BIOTIME INC
Form 10-K
March 31, 2005

Table of Contents

SECURITIES AND EXCHANGE COMMISSION
Washington, D.C. 20549

FORM 10-K

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

For the fiscal year ended December 31, 2004

OR

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

For the transition period from_____ to _____

Commission file number 1-12830

BioTime, Inc.

(Exact name of registrant as specified in its charter)

California	**94-3127919**
(State or other jurisdiction of incorporation or organization)	**(I.R.S. Employer Identification No.)**
935 Pardee Street, Berkeley, California	**94710**
(Address of principal executive offices)	**(Zip Code)**

Registrant s telephone number, including area code (510) 845-9535

Securities registered pursuant to Section 12(b) of the Act:

Title of each class	Name of exchange on which registered
Common Shares, no par value	American Stock Exchange
Common Share Purchase Warrants	American Stock Exchange

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 þ **No** o

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. þ

Indicate by check mark whether the registrant is an accelerated filer (as defined in Rule 12b-2 of the Act). Yes o **No** þ

The approximate aggregate market value of voting common stock held by nonaffiliates of the registrant computed by reference to the price at which the common stock was last sold as of the last business day of the registrant s most recently completed second fiscal quarter was $20,095,885. Shares held by each executive officer and director and by each person who beneficially owns more than 5% of the outstanding common shares have been excluded in that such persons may under certain circumstances be deemed to be affiliates. This determination of affiliate status is not necessarily a conclusive determination for other purposes.

17,851,450
(Number of common shares outstanding as of March 4, 2005)

Documents Incorporated by Reference
None

TABLE OF CONTENTS

Table of Contents

PART I

Statements made in this Form 10-K that are not historical facts may constitute forward-looking statements that are subject to risks and uncertainties that could cause actual results to differ materially from those discussed. Words such as expects, may, will, anticipates, intends, plans, believes, seeks, estimates, and similar expressions forward-looking statements. See Risk Factors and Note 1 to Financial Statements.

Item 1. Description of Business

Overview

BioTime, Inc. is engaged in the research and development of synthetic solutions that can be used as blood plasma volume expanders, blood replacement solutions during hypothermic (low temperature) surgery, and organ preservation solutions. Plasma volume expanders are used to treat blood loss in surgical or trauma patients until blood loss becomes so severe that a transfusion of packed red blood cells or other blood products is required. We are also developing a specially formulated hypothermic blood substitute solution that would have a similar function and would be used for the replacement of very large volumes of a patient s blood during cardiac surgery, neurosurgery and other surgeries that involve lowering the patient s body temperature to hypothermic levels.

Our first product, Hextend®, is a sterile, physiologically balanced blood plasma volume expander, for the treatment of hypovolemia. Hypovolemia is a condition caused by low blood volume, often from blood loss during surgery or from injury. Hextend maintains circulatory system fluid volume and blood pressure and helps sustain vital organs during surgery. Hextend, approved for use in major surgery, is the only blood plasma volume expander that contains lactate, multiple electrolytes, glucose, and a medically approved form of starch called hetastarch. Hextend is designed to compete with and to replace products that have been used to maintain fluid volume and blood pressure during surgery. These competing products include albumin and other colloid solutions, and crystalloid solutions. Commercial sources of albumin are generally human blood. Other colloid solutions contain proteins or a starch that keep the fluid in the patient s circulatory system in order to maintain blood pressure. Crystalloid solutions generally contain salts and may also contain other electrolytes, and have certain disadvantages in maintaining a patient s circulatory system fluid volume and pressure. Health insurance reimbursements and HMO coverage now include the cost of Hextend used in surgical procedures.

We are also developing two other blood volume replacement products, PentaLyte® and HetaCool®, that, like Hextend, have been formulated to maintain the patient s tissue and organ function by sustaining the patient s fluid volume and physiological balance.

Hextend is being distributed in the United States and Canada by Hospira, Inc. under an exclusive license from us. During March 2003, we granted to CJ Corp. (CJ) an exclusive license to manufacture and sell Hextend and PentaLyte, in South Korea. CJ has obtained regulatory approval to manufacture and market Hextend, and has recently obtained Korean Health Insurance pricing, a step that was required to occur before sales could begin. CJ is also responsible for

Table of Contents

obtaining the regulatory approvals required to manufacture and market PentaLyte in South Korea, including conducting any clinical trials that may be required, and will bear all related costs and expenses. See Licensing for more information about the licenses granted to Hospira and CJ.

We have entered into an agreement with Summit Pharmaceuticals International Corporation (Summit) to develop Hextend and PentaLyte for the Japanese market. BioTime and Summit do not plan to manufacture and market Hextend and PentaLyte themselves. Instead, we will seek to license manufacturing and marketing rights to a third party such as a pharmaceutical company. See Licensing for more information about our agreement with Summit.

Various colloid and crystalloid products are being marketed by other companies for use in maintaining patient fluid volume in surgery and trauma care, but those solutions do not contain the unique comprehensive combination of electrolytes, glucose, lactate and hydroxyethyl starch found in Hextend, PentaLyte, and HetaCool. The use of competing solutions has been reported in some studies to correlate with patient morbidity, fluid accumulation in body tissues, impaired blood clotting, and a disturbance of the delicate chemical balances on which most of the body s chemical reactions depend. One of these competing products is 6% hetastarch in saline solution. The United States Food and Drug Administration (the FDA) has recently required the manufacturers of 6% hetastarch in saline solutions to change their product labeling by adding a warning stating that those products are not recommended for use as a cardiac bypass prime solution, or while the patient is on cardiopulmonary bypass, or in the immediate period after the pump has been disconnected. We have not been required to add that warning to the labeling of Hextend.

Another competing product is albumin produced from human plasma. Albumin is currently more expensive than Hextend and is subject to supply shortages. An FDA warning has cautioned physicians about the risk of administering albumin to seriously ill patients.

We are beginning a Phase II clinical trial using PentaLyte in the treatment of hypovolemia in cardiac surgery. PentaLyte contains a lower molecular weight hydroxyethyl starch than Hextend, and is more quickly metabolized. PentaLyte is designed for use when short lasting volume expansion is desirable. Our ability to complete clinical studies of PentaLyte will depend on our cash resources and the costs involved, which are not presently determinable.

We are also continuing to develop solutions for low temperature surgery and trauma care. A number of physicians have reported using Hextend to treat hypovolemia under mild hypothermic conditions during cardiac surgery. Additional cardiac surgeries have been performed at deeper hypothermic temperatures. In one case, Hextend was used to treat hypovolemia in a cancer patient operated on under deep hypothermic conditions in which the heart was arrested. Once a sufficient amount of data from successful low temperature surgery has been compiled, we plan to seek permission to conduct trials using Hextend as a complete replacement for blood under near-freezing conditions. We currently plan to market Hextend for complete blood volume replacement at very low temperatures under the trademark HetaCool after FDA approval is obtained.

During April 2004, we were awarded a research grant by the National Heart, Lung, and Blood Institute division of the National Institutes of Health (NIH) for use in the development of

Table of Contents

HetaCool. The grant is being used to fund a project entitled Resuscitating Blood-Substituted Hypothermic Dogs at the Texas Heart Institute in Houston under the guidance of Dr. George V. Letsou. Dr. Letsou is Associate Professor of Surgery and Director of the Heart Failure Center at the University of Texas Medical School in Houston, Texas. We were granted $149,994 for the project during 2004, and as of December 31, 2004, we have submitted a request for reimbursement for $20,160. Subject to availability of funds and satisfactory progress on the project, we may be granted an additional $149,996 during 2005.

In order to commence clinical trials for regulatory approval of new products (e.g., PentaLyte), or new therapeutic uses of Hextend, it will be necessary for us to prepare and file with the FDA an Investigational New Drug Application (IND) or an amendment to expand the present IND for additional clinical studies. Filings with foreign regulatory agencies will be required to commence clinical trials overseas. The cost of preparing regulatory filings and conducting clinical trials is not presently determinable, but could be substantial. It will be necessary for us to obtain additional funds in order to complete any clinical trials that we may conduct for our new products or for new uses of Hextend.

In addition to developing clinical trial programs, we plan to continue to provide funding for our laboratory testing programs at selected universities, medical schools and hospitals for the purpose of developing additional uses of Hextend, PentaLyte, HetaCool, and other new products, but the amount of research that will be conducted at those institutions will depend upon our financial status.

BioTime was incorporated under the laws of the State of California on November 30, 1990. Our principal office is located at 935 Pardee Street, Berkeley, California 94710. Our telephone number is (510) 845-9535.

Hextend,® PentaLyte,® and HetaCool® are registered trademarks of BioTime, Inc.

Products for Surgery, Plasma Volume Replacement and Emergency Care

The Market for Plasma Volume Expanders

We are developing Hextend, PentaLyte, HetaCool and other synthetic plasma expander solutions to treat acute blood loss that occurs as a result of trauma injuries and during many kinds of surgery. These products are synthetic, can be sterilized, and can be manufactured in large volumes. Hextend, PentaLyte, and HetaCool contain constituents that may maintain physiological balance when used to replace lost blood volume.

Hextend is also currently being used to treat hypovolemia subsequent to trauma or low blood pressure due to shock by emergency room physicians. After appropriate clinical testing and regulatory approval, it may be used by paramedics to treat acute blood loss in trauma victims being transported to the hospital. Hextend has also been purchased by the United States armed forces and may be used in cases of battlefield trauma.

Table of Contents

Approximately 10,000,000 surgeries take place in the United States each year, and blood transfusions are required in approximately 3,000,000 of those cases. Transfusions are also required to treat patients suffering severe blood loss due to traumatic injury. Many more surgical and trauma cases do not require blood transfusions but do involve significant bleeding that can place the patient at risk of suffering from shock caused by the loss of fluid volume (hypovolemia) and physiological balance. Whole blood and packed red cells generally cannot be administered to a patient until the patient s blood has been typed and sufficient units of compatible blood or red cells can be located. Periodic shortages of supply of donated human blood are not uncommon, and rare blood types are often difficult to locate. The use of human blood products also poses the risk of exposing the patient to blood-borne diseases such as AIDS and hepatitis.

Due to the risks and cost of using human blood products, even when a sufficient supply of compatible blood is available, physicians treating patients suffering blood loss are generally not permitted to transfuse red blood cells until the patient s level of red blood cells has fallen to a level known as the transfusion trigger. During the course of surgery, while blood volume is being lost, the patient is infused with plasma volume expanders to maintain adequate blood circulation. During the surgical procedure, red blood cells are not generally replaced until the patient has lost approximately 45% to 50% of his or her red blood cells, thus reaching the transfusion trigger at which point the transfusion of red blood cells may be required. After the transfusion of red blood cells, the patient may continue to experience blood volume loss, which will be replaced with plasma volume expanders. Even in those patients who do not require a transfusion, physicians routinely administer plasma volume expanders to maintain sufficient fluid volume to permit the available red blood cells to circulate throughout the body and to maintain the patient s physiological balance.

Several units of fluid replacement products are often administered during surgery. The number of units will vary depending upon the amount of blood loss and the kind of plasma volume expander administered. Crystalloid products must be used in larger volumes than colloid products such as Hextend.

The Market for Products for Hypothermic Surgery

In 2003, more than 400,000 coronary bypass and other open-heart surgeries were performed in the United States. Current estimates indicate that more than one million people over age 55 have pathological changes associated with the aortic arch. Open-heart procedures often require the use of cardio-pulmonary bypass equipment to do the work of the heart and lungs during the surgery. During open-heart surgery and surgical procedures for the treatment of certain cardiovascular conditions such as large aneurysms, cardiovascular abnormalities and damaged blood vessels in the brain, surgeons must temporarily interrupt the flow of blood through the body. Interruption of blood flow can be maintained only for short periods of time at normal body temperatures because many critical organs, particularly the brain, are quickly damaged by the resultant loss of oxygen. As a result, certain surgical procedures are performed at low temperatures because lower body temperature helps to minimize the chance of damage to the patient s organs by reducing the patient s metabolic rate, thereby decreasing the patient s needs during surgery for oxygen and nutrients that normally flow through the blood.

Table of Contents

Current technology limits the degree to which surgeons can lower a patient s temperature and the amount of time the patient can be maintained at a low body temperature because blood, even when diluted, cannot be circulated through the body at near-freezing temperatures. As a result, surgeons face severe time constraints in performing surgical procedures requiring blood flow interruption, and those time limitations prevent surgeons from correcting certain cardiovascular abnormalities.

Hypothermic techniques may also have an important use in treating trauma patients that have experienced severe blood loss. We are sponsoring a new project at the State University of New York Health Sciences Center in Brooklyn to study hypothermia and complete blood volume replacement with HetaCool in an animal model of civilian trauma.

Hextend, PentaLyte and HetaCool

Our first three blood volume replacement products, Hextend, PentaLyte, and HetaCool, have been formulated to maintain the patient s tissue and organ function by sustaining the patient s fluid volume and physiological balance. Hextend, PentaLyte, and HetaCool are composed of a hydroxyethyl starch, electrolytes, sugar and lactate in an aqueous base. Hextend and HetaCool use a high molecular weight hydroxyethyl starch (hetastarch) whereas PentaLyte uses a lower, molecular weight hydroxyethyl starch (pentastarch). The hetastarch is retained in the blood longer than the pentastarch, which may make Hextend and HetaCool the products of choice when a larger volume of plasma expander or blood replacement solution for low temperature surgery is needed, or where the patient s ability to restore his own blood proteins after surgery is compromised. PentaLyte, with pentastarch, would be eliminated from the blood faster than Hextend and HetaCool and might be used when less plasma expander is needed or where the patient is more capable of quickly restoring lost blood proteins. We have also tested HexaLyte, a new plasma volume expander that contains a low molecular weight hydroxyethyl starch and that would be eliminated from the body more rapidly than Hextend and HetaCool, but not as rapidly as PentaLyte. We believe that by testing and bringing these products to the market, we can increase our market share by providing the medical community with solutions to match patients needs.

Certain clinical test results indicate that Hextend is effective at maintaining blood calcium levels when used to replace lost blood volume. Calcium can be a significant factor in regulating blood clotting and cardiac function. Clinical studies have also shown that Hextend maintains acid-base better than saline-based surgical fluids. We expect that PentaLyte will also be able to maintain blood calcium levels and acid-base balance based upon laboratory studies and the fact that the formulation of PentaLyte is similar to that of Hextend.

Albumin produced from human plasma is also used as plasma volume expander, but it is currently expensive and subject to supply shortages. Additionally, an FDA warning has cautioned physicians about the risk of administering albumin to seriously ill patients.

We have not attempted to synthesize oxygen-carrying molecules such as hemoglobin because the loss of fluid volume and physiological balance may contribute as much to shock as the loss of the oxygen-carrying component of the blood, and such products can, in our view, be potentially toxic

Table of Contents

and costly. Surgical and trauma patients are routinely given supplemental oxygen and retain a substantial portion of their own red blood cells. Whole blood or packed red blood cells are generally not transfused during surgery or in trauma care until several units of plasma volume expanders have been administered and the patient s blood cell count has fallen to the transfusion trigger. Therefore, the lack of oxygen-carrying molecules in BioTime solutions should not pose a significant contraindication to use.

However, our scientists have conducted laboratory animal experiments in which we have shown that Hextend can be successfully used in conjunction with a hemoglobin-based oxygen carrier solution approved for veterinary purposes to completely replace the animal s circulating blood volume without any subsequent transfusion and without the use of supplemental oxygen. By diluting these oxygen carrier solutions, Hextend may reduce the potential toxicity and costs associated with the use of those products. Once such solutions have received regulatory approval and become commercially available, this sort of protocol may prove valuable in markets in parts of the developing world where the blood supply is extremely unsafe. These applications may also be useful in combat where logistics make blood use impracticable.

Hextend is our proprietary hetastarch-based synthetic blood plasma volume expander, designed especially to treat hypovolemia in surgery where patients experience significant blood loss. An important goal of the Hextend development program was to produce a product that can be used in multi-liter volumes. The safety-related secondary endpoints targeted in the U.S. clinical study included those involving coagulation. We believe that the low incidence of adverse events related to blood clotting in the Hextend patients demonstrates that Hextend may be safely used in amounts exceeding 1.5 liters. An average of 1.6 liters of Hextend was used in the Phase III clinical trials, with an average of two liters for patients who received transfused blood products. Since then, more than 1.1 million units (500 ml bags) have been sold for commercial purposes, and the use of quantities of 7 to 8 liters per patient have been reported. There have been no serious adverse events directly related to the use of Hextend even when used in these large volumes.

Hextend is also being used in surgery with cardio-pulmonary bypass circuits. In order to perform heart surgery, the patient s heart must be stopped and a mechanical apparatus is used to oxygenate and circulate the blood. The cardio-pulmonary bypass apparatus requires a blood compatible fluid such as Hextend to commence and maintain the process of diverting the patient s blood from the heart and lungs to the mechanical oxygenator and pump. In a recent clinical trial, cardiac surgery patients treated with Hextend, maintained more normal kidney function, experienced less pain and nausea, showed no deep venous thrombosis, avoided dialysis, and had shorter delay times to first meal compared to those treated with other fluids.

PentaLyte is our proprietary pentastarch-based synthetic plasma expander, designed especially for use when a faster elimination of the starch component is desired and acceptable. Although Hextend can be used in these cases, some physicians appear to prefer a solution which can be metabolized faster and excreted earlier when the longer term protection provided by Hextend is not required. PentaLyte combines the physiologically balanced Hextend formulation with pentastarch that has a lower molecular weight and degree of substitution than the hetastarch used in Hextend. Plasma expanders containing pentastarch are currently widely used around the world. We

Table of Contents

have completed our PentaLyte Phase I clinical study and we are planning more advanced PentaLyte clinical trials. Our present plan is to seek approval of PentaLyte for use in the treatment of hypovolemia.

HetaCool is a modified formulation of Hextend. HetaCool is specifically designed for use at low temperatures. Surgeons are already using Hextend and a variety of other solutions to carry out certain limited procedures involving shorter term (up to nearly one hour) arrest of brain and heart function at temperatures between 15° and 25° C. However, we are not aware of any fluid currently used in medical practice or any medically approved protocol allowing operations that can completely replace all of a patient s blood at temperatures close to the ice point. We believe that very low temperature bloodless surgical techniques could be developed for open heart and minimally invasive closed chest cardiovascular surgeries, removal of tumors from and the repair of aneurysms in the brain, heart, and other areas, as well as in the treatment of trauma, toxicity and cancer.

We are in the process of preparing an amendment to our Hextend IND to conduct clinical trials using HetaCool as a solution to replace all of a patient s circulating blood volume during profound hypothermic (carried out at near-freezing temperatures) surgical procedures. The experimental protocol for the planned blood replacement clinical trial is being tested on animal subjects. HetaCool would be introduced into the patient s body during the cooling process. Once the patient s body temperature is nearly ice cold, and heart and brain function are temporarily arrested, the surgeon would perform the operation. During the surgery, HetaCool may be circulated throughout the body in place of blood, or the circulation may be arrested for a period of time if an interruption of fluid circulation is required. Upon completion of the surgery, the patient would be slowly warmed and blood would be transfused.

Cardiac surgeons are working to develop innovative procedures to repair damaged coronary arteries and heart valves. If optically guided surgical instruments can be inserted into the heart through blood vessels or small incisions, there may be no need to open the patient s chest cavity. We believe that HetaCool may be useful in these minimally invasive closed chest cardiac procedures because the solution is transparent; if it were used to completely replace blood at low temperatures it would permit surgeons to use their optically guided instruments inside the heart or blood vessels without having their view obstructed by blood. The use of BioTime solutions may also allow better control over stopping and starting the heart, as well as extending the time period of such surgeries.

HetaCool has been used to completely replace the blood volume of hamsters, dogs, pigs, and baboons at temperatures approaching freezing. Many of these animal subjects survived long term after hypothermic blood substitution with HetaCool. In these laboratory tests, the animals blood was replaced by HetaCool and they were chilled for one to more than four hours with deep body temperatures between 1°C and 10°C. Hextend was used to partially replace blood during cancer surgery in which a patient s body temperature was lowered to 19°C and his heart was stopped for 27 minutes while the tumor was removed. The patient recovered without incident, and a case study of the procedure was published in the April 2002 issue of the *Canadian Journal of Anesthesia*.

We have launched a research program using HetaCool in animal models of trauma at the State University of New York Health Science Center in Brooklyn. Preliminary laboratory results there

Table of Contents

have already supported the feasibility of using HetaCool to treat subjects following severe hemorrhage. The use of HetaCool at near-freezing temperatures also will be studied in animal models of cardiovascular surgery at the Texas Heart Institute in Houston. The project has been approved by the appropriate internal committees, and is awaiting the beginning of experimentation.

We are developing a new formulation that has allowed the revival of hamsters after as long as 6.5 hours of hypothermic blood substitution during which time the animals heartbeat and circulation were stopped.

Organ Transplant Products

The Market for Organ Preservation Solutions

Organ transplant surgery is a growing field. Each year in the United States, approximately 5,000 donors donate organs, and approximately 5,000 people donate skin, bone and other tissues. As more surgeons have gained the necessary expertise, and surgical methods have been refined, the number of transplant procedures has increased, as has the percentage of successful transplants. Organ transplant surgeons and their patients face two major obstacles: the shortage of available organs from donors, and the limited amount of time that a transplantable organ can be kept viable between the time it is harvested from the donor and the time it is transplanted into the recipient.

The scarcity of transplantable organs makes them too precious to lose and increases the importance of effective preservation technology and products. Current organ removal and preservation technology generally requires multiple preservation solutions to remove and preserve effectively different groups of organs. The removal of one organ can impair the viability of other organs. Available technology does not permit surgeons to keep the remaining organs viable within the donor s body for a significant time after the first organ is removed. Currently, an organ available for transplant is flushed with an ice-cold solution during the removal process to deactivate the organ and preserve its tissues, and then the organ is transported on ice to the donee. The ice-cold solutions currently used, together with transportation on ice, keep the organ healthy for only a short period of time. For example, the storage time for hearts is limited to approximately six hours. Because of the short time span available for removal and transplant of an organ, potential organ donees may not receive the needed organs.

We are seeking to address this problem by developing a more effective organ preservation solution that will permit surgeons to harvest all transplantable organs from a single donor. We believe that preserving the viability of all transplantable organs and tissues simultaneously, at low temperatures, would extend by several hours the time span in which the organs can be preserved prior to transplant.

Using HetaCool for Multi-Organ Preservation. We are seeking to develop HetaCool for use as a single solution that can simultaneously preserve all of a single donor s organs. When used as an organ preservation solution, HetaCool would be perfused into the donor s body while the body is chilled, thereby eliminating an undesirable condition called warm ischemia, caused when an organ is warm while its blood supply is interrupted. The use of HetaCool in conjunction with the

Table of Contents

chilling of the body should help to slow down the process of organ deterioration by a number of hours so that a surgeon can remove all organs for donation and transplant. We currently estimate that each such preservation procedure could require as much as 50 liters of HetaCool.

We believe that the ability to replace an animal s blood with HetaCool, to maintain the animal at near freezing temperatures for several hours, and then revive the animal, would demonstrate that the solution could be used for human multi-organ preservation. BioTime scientists have revived animals after more than six hours of cold blood-substitution, and have observed heart function in animals maintained cold and blood-substituted for more than eight hours. An objective of our research and development program is to extend the time span in which animal subjects can be maintained in a cold, blood-substituted state before revival or removal of organs for transplant purposes. Organ transplant procedures using animal subjects could then be conducted to test the effectiveness of Hextend as an organ preservative.

A successful transplant of a lung cooled inside the donor s body prior to transplant has recently been reported in Sweden. The patient who received the lung was reported to be doing well several months later. The success of that transplant, which did not involve the use of a BioTime product, involved the preservation and transplant of a single organ, but indicates that hypothermic techniques can be used to preserve organs in the donor prior to removal for transplant.

Long-term Tissue and Organ Banking

The development of marketable products and technologies for the preservation of tissues and vital organs for weeks and months is a long-range goal of our research and development plan. To permit such long-term organ banking we are attempting to develop products and technologies that can protect tissues and organs from the damage that occurs when human tissues are subjected to subfreezing temperatures.

HetaFreeze® is one of a family of BioTime freeze-protective solutions that may ultimately allow the extension of time during which organs and tissues can be stored for future transplant or surgical grafting. In laboratory experiments, our proprietary freeze-protective compounds have already been used to preserve skin. Silver dollar-sized full thickness shaved skin samples have been removed after saturation with HetaFreeze solution, frozen at liquid nitrogen temperatures and stored for periods ranging from days to weeks. The grafts were then warmed and sewn onto the backs of host animals. Many of these grafts survived. In more recent experiments, rat femoral arteries were frozen to liquid nitrogen temperatures, later thawed and then transplanted into host rats. These grafts were proven to last up to four months. The work was published in the October 2002 issue of the *Annals of Plastic Surgery*.

In other laboratory experiments, our scientists have shown that animals can be revived to consciousness after partial freezing with their blood replaced by HetaFreeze. While this technology has not developed to an extent that allows long term survival of the laboratory subjects and their organs, a better understanding of the effects of partial freezing could allow for extended preservation times for vital organs, skin and blood vessels.

Table of Contents

Other Potential Uses of BioTime Solutions

Isolated regional perfusion of anti-cancer drugs has been used to treat melanoma of the limbs, and inoperable tumors of the liver. We believe that employing such a procedure while the patient is kept in ice-cold blood-substitution may allow high doses of toxic anti-cancer drugs to be directed at inoperable tumors within vital organs, which would selectively be warmed. Keeping the rest of the patient in a cold, blood-substituted state may reduce or eliminate the circulation of the toxic drugs to healthy tissues.

We consider such surgical techniques to be a longer-range goal of our research and development program for hypothermic surgery products. Use of this complex technology in the practice of oncology can occur only after ice-cold blood-substitution has advanced to an appropriate level of safety and effectiveness.

Research and Development Strategy

The greatest portion of our research and development efforts have been devoted to the development of Hextend, PentaLyte and HetaCool for conventional surgery, emergency care, low temperature surgery, and multi-organ preservation. A lesser portion of our research and development efforts have been devoted to developing solutions and protocols for storing organs and tissues at subfreezing temperatures. In the future we may explore other applications of our products and technologies, including cancer chemotherapy. As the first products achieve market entry, more effort will be expended to bring the next tier of products to maturity.

A major focus of our research and development effort has been on products and technology to significantly reduce or eliminate the need for blood products in surgery and trauma care. We have conducted preliminary studies using Hextend in a pressurized oxygen environment and found that Hextend can replace nearly all, or in some cases all, of the circulating blood of rats. Some of the rats were able to live long term without a subsequent transfusion, while others received their own blood back. In other cases, Hextend was used in large volumes in association with a hemoglobin-based oxygen carrier solution approved for veterinary use. When used in this way, rats were able to live long term after all their circulating blood was replaced at normal body temperature while breathing room air.

In still other experiments, rats were allowed to lose approximately half their circulating blood volume, and then allowed to develop and remain in respiratory arrest from 10-18 minutes. They were then resuscitated with Hextend and either ventilated with 100% oxygen, or in a hyperbaric oxygen chamber containing 100% oxygen at two atmospheres above normal pressure. Some of the rats recovered and lived long term after as long as 15 minutes of respiratory arrest. The hyperbaric chamber appeared to have improved the outcome in a number of cases.

These studies indicate that Hextend can potentially be used in a variety of protocols in which donor blood is difficult or impossible to use, such as on the battlefield, or in parts of the world where there is a shortage of disease-free blood.

Table of Contents

Another major focus of our research and development effort has been on products and technology to extend the time animals can be kept cold and blood-substituted, and then revived without physical impairment. An integral part of that effort has been the development of techniques and procedures or protocols for use of our products. A substantial amount of data has been accumulated through animal tests, including the proper surgical techniques, drugs and anesthetics, the temperatures and pressures at which blood and blood replacement solutions should be removed, restored and circulated, solution volume, the temperature range, and times, for maintaining circulatory arrest, and the rate at which the subject should be rewarmed.

Experiments intended to test the efficacy of our low temperature blood replacement solutions and protocols for surgical applications involve replacing the animal s blood with our solution, maintaining the animal in a cold blood-substituted state for a period of time, and then attempting to revive the animal. Experiments for multi-organ preservation involve the maintenance of the animal subjects at cold temperatures for longer periods of time than would be required for many surgical applications, followed by transplant procedures to test the viability of one or more of the subject s vital organs.

We are conducting experiments at hospitals, medical schools, and university research facilities. These collaborative research programs are testing solutions and protocols developed in our laboratories and, in some cases, comparing the efficacy of our products with commercially available FDA-approved products manufactured by other companies. Collaborative gerontological research is being conducted at the University of California at Berkeley. We intend to continue to foster relations with research hospitals and medical schools for the purpose of conducting collaborative research projects because we believe that such projects will introduce our potential products to members of the medical profession and provide us with objective product evaluations from independent research physicians and surgeons.

We have also expanded our product development efforts by initiating an interventive gerontology program focused on the identification of specific factors central to aging of the brain. The program, which is being undertaken with the cooperation of the University of California at Berkeley, is focused on the development of medical and pharmacological strategies to treat senescence-related consequences, and is currently ongoing.

Licensing

Hospira

On April 23, 1997, we entered into a License Agreement with Abbott Laboratories under which we granted to Abbott an exclusive license to manufacture and sell Hextend in the United States and Canada for all therapeutic uses other than those involving hypothermic surgery where the patient s body temperature is lower than 12°C (Hypothermic Use), or replacement of substantially all of a patient s circulating blood volume (Total Body Washout). We retained all rights to manufacture, sell or license Hextend and other products in all other countries.

During 2004, Abbott spun-off of a substantial portion of its hospital products business into a

Table of Contents

new company called Hospira, Inc. Abbott has assigned to Hospira the license to manufacture and market Hextend.

Under the Hospira License Agreement, we may receive up to $40,000,000 in license fees, of which $2,500,000 has been paid to date for the grant of the license and the achievement of certain milestones. Up to $37,500,000 of additional license fees will be payable based upon annual net sales of Hextend, at the rate of 10% of annual net sales if annual net sales exceed $30,000,000 or 5% if annual net sales are between $15,000,000 and $30,000,000. Hospira s obligation to pay licensing fees on sales of Hextend will expire on the earlier of January 1, 2007 or, on a country by country basis, when all patents protecting Hextend in the applicable country expire or any third party obtains certain regulatory approvals to market a generic equivalent product in that country. The relevant patents begin to expire in 2019.

In addition to the license fees, Hospira will pay us a royalty on total annual net sales of Hextend. The royalty rate will be 5% plus an additional .22% for each $1,000,000 of annual net sales, up to a maximum royalty rate of 36%. The royalty rate for each year will be applied on a total net sales basis. Hospira s obligation to pay royalties on sales of Hextend will expire in the United States or Canada when all patents protecting Hextend in the applicable country expire and any third party obtains certain regulatory approvals to market a generic equivalent product in that country.

We have the right to convert Hospira s exclusive license to a non-exclusive license or to terminate the license outright if certain minimum sales and royalty payments are not met. In order to terminate the license outright, we would pay a termination fee in an amount ranging from the milestone payments made by Abbott to an amount equal to three times prior year net sales, depending upon when termination occurs. Hospira has agreed to manufacture Hextend for sale by us in the event that the exclusive license is terminated.

Hospria has certain rights to acquire additional licenses to manufacture and sell our other plasma expander products in the United States and Canada. If Hospira exercises these rights to acquire a license to sell such products for uses other than Hypothermic Surgery or Total Body Washout, in addition to paying royalties, Hospira will be obligated to pay a license fee based upon our direct and indirect research, development and other costs allocable to the new product. If Hospira desires to acquire a license to sell any of our products for use in Hypothermic Surgery or Total Body Washout, the license fees and other terms of the license will be subject to negotiation between the parties. For the purpose of determining the applicable royalty rates, net sales of any such new products licensed by Hospira will be aggregated with sales of Hextend. If Hospira does not exercise its right to acquire a new product license, we may manufacture and sell the product ourselves or we may license others to do so.

Hospira is supplying us with batches of PentaLyte, and will perform characterization and stability studies, and other regulatory support needed for us to file an IND and conduct clinical studies. The foregoing description of the Hospira License Agreement is a summary only and is qualified in all respects by reference to the full text of that License Agreement.

Table of Contents

CJ Corp.

During March 2003, we granted to CJ an exclusive license to manufacture and sell Hextend and PentaLyte in South Korea (the CJ Agreement). Under the CJ Agreement, through December 31, 2004, CJ has paid us a license fee of $800,000 in two installments, less Korean taxes of $132,000 withheld. In connection with these installments, we have paid a total finder s fee of $80,000 to an unrelated third party. CJ began marketing Hextend during the first quarter of 2005. CJ will pay us a royalty on sales of the licensed products. The initial royalty will be $1.30 per 500 ml unit of product sold, but the royalty may increase up to a maximum of $2.60 per 500 ml unit if the price approved by Korea s National Health Insurance increases in the future. CJ is also responsible for obtaining the regulatory approvals required to manufacture and market PentaLyte, including conducting any clinical trials that may be required, and will bear all related costs and expenses.

The foregoing description of the CJ Agreement is a summary only and is qualified in all respects by reference to the full text of the CJ Agreement.

Summit

During December 2004, we entered into an agreement with Summit to develop Hextend and PentaLyte for the Japanese market. Under the terms of the agreement, Summit will apply for regulatory approval to manufacture and market Hextend and PentaLyte in Japan for use at body temperatures above 12°C. Summit has begun by preparing a development plan for Hextend. Summit will fund all laboratory, preclinical and clinical testing and developmental activities regarding the products, and will pay all application filing and similar fees for purposes of obtaining and maintaining regulatory approvals in Japan. Summit will not be obligated to begin to seek regulatory approval for PentaLyte until BioTime completes its Phase II clinical trial of PentaLyte in the United States and makes the results available to Summit.

Under the Agreement, Summit has paid us $300,000, and will pay us an additional $450,000 by April 15, 2005, and an additional $150,000 by October 31, 2005. A portion of the cash payments will be a partial reimbursement of BioTime s development costs of Hextend and a portion will be a partial reimbursement of BioTime s development costs of PentaLyte. Within ten days after we approve Summit s development plan for Hextend, we will pay Summit a one-time fee of $130,000 for Summit s services in preparing the development plan.

BioTime and Summit do not plan to manufacture and market Hextend and PentaLyte themselves. Instead, we will seek to license manufacturing and marketing rights to a third party such as a pharmaceutical company. When Hextend and PentaLyte are licensed and sold in Japan, the revenues from licensing fees, royalties, and net sales, and any other payments made for co-development, manufacturing, or marking rights, will be shared between BioTime and Summit as follows: 40% to us and 60% to Summit. Net sales means the gross revenues from the sale of a product, less rebates, discounts, returns, transportation costs, sales taxes and import/export duties.

We will pay to Summit 8% of all net royalties that we actually receive from the sale of PentaLyte in the United States, plus 8% of any license fees that we receive in consideration of

Table of Contents

granting a license to develop, manufacture and market PentaLyte in the United States. Net royalties means royalty payments received during a calendar year, minus the following costs and expenses incurred during such calendar year: (a) all taxes assessed (other than taxes determined with reference to our net income) and credits given or owed by us in connection with the receipt of royalties on the sale of PentaLyte in the United States, and (b) all fees and expenses payable by us to the United States Food and Drug Administration (directly or as a reimbursement of any licensee) with respect to PentaLyte. In the case of license fees received from Hospira based upon the combined sale of PentaLyte and Hextend, the portion of that license fee that will be deemed to be a paid on account of the sale of PentaLyte will be determined by multiplying the total license fee paid by a fraction, the numerator of which will be the total net sales of PentaLyte in the United States for the applicable period and the denominator of which shall be the total net sales of Hextend and PentaLyte in the United States for the same period.

Either BioTime or Summit may terminate the agreement as follows:

By giving to the other party 60 days prior written notice following the bankruptcy or the insolvency of the other party; or

Upon the breach of any material provision of the agreement by the other party if the breach is not cured within 60 days after written notice thereof to the party in default.

We may terminate the agreement upon 60 days prior written notice at any time following Summit s failure to use diligent efforts to achieve any one of the following milestones: (A) submitting to us for approval a development plan that is substantially complete in all material respects within six months after the signing of the agreement, (B) initiating and conducting to completion clinical studies needed for regulatory approval of either Hextend or PentaLyte in accordance with the timetable included in the development plan we approve; or (C) obtaining regulatory approval of either Hextend or PentaLyte after the clinical studies are complete.

Summit may terminate the agreement at any time upon 90 days prior written notice to us if they determine that they no longer wish to pursue obtaining regulatory approval of Hextend and PentaLyte.

If we become bankrupt or insolvent or breach a material provision of the agreement such that Summit would have the right to terminate the agreement, Summit may elect to keep the agreement in effect, and in lieu of any other remedy that they might have (1) if any of the cash installment payments are not yet payable, Summit will be exempted from making those payments, and (2) our 40% share of revenues will be reduced to 20%.

The foregoing description of the Summit agreement is a summary only and is qualified in all respects by reference to the full text of the Summit agreement.

Table of Contents

Other Licensing Efforts

We are discussing prospective licensing arrangements with other pharmaceutical companies that have expressed their interest in marketing our products abroad. In licensing arrangements that include marketing rights, the participating pharmaceutical company would be entitled to retain a large portion of the revenues from sales to end users and would pay us a royalty on net sales. There is no assurance that any such licensing arrangements can be made.

Manufacturing

Manufacturing Arrangements

Hospira manufactures Hextend for use in the North American market, and NPBI International, BV, a Netherlands company (NPBI), has manufactured lots of Hextend for our use in seeking regulatory approval in Europe. Hospira and NPBI have the facilities to manufacture Hextend and other BioTime products in commercial quantities. If Hospira chooses not to obtain a license to manufacture and market another BioTime product, and if NPBI declines to manufacture BioTime products on a commercial basis, other manufacturers will have to be found that would be willing to manufacture products for us or any licensee of our products.

CJ obtains starch for the manufacture of Hextend from Ajinomoto Corp., and then manufactures the final product itself for use in the Korean market.

Facilities Required

Any products that are used in clinical trials for regulatory approval in the United States or abroad, or that are approved by the FDA or foreign regulatory authorities for marketing, have to be manufactured according to good manufacturing practices at a facility that has passed regulatory inspection. In addition, products that are approved for sale will have to be manufactured in commercial quantities, and with sufficient stability to withstand the distribution process, and in compliance with such domestic and foreign regulatory requirements as may be applicable. The active ingredients and component parts of the products must be medical grade or themselves manufactured according to FDA-acceptable good manufacturing practices.

We do not have facilities to manufacture our products in commercial quantities, or under good manufacturing practices. Acquiring a manufacturing facility would involve significant expenditure of time and money for design and construction of the facility, purchasing equipment, hiring and training a production staff, purchasing raw material and attaining an efficient level of production. Although we have not determined the cost of constructing production facilities that meet FDA requirements, we expect that the cost would be substantial, and that we would need to raise additional capital in the future for that purpose. To avoid the incurrence of those expenses and delays, we are relying on contract and licensing arrangements with established pharmaceutical companies for the production of our products, but there can be no assurance that satisfactory arrangements will be made for any new products that we may develop.

Table of Contents

Raw Materials

Although most ingredients in the products we are developing are readily obtainable from multiple sources, we know of only a few manufacturers of the hydroxyethyl starches that serve as the primary drug substance in Hextend, PentaLyte and HetaCool. Hospira and CJ presently have a source of supply of the hydroxyethyl starch used in Hextend, PentaLyte and HetaCool, and have agreed to maintain a supply sufficient to meet market demand for Hextend in the countries in which they market the product. We believe that we will be able to obtain a sufficient supply of starch for our needs in the foreseeable future, although we do not have supply agreements in place. If for any reason a sufficient supply of hydroxyethyl starch could not be obtained, we or a licensee would have to acquire a manufacturing facility and the technology to produce the hydroxyethyl starch according to good manufacturing practices. We would have to raise additional capital to participate in the development and acquisition of the necessary production technology and facilities.

If arrangements cannot be made for a source of supply of hydroxyethyl starch, we would have to reformulate our solutions to use one or more other starches that are more readily available. In order to reformulate our products, we would have to perform new laboratory testing to determine whether the alternative starches could be used in a safe and effective synthetic plasma volume expander, low temperature blood substitute or organ preservation solution. If needed, such testing would be costly to conduct and would delay our product development program, and there is no certainty that any such testing would demonstrate that an alternative ingredient, even if chemically similar to the one currently used, would be as safe or effective.

Marketing

Hextend is being distributed in the United States and Canada by Hospira and in South Korea by CJ under exclusive licenses from us. Because Hextend is a surgical product, sales efforts must be directed to physicians and hospitals. The Hextend marketing strategy is designed to reach its target customer base through sales calls and an advertising campaign focused on the use of a plasma-like substance to replace lost blood volume and the ability of Hextend to support vital physiological processes.

Hextend competes with other products used to treat or prevent hypovolemia, including albumin, generic 6% hetastarch solutions, and crystalloid solutions. The competing products have been commonly used in surgery and trauma care for many years, and in order to sell Hextend, physicians must be convinced to change their product loyalties. Although albumin is expensive, crystalloid solutions and generic 6% hetastarch solutions sell at low prices. In order to compete with other products, particularly those that sell at lower prices, Hextend will have to be recognized as providing medically significant advantages.

Table of Contents

The FDA has required the manufacturers of 6% hetastarch in saline solutions to change their product labeling by adding a warning stating that those products are not recommended for use as a cardiac bypass prime solution, or while the patient is on cardiopulmonary bypass, or in the immediate period after the pump has been disconnected. We have not been required to add that warning to the labeling of Hextend. An article discussing this issue entitled 6% Hetastarch in Saline Linked To Excessive Bleeding in Bypass Surgery appeared in the December 2002 edition of *Anesthesiology News*. We understand that a number of hospitals have switched from 6% hetastarch in saline to Hextend due to these concerns.

As part of the marketing program, a number of studies have been conducted that show the advantages of receiving Hextend and other BioTime products during surgery. As these studies are completed, the results are presented at medical conferences and articles written for publication in medical journals. We are also aware of independent studies using Hextend that are being conducted by physicians and hospitals who may publish their findings in medical journals or report their findings at medical conferences. The outcome of future medical studies and timing of the publication or presentation of the results could have an effect on Hextend sales.

Government Regulation

The FDA and foreign regulatory authorities will regulate our proposed products as drugs, biologicals, or medical devices, depending upon such factors as the use to which the product will be put, the chemical composition and the interaction of the product on the human body. In the United States, products that are intended to be introduced into the body, such as blood substitute solutions for low temperature surgery and plasma expanders, will be regulated as drugs and will be reviewed by the FDA staff responsible for evaluating biologicals.

Our domestic human drug products will be subject to rigorous FDA review and approval procedures. After testing in animals, an Investigational New Drug Application (IND) must be filed with the FDA to obtain authorization for human testing. Extensive clinical testing, which is generally done in three phases, must then be undertaken at a hospital or medical center to demonstrate optimal use, safety and efficacy of each product in humans. Each clinical study is conducted under the auspices of an independent Institutional Review Board (IRB). The IRB will consider, among other things, ethical factors, the safety of human subjects and the possible liability of the institution. The time and expense required to perform this clinical testing can far exceed the time and expense of the research and development initially required to create the product. No action can be taken to market any therapeutic product in the United States until an appropriate New Drug Application (NDA) has been approved by the FDA. Even after initial FDA approval has been obtained, further studies may be required to provide additional data on safety or to gain approval for the use of a product as a treatment for clinical indications other than those initially targeted. In addition, use of these products during testing and after marketing could reveal side effects that could delay, impede or prevent FDA marketing approval, resulting in a FDA-ordered product recall, or in FDA-imposed limitations on permissible uses.

Table of Contents

The FDA regulates the manufacturing process of pharmaceutical products, requiring that they be produced in compliance with good manufacturing practices. See Manufacturing. The FDA also regulates the content of advertisements used to market pharmaceutical products. Generally, claims made in advertisements concerning the safety and efficacy of a product, or any advantages of a product over another product, must be supported by clinical data filed as part of an NDA or an amendment to an NDA, and statements regarding the use of a product must be consistent with the FDA approved labeling and dosage information for that product.

Sales of pharmaceutical products outside the United States are subject to foreign regulatory requirements that vary widely from country to country. Even if FDA approval has been obtained, approval of a product by comparable regulatory authorities of foreign countries must be obtained prior to the commencement of marketing the product in those countries. The time required to obtain such approval may be longer or shorter than that required for FDA approval.

Patents and Trade Secrets

We currently hold 21 issued United States patents having composition and methods of use claims covering our proprietary solutions, including Hextend and PentaLyte. The most recent U.S. patents were issued during 2002. Some of our allowed claims in the United States, which include the composition and methods of use of Hextend and PentaLyte, are expected to remain in force until 2019. Forty patents covering certain of our solutions have also been issued in several of the countries of the European Union, Australia, Israel, Russia, Hong Kong, South Africa, Japan, China, Taiwan, Singapore and South Korea. Additional patent applications have been filed in the United States and numerous other countries for Hextend, PentaLyte and other solutions. Certain device patents describing our hyperbaric (high pressure oxygen) chamber, and proprietary microcannula (a surgical tool) have also been issued in the United States and overseas, both of which - although only used in research so far - have possible indications in clinical medicine.

There is no assurance that any additional patents will be issued. There is also the risk that any patents that we hold or later obtain could be challenged by third parties and declared invalid or infringing of third party claims. Further, the enforcement of patent rights often requires litigation against third party infringers, and such litigation can be costly to pursue.

In addition to patents, we rely on trade secrets, know-how and continuing technological advancement to maintain our competitive position. We have entered into intellectual property, invention and non-disclosure agreements with our employees and it is our practice to enter into confidentiality agreements with our consultants. There can be no assurance, however, that these measures will prevent the unauthorized disclosure or use of our trade secrets and know-how or that others may not independently develop similar trade secrets and know-how or obtain access to our trade secrets, know-how or proprietary technology.

Table of Contents

Competition

Our plasma volume expander solutions will compete with products currently used to treat or prevent hypovolemia, including albumin, other colloid solutions, and crystalloid solutions presently manufactured by established pharmaceutical companies, and with human blood products. Some of these products, in particular crystalloid solutions, are commonly used in surgery and trauma care and sell at low prices. In order to compete with other products, particularly those that sell at lower prices, our products will have to be recognized as providing medically significant advantages. Like Hextend, the competing products are being manufactured and marketed by established pharmaceutical companies that have large research facilities, technical staffs and financial and marketing resources. B.Braun presently markets Hespan, an artificial plasma volume expander containing 6% hetastarch in saline solution. Hospira and Baxter International manufacture and sell a generic equivalent of Hespan. As a result of the introduction of generic plasma expanders intended to compete with Hespan, competition in the plasma expander market has intensified and wholesale prices have declined. Hospira, which markets Hextend in the United States and Canada, is also the leading seller of generic 6% hetastarch in saline solution. Aventis Behring, LLC, Baxter International, and Alpha Therapeutics sell albumin, and Hospira, Baxter International and B.Braun sell crystalloid solutions.

To compete with new and existing plasma expanders, we have developed products that contain constituents that may prevent or reduce the physiological imbalances, bleeding, fluid overload, edema, poor oxygenation, and organ failure that can occur when competing products are used. To compete with existing organ preservation solutions, we have developed solutions that can be used to preserve all organs simultaneously and for long periods of time.

A number of other companies are known to be developing hemoglobin and synthetic red blood cell substitutes and technologies. Our products have been developed for use either before red blood cells are needed or in conjunction with the use of red blood cells. In contrast, hemoglobin and other red blood cell substitute products are designed to remedy ischemia and similar conditions that may result from the loss of oxygen-carrying red blood cells. Those products would not necessarily compete with our products unless the oxygenating molecules were included in solutions that could replace fluid volume and prevent or reduce the physiological imbalances as effectively as our products. Generally, red blood cell substitutes are more expensive to produce and potentially more toxic than Hextend and PentaLyte.

The competition we face is likely to intensify further as new products and technologies reach the market. Superior new products are likely to sell for higher prices and generate higher profit margins once acceptance by the medical community is achieved. Those companies that are successful in introducing new products and technologies to the market first may gain significant economic advantages over their competitors in the establishment of a customer base and track record for the performance of their products and technologies. Such companies will also benefit from revenues from sales that could be used to strengthen their research and development, production, and marketing resources. All companies engaged in the medical products industry face the risk of obsolescence of their products and technologies as more advanced or cost effective products and technologies are developed by their competitors. As the industry matures, companies will compete based upon the performance and cost effectiveness of their products.

Table of Contents

Employees

As of December 31, 2004, we employed nine persons on a full-time basis and one person on a part-time basis. Four full-time employees hold Ph.D. Degrees in one or more fields of science.

Risk Factors

Some of the factors that could materially affect our operations and prospects are discussed below. There may be other factors that are not mentioned here or of which we are not presently aware that could also affect our operations.

We May Not Succeed In Marketing Our Products Due to the Availability of Competing Products

Our ability to generate operating revenue depends upon our success in developing and marketing our products. We may not succeed in marketing our products and we may not receive sufficient revenues from product sales to meet our operating expenses or to earn a profit. In this regard, sales of Hextend to date have not been sufficient to generate an amount of royalties or licensing fees sufficient to cover our operating expenses. Factors that affect the marketing of our products include the following:

Hextend and our other plasma expander products will compete with other products that are commonly used in surgery and trauma care and sell at lower prices.

In order to compete with other products, particularly those that sell at lower prices, our products will have to provide medically significant advantages.

Physicians and hospitals may be reluctant to try a new product due to the high degree of risk associated with the application of new technologies and products in the field of human medicine.

Competing products are being manufactured and marketed by established pharmaceutical companies. For example, B. Braun/McGaw presently markets Hespan, an artificial plasma volume expander, and Hospira and Baxter International, Inc. manufacture and sell a generic equivalent of Hespan.

There also is a risk that our competitors may succeed in developing safer or more effective products that could render our products and technologies obsolete or noncompetitive.

We Will Spend a Substantial Amount of Our Capital on Research and Development But We Might Not Succeed in Developing Products and Technologies That Are Useful In Medicine.

We are attempting to develop new medical products and technologies.

Many of our experimental products and technologies have not been applied in human medicine and have only been used in laboratory studies on animals. These new products and

Table of Contents

technologies might not prove to be safe and efficacious in the human medical applications for which they were developed.

The experimentation we are doing is costly, time consuming and uncertain as to its results.

If we are successful in developing a new technology or product, refinement of the new technology or product and definition of the practical applications and limitations of the technology or product may take years and require the expenditure of large sums of money. For example, we spent approximately $5,000,000 on research and development of Hextend before commencing clinical trials on humans during October 1996. The cost of completing the Hextend clinical trials and preparing our FDA application was approximately $3,000,000. These costs exclude corporate overhead included in general and administrative costs in our financial statements.

Future clinical trials of new products such as PentaLyte may take longer and may be more costly than our Hextend clinical trials. The FDA permitted us to proceed directly into a Phase III clinical trial of Hextend involving only 120 patients because the active ingredients in Hextend had already been approved for use by the FDA in other products$ Because PentaLyte contains a starch that has not been approved by the FDA for use in a plasma volume expander, we have had to complete a Phase I clinical trial of PentaLyte, and we will have to complete a Phase II clinical trial in addition to a Phase III trial, that will involve more patients than our Hextend trials. We do not yet know the scope or cost of the clinical trials that the FDA will require for PentaLyte or the other products we are developing.

We Have Incurred Operating Losses Since Inception and We Do Not Know If We Will Attain Profitability

Our net losses for the fiscal years ended December 31, 2002, 2003 and 2004 were $2,844,932, $1,742,074, and $3,085,324, respectively. Our ability to generate sufficient operating revenue to earn a profit depends upon our success in developing and marketing or licensing our products and technology for medical use.

We Might Not Be Able To Raise Additional Capital Needed To Pay Our Operating Expenses

We plan to continue to incur substantial research, product development, and regulatory expenses, and we will need to raise additional capital to pay operating expenses until we are able to generate sufficient revenues from product sales, royalties, and license fees. We have not received an amount of royalties and licensing fees from the sale of Hextend sufficient to cover our operating expenses. As of December 31, 2004, we had $1,370,762 of cash and cash equivalents on hand. At our current rate of spending, our cash on hand, reimbursable product development fees receivable from Summit, and anticipated royalties from Hospira, will last approximately 15 months. The amount and pace of research and development work that we can do or sponsor, and our ability to commence and complete clinical trials required to obtain FDA and foreign regulatory approval of our products, depends upon the amount of money we have. We plan to spend at least $1,000,000 on clinical trials of PentaLyte. The costs of clinical trials and future research work are not presently

Table of Contents

determinable due to many factors, including the inherent uncertainty of those costs and the uncertainty as to the timing, source, and amount of capital that will become available for those projects. We have already curtailed the pace of our product development efforts due to the limited amount of funds available, and we may have to postpone further laboratory and clinical studies, unless our cash resources increase through a growth in revenues or additional equity investment or borrowing. Although we will continue to seek licensing fees from pharmaceutical companies for licenses to manufacture and market our products abroad, it is likely that additional sales of equity or debt securities will be required to meet our short-term capital needs. Sales of additional equity securities could result in the dilution of the interests of present shareholders. We may not be able to raise a sufficient amount of additional funds to permit us to develop and market our products. Unless we are able to generate sufficient revenue or raise additional funds when needed, it is likely that we will be unable to continue our planned activities, even if we are making progress with our research and development projects.

If We Are Unable To Enter Into Additional Licensing Or Manufacturing Arrangements, We May Have to Incur Significant Expense To Acquire Manufacturing Facilities And A Marketing Organization

We presently do not have adequate facilities or resources to manufacture our products and the ingredients used in our products. We plan to enter into arrangements with pharmaceutical companies for the production and marketing of our products. We have granted Hospira an exclusive license to manufacture and market Hextend in the United States and Canada, and we have granted CJ an exclusive license to manufacture and market Hextend and PentaLyte in Korea. We have also entered into an agreement with Summit to develop Hextend and PentaLyte for the Japanese market. Hospira s obligation to pay royalties on sales of Hextend will expire in the United States or Canada when all patents protecting Hextend in the applicable country expire (this will begin to occur in 2019) and any third party obtains certain regulatory approvals to market a generic equivalent product in that country. CJ will not be able to commence sales of Hextend or PentaLyte in Korea until they obtain pricing approval. CJ s obligation to pay royalties on sales of Hextend and PentaLyte, respectively, will expire when the patents protecting those products in Korea expire. Although a number of other pharmaceutical companies have expressed their interest in obtaining licenses to manufacture and market our products in other countries, we might not be successful in negotiating other licensing arrangements. If licensing or manufacturing arrangements cannot be made on acceptable terms, we will have to construct or acquire our own manufacturing facilities and establish our own marketing organization, which would entail significant expenditures of time and money.

Our Business Could Be Adversely Affected If We Lose the Services Of The Key Personnel Upon Whom We Depend

During 2003, we lost our Chairman and Chief Executive Officer, Paul Segall, who passed away in June. Following the passing of Dr. Segall, we formed the Office of the President, a three-person executive office comprised of the three remaining founders: Dr. Hal Sternberg, Dr. Harold Waitz, and Judith Segall. The Office of the President is charged with assuming those executive duties previously attended to by Dr. Segall. We believe that the Office of the President has provided a smooth management transition without entailing additional operating costs. So long as the Office of

Table of Contents

the President meets our needs, we will defer appointing a new chief executive officer until our cash flow improves and we have sufficient capital to finance the additional executive compensation expenses. It is not possible to determine what impact, if any, this will have on our operations. Scientific concerns, such as product development and laboratory research, will continue to be addressed primarily by Dr. Sternberg, the Vice-President of Research, who worked very closely with Dr. Segall for many years on all matters of scientific importance and strategy.

The loss of the services of any of our other executive officers could have a material adverse effect on us. We do not presently have long-term employment agreements with any of our executive officers because our present financial situation precludes us from making long-term compensation commitments in amounts commensurate with prevailing salaries of executive officers of similar companies in the San Francisco Bay Area. This may also limit our ability to engage a new Chief Executive Officer.

Risks Related to Our Industry

We will face certain risks arising from regulatory, legal, and economic factors that affect our business and the business of other pharmaceutical development companies. Because we are a small company with limited revenues and limited capital resources, we may be less able to bear the financial impact of these risks than larger companies that have substantial income and available capital.

If We Do Not Receive FDA and Other Regulatory Approvals We Will Not Be Permitted To Sell Our Products

The products that we develop cannot be sold until the FDA and corresponding foreign regulatory authorities approve the products for medical use. Hextend has been approved for use in the United States, Canada and Korea only. We are beginning a Phase II clinical trial of PentaLyte to demonstrate that PentaLyte can be used safely and effectively as a plasma volume expander in surgery.

The need to obtain regulatory approval to market a new product means that:

- We will have to conduct expensive and time consuming clinical trials of new products. We plan to spend at least $1,000,000 for Phase II clinical trials of PentaLyte. However, the full cost of completing a Phase II clinical trial and future Phase III clinical trials necessary to obtain FDA approval of PentaLyte cannot be presently determined and may exceed our financial resources.

- We will incur the expense and delay inherent in seeking FDA and foreign regulatory approval of new products. For example, 12 months elapsed between the date we filed our application to market Hextend in the United States and the date on which our application was approved. Approximately 36 months elapsed between the date we filed our application for approval to market Hextend in Canada, and the date on which our application was approved, even though we did not have to conduct any additional clinical trials.

Table of Contents

A product that is approved may be subject to restrictions on use.

The FDA can recall or withdraw approval of a product if problems arise.

We will face similar regulatory issues in foreign countries.

Our Patents May Not Protect Our Products From Competition

We have patents in the United States, Canada, several of the European Union countries, Australia, Israel, Russia, South Africa, South Korea, Japan, Hong Kong, Taiwan, China, and Singapore, and have filed patent applications in other foreign countries, for certain products, including Hextend, HetaCool, and PentaLyte. We might not be able to obtain any additional patents, and any patents that we do obtain might not be comprehensive enough to provide us with meaningful patent protection. Also, there will always be a risk that our competitors might be able to successfully challenge the validity or enforceability of any patent issued to us. The costs required to uphold the validity and prevent infringement of any patent issued to us could be substantial, and we might not have the resources available to defend our patent rights.

The Price and Sale of Our Products May Be Limited By Health Insurance Coverage And Government Regulation

Success in selling our products may depend in part on the extent to which health insurance companies, HMOs, and government health administration authorities such as Medicare and Medicaid will pay for the cost of the products and related treatment. Presently, most health insurance plans and HMOs will pay for Hextend when it is used in a surgical procedure that is covered by the plan. However, until we actually introduce a new product into the medical market place we will not know with certainty whether adequate health insurance, HMO, and government coverage will be available to permit the product to be sold at a price high enough for us to generate a profit. In some foreign countries, pricing or profitability of health care products is subject to government control which may result in low prices for our products. In the United States, there have been a number of federal and state proposals to implement similar government controls, and new proposals are likely to be made in the future.

Risks Pertaining to Our Common Shares

Before purchasing BioTime common shares or warrants, investors should consider the price volatility of our shares and warrants and the fact that we do not pay dividends.

Because We Are a Drug Development Company, The Price Of Our Stock May Rise And Fall Rapidly

The market price of BioTime shares and warrants, like that of the shares of many biotechnology companies, has been highly volatile. The price of BioTime shares and warrants may rise rapidly in response to certain events, such as the commencement of clinical trials of an experimental new drug, even though the outcome of those trials and the likelihood of ultimate FDA approval remain

Table of Contents

uncertain. Similarly, prices of BioTime shares and warrants may fall rapidly in response to certain events such as unfavorable results of clinical trials or a delay or failure to obtain FDA approval. The failure of our earnings to meet analysts expectations could result in a significant rapid decline in the market price of our common shares and warrants. In addition, the stock market has experienced and continues to experience extreme price and volume fluctuations which have affected the market price of the equity securities of many biotechnology companies and which have often been unrelated to the operating performance of these companies. Broad market fluctuations, as well as general economic and political conditions, may adversely affect the market price of the common shares and warrants.

Because BioTime Currently Does Not Meet Certain Exchange Continued Listing Requirements the Shares and Warrants Could Be Delisted

We are presently not in compliance with some of the American Stock Exchange (the AMEX) continued listing standards in that we have shareholders equity of less than $6,000,000 and have incurred losses during each of the last four years, which could lead the AMEX to delist BioTime shares and warrants. The AMEX has granted us an extension of time until April 2005 to regain compliance with the continued listing standards based upon a plan of compliance that we submitted. In order to comply with the continued listing standards, we need to have a total market capitalization (based upon the market price of our outstanding common shares) of at least $50,000,000 (of which $15,000,000 must be part of the public float) or we must have positive shareholders equity of at least $6,000,000 by April 2005. At December 31, 2004, we had shareholders equity of $344,770, and the operating losses that we will incur during the first quarter of 2005 will reduce our shareholders equity. Failure to regain compliance with the continued listing standards by the end of the extension period could result in our common shares and warrants being delisted from the AMEX. We plan to use our best efforts to maintain the AMEX listing of our common shares, but if the common shares were to be delisted by the AMEX, the market value and liquidity for the common shares would be adversely affected and it could be more difficult for us to raise capital in the future. If the common shares were no longer traded on the AMEX, they could be traded in the over-the-counter market on an electronic bulletin board established for securities that do not meet the listing requirements of the Nasdaq stock market or the major national securities exchanges. Also, if our common shares were to be delisted by the AMEX, the warrants would be delisted as well.

If the Common Shares and Warrants Are Delisted from the AMEX They Would Be Subject to the So-called Penny Stock Rules That Impose Restrictive Sales Practice Requirements

If the common shares and warrants are delisted from the AMEX they would be subject to the so-called penny stock rules that impose restrictive sales practice requirements on broker-dealers who sell penny stocks to persons other than established customers and accredited investors. An accredited investor generally is a person who has a net worth in excess of $1,000,000 or individual annual income exceeding $200,000, or joint annual income with a spouse exceeding $300,000. For transactions covered by this rule, the broker-dealer must make a special suitability determination for the purchaser and must have received the purchaser s written consent to the transaction prior to sale.

Table of Contents

This means that delisting could affect the ability of shareholders to sell their common shares and warrants in the secondary market.

The Securities and Exchange Commission (the Commission) has adopted regulations that define a penny stock to be any equity security that has a market price of less than $5.00 per share or an exercise price of less than $5.00 per share, subject to certain exceptions. AMEX listed securities are exempt from the definition of penny stock. If a transaction involving a penny stock is not exempt from the Commission s rule, a broker-dealer must deliver a disclosure schedule relating to the penny stock market to the investor prior to a transaction. The broker-dealer also must disclose the commissions payable to both the broker-dealer and the registered representative, current quotations for the penny stock, and, if the broker-dealer is the sole market-maker, the broker-dealer must disclose this fact and the broker-dealer s presumed control over the market. Finally, monthly statements must be sent disclosing recent price information for the penny stock held in the customer s account and information on the limited market in penny stocks.

Because We Do Not Pay Dividends, Our Stock May Not Be A Suitable Investment For Anyone Who Needs To Earn Dividend Income

We do not pay cash dividends on our common shares. For the foreseeable future we anticipate that any earnings generated in our business will be used to finance the growth of BioTime and will not be paid out as dividends to our shareholders. This means that our stock may not be a suitable investment for anyone who needs to earn income from their investments.

BioTime Warrants Cannot Be Exercised Unless a Registration Statement is in Effect Under Federal and State Securities Laws.

A registration statement under the Securities Act of 1933, as amended, must be in effect in order for warrant holders to exercise their BioTime warrants. This means that we will have to periodically update our registration statement and prospectus by filing post-effective amendments or by filing our annual report on Form 10-K, our quarterly reports on Form 10-Q, and current reports on Form8-K as required under the Securities Exchange Act of 1934, as amended. We intend to use our best efforts to keep our registration statement effective. However, if we are unable to do so for any reason, warrant holders would not be able to exercise their warrants, even if the market price of our common shares was then greater than the exercise price.

So long as our common shares are listed on the AMEX, they will be exempt from registration or qualification under state securities laws, but that exemption would be lost if the shares were to be delisted from the AMEX and not subsequently listed on the Nasdaq Stock Market or a regional securities exchange for which an exemption would apply under the various state laws. If our common shares are not exempt from state registration or qualification, most states will require us to obtain a permit, issued through an application for registration or qualification, and to maintain that permit in effect in order for warrant holders in the state to exercise their warrants.

Table of Contents

Item 2. Facilities.

We occupy our office and laboratory facility in Berkeley, California under a lease that will expire on March 31, 2005. We presently occupy approximately 8,890 square feet of space and pay rent in the amount of $11,696 per month. The facility we occupy has been sold and we are currently considering options for a new location.

Item 3. Legal Proceedings.

We are not presently involved in any material litigation or proceedings, and to our knowledge no such litigation or proceedings are contemplated.

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

BioTime held its annual meeting of shareholders on December 10, 2004. At the meeting, the shareholders elected directors and voted to approve an amendment to our 2002 Stock Option Plan and to ratify the appointment of BDO Seidman, LLP as our independent auditors.

The following table presents the results of the vote for the election of directors.

Director	Votes For	Votes Withheld
Milton H. Dresner	15,961,285	219,222
Katherine Gordon	15,952,703	227,804
Valeeta Gregg	15,974,851	205,656
Judith Segall	15,991,495	189,012
Hal Sternberg	15,996,615	183,892
Harold Waitz	15,996,665	183,842
Michael D. West	15,962,602	217,905

There were 7,393,396 votes for the approval of the amendment of our 2002 Stock Option Plan, 421,932 votes against, 19,076 abstentions, and 8,346,103 broker non-votes. The amendment increased by 1,000,000 the number of common shares available under the Plan.

There were 16,121,273 votes for the ratification of the appointment of BDO Seidman, LLP as our independent auditors, 37,995 votes against, and 21,239 abstentions.

Table of Contents

Part II

Item 5. Market for Registrant s Common Equity and Related Stockholder Matters.

BioTime common shares have been trading on the American Stock Exchange since August 31, 1999, and traded on the Nasdaq National Market from April 28, 1998 to August 30,1999, and on the Nasdaq SmallCap Market from March 5, 1992 through April 27, 1998. The closing price of our common shares on the AMEX on March 4, 2005 was $1.26.

Our common share purchase warrants have been trading on the AMEX since January 26, 2004. The closing price of our warrants on the AMEX on March 4, 2005 was $0.32.

The following table sets forth the range of high and low sale prices for the common shares for the fiscal years ended December 31, 2003 and 2004 based on transaction data as reported by the AMEX.

Quarter Ended	High	Low