distribution agreement and legal settlement with Genzyme as discussed in Note 14.

The Company records contract revenue for research and development as it is earned based on the performance requirements of the contract. Non-refundable contract fees for which there are neither further performance obligations nor continuing involvement by the Company are recognized on the earlier of when the fees are received or when collection is reasonably assured. The Company recognizes revenue from non-refundable up-front license fees and milestone payments where TKT has continuing involvement through development collaboration or an obligation to supply product, as the obligation is fulfilled or ratably over the development period or the period of the manufacturing obligation, as appropriate. The Company recognizes revenue associated with substantive performance milestones upon the achievement of the milestones, as defined in the respective agreements. Advance payments received in excess of amounts earned are classified as deferred revenue.

Research and Development Costs

Research and development costs are expensed as they are incurred. These costs include expenditures relating to basic research, preclinical testing, clinical trials, including the manufacture of clinical supplies, regulatory filings and the development of large-scale manufacturing processes for the Company's products.

Shipping and Handling Costs

Shipping and handling costs incurred for product shipments were $709,000, $635,000 and $209,000 for 2003, 2002 and 2001, respectively. These amounts were recorded in Selling, general and administrative expenses in the Consolidated Statements of Operations.

Financial Instruments

Cash equivalents include funds held in investments with original maturities of three months or less at the time of purchase. Marketable securities principally consist of United States government and agency obligations. The fair values of marketable securities are based on quoted market prices. At December 31, 2003, the Company had $64,508,000 in foreign accounts held by TKT Europe, primarily denominated in Swedish Krona, British Pound, and Euro, which is subject to foreign currency fluctuation risk.

The Company determines the classification of marketable securities at the time of purchase and re-evaluates such designation as of each balance sheet date. The Company has classified such holdings as available-for-sale securities, which are carried at fair value, with unrealized gains and losses reported as a separate component of accumulated other comprehensive income (loss).

Concentrations of Credit Risk

Financial instruments that potentially subject the Company to concentrations of credit risk consist of cash, temporary cash investments, marketable securities and accounts receivable. The Company maintains cash and cash equivalents with high credit-quality financial institutions and limits the amount of credit exposure to any one institution.

The Company's credit exposure on its marketable securities is limited by its diversification among United States government and agency obligations. However, further decreases in interest rates will reduce TKT's interest income from short-term investments.

In certain European countries such as Italy and Belgium, customary payment terms on accounts receivable are significantly longer than in the United States, particularly for products treating orphan drug indications. In these countries, the Company historically has received and expects to continue to receive, payments approximately one year from the invoice date. Accounts receivable balances for Italy and Belgium were 56% and 49% of total accounts receivable at December 31, 2003 and 2002, respectively. The Company monitors its days' sales outstanding and collections in these countries. To date, customers in these countries have been paying within the customary payment terms. The Company has not recorded an allowance for doubtful accounts to date.

The Company had three significant customers who accounted for 18%, 12% and 12% of the Company's product sales in 2003. The same customers accounted for 8%, 6% and 22% of the Company's product sales in 2002.

Inventories and Cost of Goods Sold

Inventories are stated at the lower of cost or market with cost determined under the first-in, first-out ("FIFO") method. Inventories are reviewed periodically for slow-moving or obsolete status based on sales activity, both projected and historical. Inventory and components of inventory produced by external contract

manufacturers, which were previously expensed as a research and development cost prior to marketing approval of Replagal in August 2001, were sold in 2001 and in the first half of 2002. As of June 30, 2002, this inventory had been fully utilized. In July 2003, TKT received European Commission's approval of its Cambridge, Massachusetts facility for commercial manufacture of Replagal products. Inventory and components of inventory produced at this location were expensed as research and development costs prior to approval.

Property and Equipment

Property and equipment are stated at cost and depreciated using the straight-line method over estimated useful lives of the respective asset, ranging from three to seven years. Leasehold improvements are stated at cost and are amortized using the straight-line method over the term of the lease or the estimated useful life of the assets, whichever is shorter.

Stock-Based Compensation

The Company accounts for qualified stock option grants under the intrinsic value method in accordance with Accounting Principles Board Opinion No. 25, *Accounting for Stock Issued to Employees* ("APB 25") and Financial Accounting Standards Board ("FASB") Interpretation No. 44, *Accounting for Certain Transactions Involving Stock Compensation*, an Interpretation of APB No. 25, and related interpretation, and, accordingly, recognizes no compensation expense for the issue thereof. For certain non-qualified stock options granted, the Company recognizes as compensation expense the excess of the fair value of the common stock issuable upon exercise over the aggregate exercise price of such options. The compensation is amortized over the vesting period of each option or the recipient's term of employment, if shorter. The Company has adopted the disclosure-only provisions of Statement of Financial Accounting Standard ("SFAS") No. 123, *Accounting for Stock-Based Compensation* as amended by SFAS No. 148, *Accounting for Stock-Based Compensation-Transition and Disclosure.*

The table below presents the combined net loss and basic and diluted net loss per common share if compensation cost for the Company's stock option plans had been determined based on the estimated fair value of awards under those plans on the grant or purchase date:

	For the twelve months ended December 31,		
	2003	2002	2001
	(in thousands, except per share prices)		
Net loss	$(75,234)	$(129,762)	$(70,243)
Add: Stock-based employee compensation included in net loss as reported	704	114	711
Deduct: Total stock-based employee compensation expense determined under the fair value based method for all awards	(19,399)	(27,515)	(20,822)
Pro forma net loss	$(93,929)	$(157,163)	$(90,354)
Basic and diluted net loss per share — as reported	$ (2.18)	$ (3.75)	$ (2.78)
Basic and diluted net loss per share — pro forma	$ (2.72)	$ (4.54)	$ (3.58)

The fair value of options granted under the stock option plans were estimated at grant or purchase dates using a Black-Scholes option pricing model. The Company used the following assumptions:

	2003	2002	2001
Expected life (years)	1.5 - 7.5	1.5 - 7.5	1.5 - 7.5
Interest rate	1.0% - 4.2%	1.5% - 4.0%	2.0% - 5.1%
Expected volatility	0.68	1.00	0.95
Weighted average fair value per share of options granted during the year	$4.02	$26.65	$19.63

The Company has never declared or paid dividends on any of its capital stock and does not expect to do so in the foreseeable future.

The pro forma effects of 2003, 2002 and 2001 net loss and net loss per share of expensing the estimated fair value of stock options issued are not necessarily representative of the effects on reporting the results of operations for future years as the Company expects to continue to grant options in future years and options will vest over several years.

In 2003, TKT recorded $704,000 of stock compensation expense related to the modification of certain vested stock options.

Income Taxes

Deferred tax assets are determined based on differences between financial reporting and income tax bases of assets and liabilities, as well as net operating loss carryforwards, and are measured using the enacted tax rates and laws that are expected to be in effect when the differences reverse. Deferred tax assets are reduced by a valuation allowance to reflect the uncertainty associated with their ultimate realization.

Segment Information

SFAS No. 131, *Disclosures about Segments of an Enterprise and Related Information*, established standards for reporting information on operating segments in interim and annual financial statements. Under SFAS 131, the Company operates in one segment as the Company's chief operating decision maker reviews the profit and loss of the Company on an aggregate basis and manages the operations of the Company as a single operating segment.

During 2003, 2002 and 2001, substantially all product sales were in Europe. The Company's investment in long-lived assets in Europe is not material.

Asset Impairment

The Company reviews its long-lived assets for impairment indicators in accordance with SFAS 144, *Accounting for the Impairment on Disposal of Long-Lived Assets* at each reporting period.

Net Loss Per Share

The Company calculates net loss per share in accordance with SFAS No. 128, *Earnings Per Share*. Basic earnings per share is computed using the weighted average shares outstanding.

Basic net loss per share was equivalent to diluted net loss per share for the years ended December 31, 2003, 2002 and 2001 since common equivalent shares from convertible preferred stock and stock options have been excluded as their effect is antidilutive.

Recent Accounting Pronouncements

In January 2003, the FASB issued Interpretation No. 46, *Consolidation of Variable Interest Entities* (FIN 46) and in December 2003, issued a revision to FIN 46 (FIN 46R). This interpretation addresses the requirements for business enterprises to consolidate related entities in which they are determined to be the primary beneficiary as a result of their variable economic interest. The interpretation is intended to provide guidance in judging multiple economic interests in an entity and in determining the primary beneficiary. The interpretation outlines disclosure requirements for Variable Interest Entities in existence prior to January 31, 2003, and outlines consolidation requirements for Variable Interest Entities created after January 31, 2003. The Company will adopt the provisions of FIN 46 in the first quarter of 2004 and the interpretation is not expected to have an impact on the Company's consolidated financial statements.

In May 2003, the FASB issued Statement 150, *Accounting for Certain Financial Instruments with Characteristics of both Liabilities and Equity*. Statement 150 establishes standards for classifying and measuring certain financial instruments with characteristics of both liabilities and equity. Statement 150 requires that an issuer classify a financial instrument that is within its scope as a liability (or an asset in some circumstances) because that financial instrument embodies an obligation of the issuer. Statement 150 is effective for financial instruments entered into or modified after May 31, 2003, and otherwise is effective for public companies during the first interim period beginning after June 15, 2003. The adoption of this pronouncement did not have a material impact on the Company's financial position, results of operations or liquidity.

3. TKT Europe — 5S AB

In April 2000, the Company established TKT Europe for the purpose of marketing, selling and distributing Replagal in Europe. The Company owns an 80% equity interest in TKT Europe and a team of European pharmaceutical executives with experience in marketing and selling pharmaceutical products in Europe own the remaining 20% equity interest in TKT Europe. The Company and TKT Europe are parties to a distribution agreement relating to Replagal, and the Company and the European stockholders of TKT Europe are parties to a stockholders' agreement relating to the operation of TKT Europe.

Under the distribution agreement, TKT granted TKT Europe exclusive marketing rights to distribute and market Replagal in all countries in Europe, and TKT Europe agreed to purchase Replagal exclusively from TKT at a negotiated transfer price. TKT is also required to pay TKT Europe a marketing service fee. The distribution agreement continues until December 31, 2010, and is subject to automatic two-year extensions unless a party provides notice of non-renewal at least one year prior to the expiration of the term.

The stockholders' agreement provides for the governance of TKT Europe. Under the agreement, the European stockholders have the right to elect three members of the Board of Directors, and the Company has the right to elect two members of the Board of Directors. Although the consent of TKT is required for various significant matters relating to the operation of TKT Europe, most day-to-day operations of TKT Europe are directed by the European stockholders.

Under the stockholders' agreement, the Company is entitled to purchase the European stockholders' 20% ownership interest in TKT Europe in September 2004 for a price determined in accordance with a formula. Should the Company not exercise that right, the European stockholders of TKT Europe can require the Company to purchase the European stockholders' ownership interest sixty days thereafter. The buyout price is equal to (a) 20% of the operating profits, as defined in the stockholders' agreement, for the period from September 1, 2003 to August 31, 2004, multiplied by a buyout factor of four, subject to adjustment, plus (b) 20% of the accumulated positive earnings of TKT Europe. As a result, the amount of the buyout price is dependent on the profits of TKT Europe and the commercial success of Replagal in Europe. The Company

estimates that the buyout price could be between $55,000,000 and $65,000,000 based on the Company's current estimates of sales and expenses.

The Company will account for the acquisition of TKT Europe's minority interest as a step acquisition pursuant to FASB Statement No. 141, *Business Combinations*. The European stockholders' put option is being accounted for under EITF 00-6, *Accounting for Freestanding Derivative Financial Instruments Indexed to, and Potentially Settled in, the Stock of a Consolidated Subsidiary*. To determine the fair market value of the put option, the Company calculated the fair value of the minority interest of TKT Europe based upon a discounted cash flow model. Due to the fact that the fair value of the minority interest of TKT Europe has been and currently is greater than the Company's estimated value of the put option exercise price, the Company has not recorded any charges related to this instrument.

4. Intellectual Property License Fee Expense

In June 2002, the Company obtained an exclusive license to certain patents and patent applications from Cell Genesys, Inc. related to Cell Genesys' approach to gene activation. In consideration for the license, the Company initially paid Cell Genesys $11,000,000 in cash and issued to Cell Genesys $15,000,000 of shares of the Company's common stock.

Under the agreement, the Company agreed that the number of shares of common stock initially issued to Cell Genesys would be adjusted at the time the Company registered such shares for resale under the Securities Act of 1933, if the market value of such shares at that time was greater or less than $15,000,000. Pursuant to the agreed upon formula at December 31, 2002 with the closing price of the Company's common stock was $9.90 per share, the Company would have been required to issue to Cell Genesys an additional 1,148,000 shares of common stock. As a result, the Company recorded an additional non-cash license fee expense of $8,660,000 million in the fourth quarter of 2002.

On January 15, 2003, the Company and Cell Genesys renegotiated the consideration paid for the license, and the Company repurchased the shares of stock issued to Cell Genesys for $15,000,000 in cash. The Company incurred an additional license expense of approximately $1,350,000 in the first quarter of 2003, which represents the further decline in the market value of the Company's common stock from December 31, 2002 to January 15, 2003.

Under the agreement, Cell Genesys also has the potential to receive certain milestone payments contingent upon the outcome of related patent matters under the license agreement. If all of the milestones occur, the Company will be obligated to pay Cell Genesys an aggregate of $17,000,000 payable in part in cash and in part in stock. The Company is not required to make royalty payments to Cell Genesys.

5. Restructuring Charges

In February 2003, TKT announced a major reorganization in an effort to reduce costs and narrow the scope of the Company's research initiatives. Under this reorganization, TKT is focusing its research, development, and commercialization efforts primarily on therapeutics for the treatment of rare genetic diseases caused by protein deficiencies. The Company is seeking collaborative partners for programs outside its core focus, including its Gene-Activated protein products, which are versions of proteins that would compete with proteins currently being marketed by third parties, and for its gene therapy programs.

As part of this restructuring, during the first quarter of 2003, TKT reduced its United States headcount by approximately 100 positions. TKT has further reduced its headcount through attrition, with the goal of having approximately 310 to 325 full-time United States employees by the end of 2003. As of December 31, 2003, TKT had 321 full-time United States employees. TKT has also consolidated its facilities as part of the restructuring.

As a result of the restructuring, the Company recorded charges of $12,461,000 in 2003, in accordance with SFAS No. 146, *Accounting for Costs Associated with Exit or Disposal Activities.* Included in the charges are $1,319,000 of employee severance and outplacement services costs for 74 employees, primarily in research and development, $10,544,000, representing the remaining lease obligation for four facilities that the Company no longer occupies, and a write-down of $598,000 of leasehold improvements that were abandoned in connection with vacating such facilities. The Company's employee-related and facility consolidation restructuring actions were completed as of December 31, 2003. The Company will continue to record restructuring charges primarily related to vacated facility expenses during the remainder of the lease terms until such facilities are sublet.

As part of the restructuring, the Company recorded charges of $10,544,000 related to the remaining lease obligation on certain facility leases, net of expected sublease income. In determining the net facilities charge, various assumptions were made, including sublease terms and expected sublease rates. These estimates were made based on a periodic review of current sublease environment and acquired market quotes. Should operating lease rental rates decline or should it take longer than expected to find suitable tenants to sublease the facilities, adjustments to the net present value of the remaining lease obligations may be necessary in future periods based upon future events and circumstances. In the fourth quarter of 2003, TKT recorded a $175,000 charge related to change in sublease rate estimates due to deterioration in market condition.

The following table outlines the components of the Company's restructuring charges and accrual as of December 31, 2003:

	Charges	Payments	Other	Ending Balance
		(in thousands)		
Employee severance and outplacement	$ 1,319	$(1,319)	$ —	$ —
Lease obligations	10,544	(2,310)	(193)	8,041
Write-off of fixed assets	598	—	(598)	—
Total	$12,461	$(3,629)	$(791)	$8,041
Less: current portion of accrued restructuring charges				(1,523)
Long-term portion of accrued restructuring charges				$6,518

6. Impairment Charge

In January 2001, the Company purchased a manufacturing facility, which it intended to use to manufacture one or more of its potential products. In the fourth quarter of 2002, the Company concluded that an impairment indicator existed in regard to the facility, in accordance with SFAS No. 144, *Accounting for the Impairment or Disposal of Long-Lived Assets,* and thus evaluated the asset for impairment. An undiscounted cash flow analysis confirmed the impairment, and the Company obtained an appraisal of the manufacturing facility to determine its fair market value, which indicated that the fair value of the facility was substantially lower than its carrying value. Accordingly, the Company recorded an impairment charge of $16,069,000 at December 31, 2002, based upon the difference between the fair market value of the facility and its carrying value at such date. The facility is classified as a held-for-sale asset in accordance with SFAS No. 144 beginning in the first quarter of 2003. The Company is actively seeking a buyer for this facility. Upon a sale of the facility, any difference between the sales price and the carrying value of the facility will be recognized as an impairment charge, or credit, in the period of the sale.

7. Financial Instruments

The following is a summary of available-for-sale securities:

	Cost	Gross Unrealized Gains	Gross Unrealized Losses	Estimated Fair Value
		(in thousands)		
December 31, 2003	$ 7,993	$ —	$ —	$ 7,993
December 31, 2002	$101,835	$286	$(17)	$102,104

These securities are classified in the accompanying balance sheets as marketable securities. The aggregate related fair values of marketable securities with unrealized losses was $5,009,000 as of December 31, 2002, all of which had maturities of less than 12 months.

Marketable securities held at December 31 mature as follows:

	2003	2002
	(in thousands)	
Less than one year	$7,993	$ 60,985
One to two years	—	30,100
Two to three years	—	11,019
	$7,993	$102,104

8. Inventories

Inventories at December 31 are summarized as follows:

	2003	2002
	(in thousands)	
Raw materials	$ 574	$ 947
Work in process	7,931	14,689
Finished goods	8,236	6,014
	$16,741	$21,650

9. Property and Equipment

Property and equipment consisted of the following at December 31:

	2003	2002
	(in thousands)	
Leasehold improvements	$46,803	$51,492
Laboratory equipment	19,497	18,101
Office furniture and equipment	15,593	14,783
Construction in process	9,389	1,887
	91,282	86,263
Less accumulated depreciation and amortization	(29,374)	(26,891)
	$61,908	$59,372

Depreciation and amortization expense on property and equipment was $ 11,554,000, $7,935,000, and $5,886,000 in 2003, 2002 and 2001, respectively.

10. Accrued Expenses

Accrued expenses as of December 31 consisted of the following:

	2003	2002
	(in thousands)	
External development services	$ 3,013	$ 5,702
Salaries and benefits	3,285	3,105
Professional fees	1,535	931
Construction costs	842	950
Facilities costs	1,602	792
Other	1,648	1,287
	$11,925	$12,767

11. Long-Term Debt

At December 1998, the Company obtained an unsecured term loan facility for up to $14,000,000 to finance the capital costs and equipment related to leased space. This loan and all interest due thereon was repaid in full in October 2001. For the year ended December 31, 2001, interest expense totaled $544,000. Interest paid on the loan facility was $808,000 for the year ended December 31, 2001.

12. Letters of Credit

As of December 31, 2003, the Company had outstanding letters of credit primarily related to lease obligations, totaling $7,000,000. Marketable securities totaling $7,993,000 and $7,989,000 are restricted and serve as collateral for the letters of credit as of December 31, 2003 and 2002, respectively.

13. Stockholders' Equity

Preferred Stock

There are 10,000,000 shares of preferred stock authorized, of which 1,000,000 shares have been designated for Series B Junior Participating Preferred Stock ("Series B Preferred Stock").

Common Stock Offerings

In December 2001, the Company sold 4,220,000 shares of its common stock at $39.00 per share and 1,000,000 shares of its common stock at $42.00 per share. Net proceeds to the Company for the two transactions totaled $159,058,000. In June 2001, the Company sold 3,565,000 shares of its common stock at $28.50 per share. Net proceeds to the Company totaled $96,161,000.

Shareholder Rights Plan

In December 2000, the Company adopted a shareholder rights plan. The plan is intended to provide TKT shareholders with an opportunity to realize the full value of their investment and to provide fair and equal treatment for all shareholders in the event that an unsolicited attempt is made to acquire TKT.

Under the plan, a dividend of one Preferred Stock purchase right was declared for each share of Common Stock held of record as of the close of business on December 26, 2000. One million shares of Preferred Stock have been designated as Series B Preferred Stock and are reserved for issuance in connection with the shareholder rights plan. Each right entitles the holder to purchase from the Company one one-thousandth of a share of Series B Preferred Stock. Initially, the rights will automatically trade with the underlying shares of Common Stock. The rights will not become exercisable unless a person acquires, or commences a tender offer

to acquire, beneficial ownership of 20% or more of the Company's outstanding Common Stock, subject to certain limited exceptions. If the rights become exercisable, each right would initially entitle shareholders of TKT, other than the acquiring person, to purchase a fractional share of Series B Preferred Stock at an initial exercise price of $289. If a person acquires beneficial ownership of 20% or more of the Company's outstanding Common Stock, each right, other than those owned by the acquiring person, would entitle its holder to purchase shares of TKT Common Stock having a market value of two times the exercise price of the right. The rights may be redeemed by the Board in certain circumstances and will expire in December 2010 unless extended.

Stock Compensation Plans

The Company has adopted several stock compensation plans, which provide for the issuance of incentive and non-qualified stock options, stock appreciation rights, restricted stock, long-term performance awards and stock grants to employees, directors and consultants of the Company at prices determined by the Board of Directors. At December 31, 2003, 3,199,495 shares of Common Stock have been reserved for issuance under the plans. 4,500,000 shares of Common Stock were authorized for grant under the plans as of December 31, 2003. Options generally vest ratably over periods ranging from two to six years and are exercisable for ten years from the date of grant.

Stock option activity under the plans is as follows:

	2003		2002		2001	
	Options	Weighted Average Exercise Price	Options	Weighted Average Exercise Price	Options	Weighted Average Exercise Price
	(in thousands, except share prices)					
Outstanding at January 1	4,871	$30.84	4,134	$27.98	3,249	$28.21
Granted	1,899	7.19	1,338	36.94	1,793	27.13
Exercised	(129)	2.14	(176)	13.71	(245)	10.79
Cancelled	(1,812)	29.57	(425)	29.33	(663)	33.15
Outstanding at December 31	4,829	22.78	4,871	30.84	4,134	27.98
Options exercisable at December 31	1,740	25.58	1,701	27.40	1,158	25.90

The exercise price and life information for significant option groups outstanding at December 31, 2003 are as follows:

	Outstanding			Exercisable	
Range Of Exercise Prices	Number Of Options Outstanding	Weighted Average Contractual Life (Years)	Weighted Average Exercise Price	Number Of Options Exercisable	Weighted Average Exercise Price
	(in thousands, except share prices)				
$0.01	154	2.05	$ 0.01	154	$ 0.01
$3.80-$4.47	351	9.12	3.80	—	—
$5.84-$7.05	756	9.27	6.00	163	5.99
$9.00-$13.25	640	9.46	10.35	113	9.94
$13.60-$20.38	322	7.16	15.31	170	15.56
$21.00-$31.50	676	6.75	28.98	318	28.81
$31.75-$46.94	1,921	7.36	37.68	817	37.03
$50.87-$69.50	5	6.13	64.74	3	63.88
$84.25	4	6.18	84.25	2	84.25
	4,829			1,740	

14. License and Research Agreements

In October 2003, TKT entered into two agreements with Genzyme Corporation ("Genzyme"). TKT and Genzyme entered into a distribution agreement whereby Genzyme will develop and commercialize iduronate-2-sulfatase (I2S), TKT's enzyme replacement therapy for the treatment of Hunter syndrome, in Japan and other Asian Pacific territories. Under the terms of the distribution agreement, Genzyme paid TKT approximately $1,500,000 in cash upfront. TKT also has the potential to receive up to an additional $8,000,000 relating to certain regulatory and commercial milestones, primarily related to a regulatory submission and approval in Japan. TKT will manufacture the bulk drug substance for clinical use and commercial sales in Genzyme's territories and will receive payments based on prices stated in the distribution agreement. In addition, Genzyme has options to obtain rights to certain other research programs being developed by TKT.

TKT and Genzyme executed a second agreement that comprised an exchange of non-suits between the companies in consideration of a payment by Genzyme to TKT totaling $1,555,000, which represents compensation for attorneys fees expended. As part of this exchange, Genzyme agreed to withdraw from the patent suit brought against TKT in July 2000 involving Replagal, TKT's enzyme replacement therapy for the treatment of Fabry disease. TKT agreed not to initiate any patent litigation relating to Aldurazyme® (laronidase), Genzyme's enzyme replacement therapy for the treatment of MPS I, which is being commercialized in a joint venture between Genzyme and BioMarin Pharmaceutical Inc. The settlement did not remove all legal risk as licensors of the patents at issue to Genzyme and TKT, respectively, could continue or commence legal actions despite Genzyme and TKT's legal settlement.

The Company evaluated the global legal settlement and the distribution agreement under EITF 00-21 and concluded that the deliverables were not separable into individual units of accounting, and thus recorded the up-front fee and the payment for legal fees totaling $3,055,000 as deferred revenue in October 2003. The Company will record this deferred revenue as revenue ratably over a thirteen year period, representing the term of the agreement over which the Company will supply bulk drug substance. The agreement also provides that the Company will refund a portion of the up-front fee of $1,500,000 if the Company terminates the distribution agreement without cause. As such, the Company will not record revenue in excess of what it might have to refund until the refundability lapses.

In 2002 and 2001, the Company received license and research revenue from Wyeth, the Company's collaborative partner for its hemophilia A gene therapy program, in the amount of $1,025,000 and $948,000,

respectively. In August 2003, TKT reacquired the rights from Wyeth for the hemophilia A in Europe. In addition to regaining the European rights, TKT received a $500,000 termination fee, which was recorded as license and research revenues during the third quarter of 2003.

TKT entered into an agreement with Aventis in May 1994 focused on the development of Dynepo. Under the agreement, TKT has the potential to receive up to $38,000,000, consisting of license fees, equity investments, milestone payments, and research funding, of which TKT had received $20,000,000 at December 31, 2003. The remaining payments are contingent upon the achievement of regulatory and commercial milestones. TKT also is entitled to a low double-digit royalty on net sales of Dynepo by Aventis. Due to the uncertainty involving both the regulatory approval of Dynepo and ongoing litigation, there can be no assurance that the Company will receive the remaining milestone payments or earn royalties on product sales.

Under the agreement, TKT granted Aventis exclusive worldwide rights to make, use, and sell Dynepo. Aventis is responsible, at its own expense, for development, manufacturing, and marketing activities for the product. The license agreement expires, on a country by country basis, on the later of the date 10 years after the first commercial sale of the covered product in such country and the last to expire of the patents licensed under such agreement with respect to such country, subject to earlier termination by either party under specified circumstances, including a material breach of the agreement by either party. Aventis has relinquished its rights to market and sell Dynepo in Japan to TKT.

The Company earned no revenues from Aventis for the years ended December 31, 2003, 2002 and 2001. At December 31, 2003, Aventis owned 2,187,000 shares of the Company's Common Stock.

The Company is a party to an exclusive distribution agreement with Sumitomo Pharmaceutical Co., Ltd. ("Sumitomo") to commercialize Replagal in Japan, Korea, and China. For the years ended December 31, 2003, 2002 and 2001, license and research revenues from Sumitomo totaled $1,033,000, $743,000, and $1,705,000, respectively.

The Company licenses certain technology from various universities and research organizations. Under the terms of these agreements, the Company is required to make payments of nonrefundable license fees and royalties on future sales of products employing the licensed technology.

15. Employee Retirement Plans

The Company maintains a qualified defined contribution plan covering substantially all employees of the Company. The Company matches 50% of employee contributions, up to 7% of compensation. Employer contributions vest ratably over five years. The related expense was $582,000, $670,000, and $795,000 in 2003, 2002 and 2001, respectively.

In 2000, the Company established a non-qualified deferred compensation plan, which permits certain management employees to annually elect to defer a portion of their compensation on a pre-tax basis. This plan generally provides payments upon retirement, death or termination of employment. The amount of compensation deferred, the Company match, and earnings on deferrals are included in accrued expenses and amounted to $449,000, $961,000, and $861,000 at December 31, 2003, 2002 and 2001, respectively. The Company funds these obligations through the establishment of trust accounts on behalf of the executives participating in the plan. The trust accounts are included in other assets in the accompanying balance sheets and amounted to $819,000, $715,000 and $682,000 at December 31, 2003, 2002 and 2001, respectively.

16. Income Taxes

At December 31, 2003, the Company had unused net operating loss carryforwards of $298,410,000 and research and development tax credits of $68,677,000, which expire through 2023. Due to the degree of

uncertainty related to the ultimate use of the loss carryforwards and tax credits, the Company has fully reserved this tax benefit. Additionally, the future utilization of the net operating loss carryforwards and tax credits may be subject to limitations under the change in stock ownership rules of the Internal Revenue Service.

Significant components of the Company's deferred tax assets are as follows:

	December 31,	
	2003	2002
	(in thousands)	
Deferred tax assets:		
Net operating loss carryforwards	$119,364	$100,002
Research and development tax credits	68,677	50,501
Intellectual property license	9,302	9,996
Impairment charge	6,180	6,428
Restructuring charges	3,216	—
Depreciation	4,181	3,901
Other	3,336	1,701
Total deferred tax assets	214,256	172,529
Valuation allowance	(214,256)	(172,529)
	$ —	$ —

The valuation allowance increased by $41,727,000 during 2003 primarily due to the increase in net operating loss carryforwards and tax credits.

The difference between the Company's expected tax benefit, as computed by applying the United States federal corporate tax rate of 34% to the loss before provision for income taxes, and the actual tax is attributable to tax losses and credits for which the Company has not recognized any tax benefit. Operating income of the Company's foreign subsidiaries is not significant.

17. Commitments and Contingencies

Litigation Expenses

The Company is a party to a number of legal proceedings. The Company can provide no assurance as to the timing and the outcome of any of these proceedings. A decision by a court in the United States or in any other jurisdiction in a manner adverse to the Company could have a material adverse effect on the Company's business, financial condition and results of operations. No reserves or provisions have been accrued for these legal proceedings.

In October 2003, the Company received $500,000 from Bain & Company in connection with a legal settlement. TKT recorded the $500,000 settlement as other income during the fourth quarter of 2003.

Replagal Patent Litigation

In July 2000, Genzyme and Mount Sinai School of Medicine of New York University filed a patent infringement action against the Company in the United States District Court of Delaware. The complaint alleges that the Company's activities relating to Replagal infringe a patent licensed by Genzyme from Mount Sinai. In January 2002, the United States District Court of Delaware dismissed this patent litigation granting the Company's motion for summary judgment of non-infringement and denying Genzyme and Mount Sinai's

motion for summary judgment of infringement. Genzyme and Mount Sinai sought monetary damages and injunctive relief.

In March 2002, Genzyme and Mount Sinai appealed the United States District Court of Delaware's ruling to the United States Court of Appeals for the Federal Circuit, and in January 2003 the United States Court of Appeals for the Federal Circuit heard oral arguments on the appeal. In October 2003, pursuant to a global legal settlement discussed in Note 14, Genzyme agreed to withdraw from this suit and paid the Company $1,555,000. Mount Sinai is not a party to the settlement. In October 2003, the United States Court of Appeals for the Federal Circuit affirmed a finding of non-infringement by the Company. In January 2004, the Federal Circuit denied Mount Sinai's petition for a rehearing en banc. The Company believes it is possible, but unlikely, that Mount Sinai will obtain further appellate review of this decision by the United States Supreme Court.

As of December 31, 2003, the Company had incurred $4,687,000 in litigation expenses associated with the Replagal litigation.

Dynepo Patent Litigation

In April 1997, Amgen commenced a patent infringement action against the Company and Aventis in the United States District Court of Massachusetts. In January 2001, the United States District Court of Massachusetts concluded that Dynepo infringed eight of the 18 claims of five patents that Amgen had asserted. Amgen did not seek and was not awarded monetary damages.

In January 2003, the United States United States Court of Appeals for the Federal Circuit issued a decision affirming in part and reversing in part the decision of the United States District Court of Massachusetts and remanded the action to the United States District Court of Massachusetts for further proceedings. In particular, the United States Court of Appeals for the Federal Circuit:

- upheld the United States District Court of Massachusetts' determination of invalidity of one of Amgen's patents;
- upheld the United States United States District Court of Massachusetts' determination that some claims of two other Amgen patents were infringed, but vacated the United States District Court of Massachusetts' determination that those patents were not invalid; and
- vacated the United States District Court of Massachusetts' determination that Dynepo infringed some claims of the two remaining Amgen patents, and vacated the United States District Court of Massachusetts' determination that one of these patents was not invalid.

As part of the United States Court of Appeals for the Federal Circuit's ruling, it remanded the case to the United States District Court of Massachusetts and instructed it to reconsider the validity of Amgen's patents in light of potentially invalidating prior art. The United States District Court of Massachusetts has recently concluded the remand proceedings and heard oral argument on some of these issues in July 2003. The Company expects that the United States District Court of Massachusetts will enter a decision on the remanded issues at some point during the first half of 2004. The United States District Court of Massachusetts also recently issued a decision upholding its earlier findings that Amgen successfully rebutted the presumption of prosecution history estoppel with respect to certain patents, and therefore, the Company and Aventis infringe such patents in light of recent Supreme Court precedents. On remand, the Company and Aventis presented affirmative defenses with respect to such patents. Both Amgen and Aventis, together with the Company, will have the right to appeal the decision of the United States District Court of Massachusetts to the United States Court of Appeals for the Federal Circuit.

In addition, in July 1999, the Company commenced legal proceedings with Aventis in the United Kingdom against Kirin-Amgen, which sought a declaration that a European patent held by Kirin-Amgen will

not be infringed by the Company's activities relating to Dynepo and that certain claims of Kirin-Amgen's U.K. patent are invalid. In April 2001, the High Court of Justice in the United Kingdom ruled that Dynepo infringed one of four claims of the patent asserted by Kirin-Amgen. In July 2002, the Court of Appeals in the United Kingdom reversed the High Court of Justice and ruled that Dynepo did not infringe Kirin-Amgen's patent. Kirin-Amgen petitioned the House of Lords to hear an appeal from the decision of the Court of Appeals. The House of Lords agreed to hear this appeal during the summer of 2004.

The Company can provide no assurance as to the outcome of either litigation. If the Company and its collaborator, Aventis, are not successful in the Dynepo litigation, the Company and Aventis would be precluded from making, using and selling Dynepo in the United States and/or in the United Kingdom. The Company is required to reimburse Aventis, which is paying the litigation expenses, for 50% of the expenses. Aventis is entitled to deduct up to 50% of any royalties due to the Company from it with respect to the sale of Dynepo until Aventis has recouped the full amount of the Company's share of litigation expenses. The Company currently estimates that its share of the expenses associated with the litigation will total between approximately $15,000,000 and $20,000,000 by the time the matter is finally adjudicated.

Purported Class Action Shareholder Suit

In January and February 2003, various parties filed purported class action lawsuits against the Company and Richard Selden, its then Chief Executive Officer, in the United States District Court for the District of Massachusetts. The complaints generally allege securities fraud during the period from January 2001 through January 2003. Each of the complaints asserts claims under Section 10(b) of the Securities Exchange Act of 1934, Rule 10b-5 promulgated thereunder, and Section 20(a) of the Exchange Act, and alleges that the Company and its officers made false and misleading statements and failed to disclose material information concerning the status and progress for obtaining United States marketing approval of its Replagal product to treat Fabry disease during that period.

In March 2003, various plaintiffs filed motions to consolidate, to appoint lead plaintiff, and to approve plaintiff's selections of lead plaintiffs' counsel. In April 2003, various plaintiffs filed a Joint Stipulation and Proposed Order of Lead Plaintiff Applicants to Consolidate Actions, To Appoint Lead Plaintiffs and to Approve Lead Plaintiffs' Selection of Lead Counsel, Executive Committee and Liaison Counsel. In April 2003, the Court endorsed the Proposed Order, thereby consolidating the various matters under one matter: *In re Transkaryotic Therapies, Inc., Securities Litigation, C.A. No. 03-10165-RWZ.*

In July 2003, the plaintiffs filed a Consolidated and Amended Class Action Complaint (the "Amended Complaint"), against the Company; Dr. Selden; Daniel Geffken, the Company's former Chief Financial Officer; Walter Gilbert, Jonathan S. Leff, Rodman W. Moorhead, III, and Wayne P. Yetter, members of the Company's Board of Directors; William R. Miller and James E. Thomas, former members of the Company's Board of Directors; SG Cowen Securities Corporation; Deutsche Bank Securities; Pacific Growth Equities, Inc.; and Leerink Swann & Company.

The Amended Complaint alleges securities fraud during the period from January 4, 2001 through January 10, 2003. The Amended Complaint alleges that the defendants made false and misleading statements and failed to disclose material information concerning the status and progress for obtaining United States marketing approval of Replagal during that period. The Amended Complaint asserts claims against each of the defendants under Section 11 of the Securities Act and against Dr. Selden under Section 15 of the Securities Act; against SG Cowen Securities Corporation, Deutsche Bank Securities, Pacific Growth Equities, Inc., and Leerink Swann & Company under Section 12(a)(2) of the Securities Act; against Dr. Selden and the Company under Section 10(b) of the Exchange Act and Rule 10b-5 promulgated thereunder; and against Dr. Selden under Section 20(a) of the Exchange Act. The plaintiffs seek equitable and monetary relief, an unspecified amount of damages, with interest, and attorney's fees and costs.

In September 2003, the Company filed a motion to dismiss the Amended Complaint. A hearing of the motion occurred in December 2003. A class has not been certified.

As of December 31, 2003, the Company has incurred approximately $1,000,000 in litigation expenses related to the shareholder lawsuit and the derivative lawsuit described below. The Company expects that the costs related to these suits will be significant.

Derivative Suit

In April 2003, South Shore Gastrointerology UA 6/6/1980 FBO Harold Jacob, and Nancy R. Jacob Ttee filed a Shareholder Derivative Complaint against Dr. Selden; against the following members of the Company's board of directors: Jonathan S. Leff, Walter Gilbert, Wayne P. Yetter, Rodman W. Moorhead III; against the following former members of the Company's Board of Directors: James E. Thomas, and William Miller; and against the Company as nominal defendant, in Middlesex Superior Court in the Commonwealth of Massachusetts, Civil Action No. 03-1669. On May 29, 2003, the parties moved to transfer venue to the Business Litigation Session in Suffolk Superior Court in the Commonwealth of Massachusetts. The parties' motion was allowed, and in June 2003 the matter was accepted into the Business Litigation Session as Civil Action No. 03-02630-BLS.

The complaint alleges that the individual defendants breached fiduciary duties owed to the Company and its shareholders by disseminating materially false and misleading statements to the market and causing or allowing the Company to conduct its business in an unsafe, imprudent and unlawful manner. The complaint purports to assert derivative claims against the individual defendants for breach of fiduciary duty, and to assert a claim for contribution and indemnification on behalf of the Company for any liability the Company incurs as a result of the individual defendants' alleged misconduct. The complaint seeks declaratory, equitable and monetary relief, an unspecified amount of damages, with interest, and attorney's fees and costs.

In August 2003, the plaintiff filed its Verified Amended Derivative Complaint (the "Amended Derivative Complaint"). The Amended Derivative Complaint alleges that the individual defendants breached fiduciary duties owed to the Company and its stockholders by causing the Company to issue materially false and misleading statements to the public, by signing its Form 10-Ks for the years 2000 and 2001 and by signing a registration statement. The Amended Derivative Complaint also alleges that defendant Dr. Selden sold the Company's stock while in possession of material non-public information. The plaintiffs seek declaratory, equitable and monetary relief, an unspecified amount of damages, with interest, and attorney's fees and costs.

In September 2003, the Company served a motion to dismiss the Amended Derivative Complaint. A hearing of the motion was held in January 2004.

SEC Investigation

In May 2003, the Company received a copy of a formal order of investigation by the SEC. The order of investigation relates to the Company's disclosures and public filings with regard to Replagal and the status of the FDA's approval process for Replagal, as well as transactions in the Company's securities. The Company is cooperating fully and will continue to cooperate fully with the SEC in the investigation. As of December 31, 2003, the Company has incurred approximately $1,400,000 related to this matter.

Lease and Product Development Commitments

The Company leases its facilities under operating leases that expire through 2012, subject to renewal provisions. The Company's future annual minimum payments under such commitments are as follows:

	(in thousands)
2004	$11,388
2005	11,201
2006	11,260
2007	12,019
2008	11,681
Thereafter	26,760
Total	$84,309

In August 2000, the Company entered into a ten-year lease for a new corporate headquarters and research and development facility in Cambridge, Massachusetts. The lease required a security deposit of $7,680,000, of which $680,000 was paid in cash and the balance provided for in the form of a letter of credit. An investment with a value of $7,993,000 collateralizes the letter of credit. The lease has two five year renewal options.

Rent expense was $10,555,000, $11,263,000, and $3,898,000 in 2003, 2002 and 2001, respectively.

At December 31, 2003, the Company had committed to pay $9,470,000 to various contract vendors for administering and executing clinical trials for the next two years.

18. Gain on Sale of Investment

In 1996, TKT made a strategic investment of $300,000 in a European biotechnology company. In 2001, TKT sold all of its investment resulting in a gain of $3,224,000.

19. Quarterly Financial Data (Unaudited)

	Quarter Ended				
	March 31	June 30	September 30	December 31	Total
	(in thousands, except per share amounts)				
2003					
Revenues	$ 12,183	$ 14,414	$ 16,718	$ 15,574	$ 58,889
Cost of goods sold	3,501	4,775	2,769	1,439	12,484
Research and development expenses	20,982	16,853	17,895	18,332	74,062
Intellectual property license	1,350	—	—	—	1,350
Restructuring charges	3,602	4,957	2,765	1,137	12,461
Total expenses	38,601	35,997	30,714	31,602	136,914
Net loss	$(25,945)	$(21,020)	$(13,553)	$(14,716)	$ (75,234)
Basic and diluted net loss per share	$ (0.75)	$ (0.61)	$ (0.39)	$ (0.43)	$ (2.18)
2002					
Revenues	$ 6,610	$ 8,865	$ 7,890	$ 13,135	$ 36,500
Cost of goods sold	548	1,650	2,743	5,570	10,511
Research and development expenses	20,409	18,868	20,450	21,582	81,309
Intellectual property license	—	26,000	—	8,660	34,660
Impairment charge	—	—	—	16,069	16,069
Total expenses	27,380	53,994	30,497	61,907	173,778
Net loss	$(18,467)	$(42,881)	$(20,902)	$(47,512)	$(129,762)
Basic and diluted net loss per share	$ (0.54)	$ (1.24)	$ (0.60)	$ (1.36)	$ (3.75)

Item 9. ***Changes In and Disagreements With Accountants on Accounting and Financial Disclosure***

None.

Item 9A. ***Controls and Procedures***

The Company's management, with the participation of the Company's President and Chief Executive Officer and Vice President, Finance and Chief Financial Officer, evaluated the effectiveness of the Company's disclosure controls and procedures (as defined in Rules 13a-15(e) and 15d-15(e) under the Exchange Act) as of December 31, 2003. Based on this evaluation, the Company's President and Chief Executive Officer and its Vice President, Finance and Chief Financial Officer concluded that, as of December 31, 2003, the Company's disclosure controls and procedures were (1) designed to ensure that material information relating to the Company, including its consolidated subsidiaries, is made known to its President and Chief Executive Officer and its Vice President, Finance and Chief Financial Officer by others within these entities, particularly during the period in which this report was being prepared and (2) effective, in that they provide reasonable assurance that information required to be disclosed by the Company in the reports that it files or submit under the Exchange Act is recorded, processed, summarized and reported within the time periods specified in the SEC's rules and forms.

No change to the Company's internal control over financial reporting (as defined in Rules 13a-15(f) and 15d-15(f) under the Exchange Act) occurred during the year ended December 31, 2003 that has materially affected, or is reasonably likely to materially affect, the Company's internal control over financial reporting.

PART III

Item 10. ***Directors and Executive Officers of the Registrant***

The information required by this item is contained in part under the caption "Executive Officers of the Company" in Part I hereof, and in the Company's Proxy Statement for the Company's Annual Meeting of Stockholders to be held on June 22, 2004 (the "Proxy Statement") under the caption " Election of Directors" and "Section 16(a) Beneficial Ownership Reporting Compliance" and is incorporated herein by this reference.

Item 11. ***Executive Compensation***

The information required by this item is contained under the caption "Executive Compensation", "Directors' Compensation", "Employment Agreements", "Severance Arrangements", and "Compensation Committee Interlocks and Insider Participation" in the Company's Proxy Statement and is incorporated herein by this reference.

Item 12. ***Security Ownership of Certain Beneficial Owners and Management and Related Stockholder Matters***

The information required by this item is contained in the Company's Proxy Statement under the caption "Security Ownership of Certain Beneficial Owners and Management" and "Securities Authorized for Issuance Under Equity Compensation Plans" is incorporated herein by this reference.

Item 13. ***Certain Relationships and Related Transactions***

The information required by this item is contained in the Company's Proxy Statement under the caption "Certain Transactions" and is incorporated herein by this reference.

Item 14. ***Principal Accountant Fees and Services***

The information required by this item is contained in the Company's Proxy Statement under the caption "Independent Auditors Fees" and is incorporated herein by reference.

PART IV

Item 15. ***Exhibits, Financial Statement Schedules, and Reports on Form 8-K***

(a) *Documents filed as a part of this Form 10-K:*

1. *Financial Statements.* The following financial statements and supplementary data are included as part of this Annual Report on Form 10-K:

Report of Independent Auditors

Consolidated Balance Sheets as of December 31, 2003 and 2002

Consolidated Statements of Operations for the years ended December 31, 2003, 2002 and 2001

Consolidated Statement of Stockholders' Equity for the years ended December 31, 2003, 2002 and 2001

Consolidated Statements of Cash Flows for the years ended December 31, 2003, 2002 and 2001

2. *Financial Statement Schedules.* The Company is not filing any financial statement schedules as part of this Annual Report on Form 10-K because they are not applicable or the required information is included in the financial statements or notes thereto.

3. *Exhibits.* The Exhibits listed in the Exhibit Index immediately preceding such Exhibits are filed as part of this Annual Report on Form 10-K, and such Exhibit Index is incorporated herein by reference.

(b) *Reports on Form 8-K:*

Report on Form 8-K furnished on October 29, 2003, announcing the results the financial results of the Company for the third quarter of 2003.

SIGNATURES

Pursuant to the requirements of Section 13 or 15(d) of the Securities Exchange Act of 1934, the Registrant has duly caused this report to be signed on its behalf by the undersigned, thereunto duly authorized.

TRANSKARYOTIC THERAPIES, INC.

By: /s/ MICHAEL J. ASTRUE
Michael J. Astrue
President and Chief Executive Officer

Date: March 15, 2004

Pursuant to the requirements of the Securities Exchange Act of 1934, this report has been signed below by the following persons on behalf of the Registrant, in the capacities and on the dates indicated.

Signature	Title	Date
/s/ MICHAEL J. ASTRUE Michael J. Astrue	President, Chief Executive Officer and Director (Principal Executive Officer)	March 15, 2004
/s/ GREGORY D. PERRY Gregory D. Perry	Vice President, Finance and Chief Financial Officer (Principal Accounting and Financial Officer)	March 15, 2004
/s/ RODMAN W. MOORHEAD, III Rodman W. Moorhead, III	Chairman of the Board of Directors	March 15, 2004
/s/ WALTER GILBERT Walter Gilbert	Director	March 15, 2004
/s/ DENNIS H. LANGER Dennis H. Langer	Director	March 15, 2004
/s/ JONATHAN S. LEFF Jonathan S. Leff	Director	March 15, 2004
/s/ WAYNE P. YETTER Wayne P. Yetter	Director	March 15, 2004
/s/ LYDIA VILLA-KOMAROFF Lydia Villa-Komaroff	Director	March 15, 2004

EXHIBIT INDEX

Exhibit No.	Description
3.1	Amended and Restated Certificate of Incorporation of the Registrant, as amended.(1)
3.2	Amended and Restated By-Laws of the Registrant, as amended.(1)
4.1	Rights Agreement dated December 13, 2000, between Registrant and Equiserve Trust Company, N.A.(4)
10.1	Lease Agreement, dated January 1, 1994, for office space at 195 Albany Street, Cambridge, Massachusetts, by and between the Trust under the Will of Harry F. Stimpson and the Registrant.(5)
10.2	Sublease Agreement, dated April 7, 1992, for office space located at 185 Albany Street, Cambridge, Massachusetts, by and between the Massachusetts Institute of Technology and the Registrant.(5)
10.3†	1993 Non-Employee Directors' Stock Option Plan.(5)(6)
10.4†	1993 Long-Term Incentive Plan.(6)(7)
10.5	Form of Letter Agreement re: Confidentiality, Inventions and Non-Disclosure.(5)
10.6	Form of Letter Agreement re: Restricted Stock.(5)
10.7	Form of Scientific Advisor Agreement.(5)
10.8†	Employment Agreement, dated June 19, 1991, by and between Dr. Richard F Selden and the Registrant.(5)(6)
10.9†	Employment Agreement, dated July 26, 1991, by and between Dr. Douglas A. Treco and the Registrant.(5)(6)
10.10	Agreement, dated September 1, 1991, by and between Mr. William R. Miller and the Registrant.(5)(6)
10.11	Collaboration and License Agreement, dated July 22, 1993 and amended on May 30, 1996, by and between Wyeth (successor to Genetics Institute, Inc.) and the Registrant.(5)(8)
10.12	Amended and Restated License Agreement, dated March 1, 1995, by and between Aventis S.A. and the Registrant.(5)(8)
10.13†	Employment Agreement, dated February 20, 1997, by and between Mr. Daniel E. Geffken and the Registrant.(6)(9)
10.14	Employment Agreement, dated April 12, 1999, by and between Mr. William H. Pursley and the Registrant.(6)(10)
10.15	Common Stock Purchase Agreement by and between each Purchaser of shares in the Registrant's private placement of common stock in November 1999 and the Registrant.(11)
10.16	Agreement, dated November 15, 1999, by and between Mr. Wayne P. Yetter and the Registrant.(6)(11)
10.17	Registration Rights Agreement, dated June 9, 2000, by and between certain holders of Series A Convertible Preferred Stock and the Registrant.(2)
10.18	Agreement, dated April 20, 2000, by and between Dr. Walter Gilbert and the Registrant.(2)(6)
10.19	Agreement, dated June 16, 2000, by and between Mr. James E. Thomas and the Registrant.(2)(6)
10.20	Lease Agreement, dated August 4, 2000, for new corporate headquarters and research and development space in Cambridge, Massachusetts, by and between the Massachusetts Institute of Technology and the Registrant.(12)
10.21	Purchase and Sale and Assignment Agreement, dated November 28, 2000, by and between Serono, Inc. and the Registrant.(3)
10.22	First Amendment to Purchase and Sale and Assignment Agreement, dated February 8, 2001, by and between Serono, Inc. and the Registrant.(3)
10.23	Lease Agreement, dated February 2001, by and between Trinet Property Partners, L.P and the Registrant.(3)
10.24	Reimbursement Agreement, dated May 18, 2000, by and between Mr. William H. Pursley and the Registrant.(3)

Exhibit No.	Description
10.25†	2001 Non-Officer Employee Stock Incentive Plan.(3)
10.26†	2000 Nonqualified Deferred Compensation Plan.(3)
10.27	Stockholders' Agreement, dated as of April 12, 2000, by and among certain other stockholders in TKT Europe 5S AB, a corporation organized under the laws of Sweden, and the Registrant.(13)
10.28†	Employment Agreement, dated December 18, 2001 by and between Dr. David D. Pendergast and the Registrant.(14)
10.29†	Employment Agreement, dated March 18, 2002, by and between Dr. Renato Fuchs and the Registrant.(14)
10.30	License Agreement, dated June 7, 2002, by and between Cell Genesys, Inc. and the Registrant.(8)(15)
10.31#	Commercial Supply and Process Validation Agreement, entered into as of December 6, 1999, by and between Chesapeake Biological Laboratories, Inc. and the Registrant.(8)(16)
10.32#	Master Production Agreement, made as of December 1, 1998, between BioScience Contract Production Corp. and the Registrant.(8)(16)
10.33	Indemnification Agreement, dated March 13, 2003, by and between Mr. Daniel E. Geffken and the Registrant.(1)
10.34	Retention Agreement, dated March 13, 2003, by and between Mr. Daniel E. Geffken and the Registrant.(1)
10.35†	2002 Stock Incentive Plan and Amendment No. 1 thereto.(1)
10.36	Indemnification Agreement, dated April 30, 2003, by and between Mr. Michael J. Astrue and the Registrant.(1)
10.37†	Employment Agreement, dated April 30, 2003, by and between Mr. Michael J. Astrue and the Registrant.(1)
10.38#	License Agreement, dated February 28, 2003, by and between Women's and Children's Hospital and the Registrant.(1)
10.39	Severance Agreement dated April 28, 2003 between Douglas A. Treco and the Registrant.(17)
10.40	Indemnification Agreement between Richard F Selden, M.D. and the Registrant.(18)
10.41*	Agreement dated May 1, 2003 between Gregory Perry and the Registrant.
21.1*	Subsidiaries of the Registrant.
23.1*	Consent of Ernst & Young LLP.
31.1*	Certification by the Registrant's President and Chief Executive Officer pursuant to Rule 13a-14 of the Securities Exchange Act of 1934, as amended, as adopted pursuant to Section 302 of the Sarbanes-Oxley Act of 2002.
31.2*	Certification by the Registrant's Chief Financial Officer pursuant to Rule 13a-14 of the Securities Exchange Act of 1934, as amended, as adopted pursuant to Section 302 of the Sarbanes-Oxley Act of 2002.
32.1*	Certification by the Registrant's President and Chief Executive Officer pursuant to Rule 13a-14(b) of the Securities Exchange Act of 1934, as amended, and 18 U.S.C. Section 1350, as adopted pursuant to Section 906 of the Sarbanes-Oxley Act of 2002.
32.2*	Certification by the Registrant's Chief Financial Officer pursuant to Rule 13a-14(b) of the Securities Exchange Act of 1934, as amended, and 18 U.S.C. Section 1350, as adopted pursuant to Section 906 of the Sarbanes-Oxley Act of 2002.

1. Filed as an exhibit to the Company's Quarterly Report on Form 10-Q for the quarter ended March 31, 2003 (File No. 0-21481) and incorporated herein by reference.
2. Filed as an exhibit to the Company's Quarterly Report on Form 10-Q for the quarter ended June 30, 2000 (File No. 0-21481) and incorporated herein by reference.

3. Filed as an exhibit to this Annual Report on Form 10-K for the year ended December 31, 2000 (File No. 0-21481) and incorporated herein by reference.

4. Filed as an exhibit to the Company's Current Report on Form 8-K filed with the SEC on December 14, 2000 (File No. 0-21481) and incorporated herein by reference

5. Filed as an exhibit to the Company's Registration Statement on Form S-1 filed with the SEC on August 27, 1996 (File No. 333-10845) and incorporated herein by reference.

6. Management contract or compensation plan or arrangement required to be filed as an exhibit pursuant to Item 15(c) of Form 10-K.

7. Filed as an exhibit to the Company's Quarterly Report on Form 10-Q for the quarter ended March 31, 1998 (File No. 0-21481) and incorporated herein by reference.

8. Confidential treatment granted as to certain portions.

9. Filed as an exhibit to the Company's Registration Statement on Form S-1 filed with the SEC on July 24, 1997 (File No. 333-31957) and incorporated herein by reference.

10. Filed as an exhibit to the Company's Quarterly Report on Form 10-Q for the quarter ended June 30, 1999 (File No. 0-21481) and incorporated herein by reference.

11. Filed as an exhibit to the Company's Annual Report on Form 10-K for the year ended December 31, 1999 (File No. 0-21481) and incorporated herein by reference.

12. Filed as an exhibit to the Company's Quarterly Report on Form 10-Q for the quarter ended September 30, 2000 (File No. 0-21481) and incorporated herein by reference.

13. Filed as an exhibit to the Company's Current Report on Form 8-K filed with the SEC on June 15, 2001 (File No. 0-21481) and incorporated herein by reference.

14. Filed as an exhibit to the Company's Annual Report on Form 10-K for the year ended December 31, 2001 (File No. 0-21481) and incorporated herein by reference.

15. Filed as an exhibit to the Company's Quarterly Report on Form 10-Q for the quarter ended June 30, 2002 (File No. 0-21481) and incorporated herein by reference.

16. Filed as an exhibit to the Company's Quarterly Report on Form 10-Q for the quarter ended September 30, 2002 (File No. 0-21481) and incorporated herein by reference.

17. Filed as an exhibit to the Company's Quarterly Report on Form 10-Q for the quarter ended June 30, 2003 (File No. 0-21481) and incorporated herein by reference.

18. Filed as an exhibit to the Company's Quarterly Report on Form 10-Q for the quarter ended September 31, 2003 (File No. 0-21481) and incorporated herein by reference.

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* Filed herewith.

\# Confidential treatment requested as to certain portions pursuant to Rule 24-b-2 promulgated under the Exchange Act of 1934, as amended.

† Management contract or compensatory plan or arrangement.

Board of Directors

Michael J. Astrue
President and Chief Executive Officer,
Transkaryotic Therapies, Inc.

Walter Gilbert, Ph.D.
Carl M. Loeb University Professor,
Harvard University;
Managing Director, BioVentures Investors

Dennis H. Langer, M.D., J.D.
President, North America,
Dr. Reddy's Laboratories

Jonathan S. Leff
Managing Director,
Warburg Pincus LLC

Rodman W. Moorhead, III
Senior Advisor,
Warburg Pincus LLC

Lydia Villa-Komaroff, Ph.D.
Chief Operating Officer,
Whitehead Institute

Wayne P. Yetter
Chairman of the Board;
Former Chairman and
Chief Executive Officer,
Synavant

TKT Management

William E. Aliski
Vice President, Commercial Operations

Michael J. Astrue
President and Chief Executive Officer

Suzanne L. Bruhn, Ph.D.
Vice President, Regulatory Affairs

William Ciambrone
Vice President, Quality

Mary S. Consalvi
Vice President and Chief Intellectual
Property Counsel

Kerry A. Flynn
Vice President, Business Development

Renato Fuchs, Ph.D.
Senior Vice President, Manufacturing
and Operations

Michael W. Heartlein, Ph.D.
Vice President, Research

Shirish Hirani, Ph.D.
Vice President, Program Management

Neil Kirby, Ph.D.
Vice President, Strategic
Product Development

Paul M. Martha, M.D.
Vice President, Clinical Affairs

Aditya Mohanty
Vice President, Manufacturing

David D. Pendergast, Ph.D.
Executive Vice President and
Chief Operating Officer

Gregory D. Perry
Vice President, Finance and
Chief Financial Officer

Linda H. Pettingell
Vice President, Human Resources and
Corporate Services

Stockholder Information

Headquarters

Transkaryotic Therapies, Inc.
700 Main Street
Cambridge, Massachusetts 02139
Telephone: (617) 349-0200

Worldwide Web

To learn more about TKT please visit us on the worldwide web at: www.tktx.com.

Stock Listing

TKT is listed on the Nasdaq Stock Market under the symbol TKTX.

Annual Meeting

The annual meeting of stockholders will be held at 10:00 a.m. Eastern Time on June 22, 2004, at Transkaryotic Therapies, Inc., 700 Main Street, Cambridge, Massachusetts 02139.

Registrar and Transfer Agent

EquiServe Trust Company, N.A.
P.O. Box 43010
Providence, Rhode Island 02940-3010
Telephone: (816) 843-4299
www.equiserve.com

Shareholder Inquiries

Communications concerning stock transfer requirements, lost certificates, or address changes should be directed to EquiServe, (816) 843-4299. For general information about TKT, contact Investor Relations at (617) 349-0271 or access the company's website at www.tktx.com.

Independent Auditors

Ernst & Young LLP, Boston, Massachusetts

Trademarks

Gene-Activated® and TKT® are registered trademarks and Replagal™ is a trademark of Transkaryotic Therapies, Inc. Dynepo™ is a trademark of Aventis Pharmaceuticals, Inc..

Forward-Looking Statements

This Annual Report contains forward-looking statements. All statements about TKT's future expectations, plans, and prospects constitute forward-looking statements for purposes of the safe harbor provisions under the Private Securities Litigation Reform Act of 1995. Actual results may differ materially from those indicated by these forward-looking statements. Important factors that could cause TKT's actual results to differ materially are discussed in the Annual Report on Form 10-K included in this annual report under the heading, "Management's Discussion and Analysis of Financial Condition and Results of Operations – Forward-Looking Statements." TKT takes no responsibility to update forward-looking statements.

Creative: Kaminsky Strategik Design

ON THE COVER: ALLISON HAJJAR, *Human Resources Representative II*

TKT