EMISPHERE TECHNOLOGIES INC
Form S-3/A
June 16, 2005

Registration No. 333-125180

# SECURITIES AND EXCHANGE COMMISSION

**WASHINGTON, D.C. 20549**

**Amendment No. 1**

# FORM S-3

**REGISTRATION STATEMENT**
***UNDER***
***THE SECURITIES ACT OF 1933***

# EMISPHERE TECHNOLOGIES, INC.

**(Exact name of Registrant as specified in its charter)**

| **DELAWARE** | **2834** | **13-3306985** |
|---|---|---|
| **(State or other jurisdiction of incorporation or organization)** | **(Primary Standard Industrial Classification Code Number)** | **(I.R.S. Employer Identification No.)** |

**765 Old Saw Mill River Road, Tarrytown, New York 10591**
**(914) 347-2220**

**(Address, including zip code, and telephone number, including area code, of Registrant s principal executive offices)**

**MICHAEL M. GOLDBERG, M.D.**
**Chairman of the Board and Chief Executive Officer**
**Emisphere Technologies, Inc.**
**765 Old Saw Mill River Road, Tarrytown, New York 10591**
**(914) 347-2220**

**(Name, address, including zip code, and telephone number, including area code, of agent for service)**

***Copies of Communications to:***
**Robert A. Cantone, Esq.**
**Proskauer Rose LLP**
**1585 Broadway, New York, New York 10036-8299**
**(212) 969-3000**

**Approximate date of commencement of proposed sale to the public:** From time to time or at one time after the effective date of this Registration Statement as determined by the Registrant.

If the only securities being registered on this Form are being offered pursuant to dividend or interest or interest investment plans, please check the following box. o

If any of the securities being registered on this Form are to be offered on a delayed or continuous basis pursuant to Rule 415 under the Securities Act of 1933, other than securities offered only in connection with dividend or interest reinvestment plans, check the following box. x

If this Form is filed to register additional securities for an offering pursuant to Rule 462(b) under the Securities Act, please check the following box and list the Securities Act registration statement number of the earlier effective registration statement for the same offering. o

If this Form is a post-effective amendment filed pursuant to Rule 462(c) under the Securities Act, check the following box and list the Securities Act registration statement number of the earlier effective registration statement for the same offering. o

If delivery of the prospectus is expected to be made pursuant to Rule 434, please check the following box. o

**The Registrant hereby amends this Registration Statement on such date or dates as may be necessary to delay its effective date until the Registrant shall file a further amendment which specifically states that this Registration Statement shall thereafter become effective in accordance with Section 8(a) of the Securities Act of 1933 as amended or until the Registration Statement shall become effective on such date as the Securities and Exchange Commission, acting pursuant to said Section 8(a), may determine.**

**CALCULATION OF REGISTRATION FEE**

| Title of Each Class of Securities To Be Registered | Amount To Be Registered (1)(2) | Proposed Maximum Aggregate Offering Price Per Share (1) | Proposed Maximum Aggregate Offering Price (1)(2) | Amount of Registration Fee |
|---|---|---|---|---|
| Common Stock, par value $.01 per share | 3,553,039 | $ 3.46 | $ 12,293,515 | $ 1,447(1) |
| Common Stock issuable upon exercise of Warrants | 250,000 | $ 3.8111(3) | $ 952,750 | $ 112 |
| Total | 3,803,039 | | $ 13,246,265 | $ 1,559(4) |

(1) In accordance with Rule 457(c), the aggregate offering price of our stock is estimated solely for calculating the registration fees due for this filing. For the initial filing of this Registration Statement, this estimate was based on the average of the high and low sales price of our stock reported by the Nasdaq National Market on May 13, 2005, which was $3.46 per share.

(2) This Registration Statement shall also cover any additional shares of common stock which become issuable by reason of any stock dividend, stock split or other similar transaction effected without the receipt of consideration which results in an increase in the number of the outstanding shares of common stock of the registrant.

(3) Represents the exercise price of the Warrants.

(4) A fee of $1,559 has previously been paid by registrant and no additional fee is due at this time.

**Prospectus**

**3,803,039 shares**

**Common Stock**

This prospectus relates to resale of up to 3,553,039 shares of our common stock that we may issue to the selling shareholder named herein pursuant to a structured secondary offering facility arrangement that we entered into with the selling shareholder, and up to 250,000 shares of our common stock that are issuable upon exercise of a warrant that we issued to the selling shareholder. The selling shareholder will receive all of the proceeds from the sale of shares of common stock hereunder. We will receive the proceeds from the sale of shares of common stock to the selling shareholder under the structured secondary offering facility and from any cash exercise of the warrant by the selling shareholder.

Our common stock is traded on the Nasdaq National Market under the symbol EMIS. On May 13, 2005, the last reported sale price for our common stock on the Nasdaq National Market was $3.40 per share.

**Investing in our common stock involves significant risks. See Risk Factors beginning on page 7.**

**Neither the Securities and Exchange Commission nor any state securities commission has approved or disapproved of these securities or determined if this prospectus is truthful or complete. Any representation to the contrary is a criminal offense.**

June 16, 2005

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You should rely only on the information contained or incorporated by reference in this prospectus and any prospectus supplement. We have not authorized anyone to provide you with different information. We are not making an offer to sell these securities in any state where the offer is not permitted. You should not assume that the information contained in this prospectus or any prospectus supplement is accurate as of any date other than the date on the front cover of those documents.

Unless the context otherwise requires, the terms we, our, us, the Company and Emisphere refer to Emisphere Technologies, Inc.

## PROSPECTUS SUMMARY

*You should read the following summary together with the more detailed information, including the consolidated financial statements and the notes to the consolidated financial statements and other information, included, or incorporated by reference, in this prospectus.*

## OUR COMPANY

### Overview

Emisphere Technologies, Inc. is a biopharmaceutical company developing products using its proprietary *e*lig*e*n® drug delivery technology. We apply this technology to orally administer therapeutic macromolecules that are not currently available in oral form. We believe that our drug delivery technology may lead to greater patient convenience and compliance, and in some cases, improved therapies. As of March 31, 2005, we have 78 patents issued and 74 applications pending in the United States, and patent and patent applications covering product candidates in the anticipated markets for such products.

We have product candidates in development across a broad range of therapeutic areas, including cardiovascular disease, diabetes, osteoporosis, growth disorders, asthma and allergies, obesity and infectious diseases. Also, we have partnerships with world-leading pharmaceutical companies. To date, we have devoted substantially all of our efforts and resources to research and development and have not generated sales of any of our products. For more information about our financial condition and prospects, please refer to the section entitled Certain Other Recent Developments below.

### Oral Drug Delivery

The pharmaceutical industry has been working for many years to overcome the challenge of delivering therapeutic macromolecules orally, with limited success. Therapeutic macromolecules are comprised of proteins and other large molecules that, if ingested, would degrade in the stomach or intestine before they are absorbed into the bloodstream. Therefore, they are administered by injection or by intravenous means (collectively referred to as parenteral administration or parenterally ). Parenteral administration is believed to be less desirable than oral administration for many reasons, including patient discomfort, inconvenience and risk of infection. In addition, parenteral therapies often include the cost of administration by a healthcare professional, since they typically require administration in hospitals or doctors offices. Poor patient acceptance of, and compliance with parenteral therapies, can lead to increased incidences of medical complications.

Our business strategy is based upon our belief that the development of an efficient and safe oral delivery system for therapeutic macromolecules that are currently administered parenterally represents a significant commercial opportunity. We believe that, given the choice, patients reluctant to commence or comply with parenteral therapies would embrace an oral alternative, thus spurring market expansion for therapeutic macromolecules.

### Our Technology

Our oral delivery technology, the *e*lig*e*n® technology, is based upon proprietary, synthetic chemical compounds, that we refer to as EMISPHERE® delivery agents (or carriers ), which facilitate the transport of therapeutic macromolecules across biological membranes, such as the membranes of the small intestine. We believe that the *e*lig*e*n® technology uses a natural transport process in the body to accomplish this objective. Our hypothesis is that EMISPHERE® delivery agents change the shape of the macromolecule without changing its chemical composition, and that the changed shape allows the macromolecule to cross the membrane. Once the therapeutic macromolecule crosses the membrane, the EMISPHERE® delivery agent separates from the macromolecule, which then reestablishes its natural shape, allowing it to remain therapeutically active. Using this technology, we have orally delivered heparin, low molecular weight heparin, insulin, PTH 1-34, rhGH, salmon calcitonin, a small molecule compound and cromolyn in humans and over 40 other compounds in laboratory animals.

**Competitive Advantages**

We believe that the *e*lig*e*n® technology has competitive advantages, including:

EMISPHERE® delivery agents are applicable across a diverse group of molecules such as proteins, peptides, carbohydrates, polar organics and other compounds;

Oral drug delivery using the *e*lig*e*n® technology does not rely upon the addition of other agents that can have adverse effects on the intestinal membranes or digestion;

EMISPHERE® delivery agents are adaptable to various types of oral formulations, including solutions, suspensions, tablets and capsules; and the technology may be compatible with controlled release dosage forms; and

We believe that the technology and manufacturing equipment required to produce EMISPHERE® delivery agent material in commercial quantities is readily available.

We have research and development collaborations and licensing agreements with corporate partners to provide development and commercialization services relating to certain of our products under development. Under these agreements, we have granted licenses or the rights to obtain licenses to our oral drug delivery technology. In return, we are entitled to reimbursement for research and development costs that we incur, payments upon the achievement of milestones, and royalties on the sales of successfully commercialized products.

**Lead Product Candidates**

*Oral Heparin*

Heparin is an anti-coagulant/anti-thrombotic used to prevent blood clots (deep vein thrombosis or DVT ) following major surgical procedures lasting longer than 30 minutes. According to the website www.dvt.org (maintained by the University of Massachusetts Medical School), the risk of developing DVT following major surgery can range as high as seventy percent. Recent studies published in *The Lancet* and the *Journal of Bone and Joint Surgery* support longer term use of heparin for prophylaxis to cover the high-risk periods for forming blood clots following major surgery. Published reports that we refer to below also suggest that unfractionated heparin ( UFH ) may have utility for indications other than anti-coagulation and anti-thrombosis. We believe that potential longer term use of heparin as a prophylaxis and other potential indications for unfractionated heparin could present opportunities for our solid oral heparin and low molecular weight heparin candidates.

On the basis of our extensive clinical testing with a liquid form of oral UFH, we believe we are well positioned to rapidly bring forward a new solid formulation into late-stage clinical trials. In the first quarter of 2004, we selected tablet and capsule prototypes for production and clinical testing in the United States. In June 2004, we completed a Phase I clinical trial to evaluate these tablet and capsule dosage forms. In August 2004, we announced that we selected a soft gelatin capsule formulation of UFH based on the results of the Phase I trial. We are currently seeking U.S. Food and Drug Administration ( FDA ) approval to begin Phase III testing. Later stage clinical trials may not support the findings of our early stage trials.

*Oral Insulin*

Injectable insulin is widely used in the treatment of Type 1 and Type 2 diabetic patients. According to the publicly filed annual reports of the leading insulin manufacturers, worldwide sales of insulin exceeded $5.8 billion in 2003. Approximately 40% of all Type 2 diabetics use insulin to control the disease, accounting for approximately 50% of total insulin use. Although many more Type 2 diabetics could benefit from insulin therapy, use of the drug has been limited because it is administered by injection. We believe that a successful oral insulin therapy would facilitate compliance for diabetic patients who are not diligent with their prescribed injection regimens, and enable those patients adverse to injections to adopt insulin therapy at an earlier stage of the disease.

Because we believe that an oral form of insulin, if approved, would gain significant market share, we have focused significant resources on its development. Most recently, we have developed a tablet dosage form of insulin for oral administration that was tested in a 13-patient Phase I clinical trial designed to provide information related to efficacy, not effectiveness, completed in January 2004. Data from this trial indicated that repeated administration of our oral insulin was not associated with clinically relevant hypoglycemic events, an adverse complication that is often associated with injected insulin and other anti-diabetic treatments. There were no adverse events attributable to the study drug. Patients receiving EMISPHERE oral insulin tablets experienced a statistically significant drop from baseline in average blood glucose levels as measured by fructosamine levels, a statistically significant drop in fasting blood glucose levels and a statistically significant drop in glucose excursions following an oral glucose tolerance test. We presented an analyzed data set from this trial at the Annual Meeting of the American Diabetes Association in June 2004. Later stage clinical trials may not support the findings of our early stage trials.

*Oral Salmon Calcitonin*

We are collaborating with Novartis AG ( Novartis ) to develop oral salmon calcitonin ( sCT ), a peptide used to treat osteoporosis. sCT is currently available as an injection or nasal spray. In February 2003, we announced favorable results of a Phase IIa study conducted by Novartis evaluating the performance of an oral tablet form of sCT in post-menopausal women. Novartis has indicated to us that it intends to commence pivotal studies for two indications in the latter part of 2005. Later stage clinical trials may not support the findings of our early stage trials.

*Oral PTH 1-34*

We have granted Novartis an option to license our technology for the development of an oral recombinant parathyroid hormone ( PTH 1-34 ), a compound that stimulates new bone formation and is used for the treatment of osteoporosis. We previously partnered this program with Eli Lilly and Company ( Lilly ), and Lilly currently markets PTH 1-34 as an injectable drug. The Emisphere/Lilly oral PTH 1-34 program successfully completed Phase I studies and Lilly was responsible for trial management and funding. We are in litigation with Lilly concerning, among other things, an alleged violation by Lilly of the research and collaboration agreements relating to PTH 1-34 and we have given Lilly notice of our termination of those agreements. Emisphere has agreed to continue to provide Lilly with technical information as needed pending resolution of the court proceedings.

*Oral rhGH*

We have a collaboration with Novartis to develop an oral formulation of recombinant human growth hormone ( rhGH ). We formed the agreement following the successful completion of pre-clinical feasibility studies for rhGH with our *e*lig*e*n® technology. We have identified delivery agents that can deliver therapeutically sufficient levels of rhGH to the bloodstream when administered orally. The lead carrier for rhGH has completed extensive formulation and pre-clinical safety studies. We will work with Novartis to initiate clinical trials of a convenient oral human growth hormone product using the *e*lig*e*n® technology. Novartis will fully fund the program including all clinical studies. Under the terms of the agreement, Novartis paid us an initial non-refundable fee of $1 million in exchange for a 12 month license to utilize our *e*lig*e*n® technology. At the end of this 12 month license period, Novartis may elect to commence development or to terminate the agreement. If they elect to commence development, we may receive up to $33 million in additional milestone payments during the course of product development, and royalties based on sales.

*Oral Small Molecule Compounds*

On November 17, 2004, we entered into a licensing agreement with Hoffmann-La Roche Inc. and F. Hoffman-La Roche LTD (collectively, Roche ) to develop oral formulations of undisclosed small molecule compounds approved for use in the field of bone-related diseases. The agreement follows successful pre-clinical studies and a human feasibility study incorporating our *e*lig*e*n® technology to treat bone disease. Later stage trials may not support the findings of our pre-clinical or feasibility studies. Roche will fund all necessary preclinical, clinical and manufacturing costs for all products. We have no payment obligations with respect to this program; we are, however, obligated to collaborate with Roche by providing access to our technology that is relevant to this program and are obligated to help manage this program through a joint steering committee with Roche. Under the terms of the agreement, Roche paid

us an initial non-refundable up-front fee of $2.5 million and may pay us future milestone payments of up to $18.5 million for each product developed using our *eligen*® technology. We may also receive royalties based on product sales. Given that the agreement with Roche was entered into in November 2004, there has not yet been sufficient time to achieve material scientific progress or development in connection with the activities to be undertaken under the agreement. Roche may terminate the agreement at will for any reason and without financial penalty or requirement to fund any further clinical studies. We retain ownership rights to developments relating to our carrier and Roche retains rights related to the drug product developed.

**Other Collaborations and Feasibility Programs**

In addition to the lead product candidates described above, we have product candidates utilizing charged molecules as well as macromolecules in various stages of development, either alone or with partners, which have the potential to address large underserved patient populations.

**Certain Other Recent Developments**

As of March 31, 2005, our accumulated deficit was approximately $326 million. Our net loss was $37.5 million and $44.9 million for the years ended December 31, 2004, and 2003 respectively. Net income was $6.5 million for the quarter ended March 31, 2005 as a result of the $14.7 million gain on the extinguishment of the note payable. Our cash outlays from operations and capital expenditures were $23.5 million for 2004 and $7.4 millon for the first quarter of 2005. Our stockholders equity decreased from $67.5 million as of December 31, 2002 to $8.4 million as of March 31, 2005. We have limited capital resources and operations to date have been funded with the proceeds from collaborative research agreements, public and private equity and debt financings and income earned on investments. These conditions raise substantial doubt about our ability to continue as a going concern. The audit report prepared by our independent registered public accounting firm relating to our consolidated financial statements for the year ended December 31, 2004 includes an explanatory paragraph expressing the substantial doubt about our ability to continue as a going concern.

As of March 31, 2005, we had cash, cash equivalents and investments totaling $23.3 million. On April 1, 2005, we paid $13 million of our cash balance to complete our repurchase of our indebtedness to Elan Pharmaceuticals, Inc. ( Elan ), leaving us with cash, cash equivalents and investments of $10.3 million. We anticipate that our existing capital resources, without implementing cost reductions, raising additional capital, or obtaining substantial cash inflows from potential partners for our products, and excluding potential proceeds of sales of shares of common stock under the Common Stock Purchase Agreement with Kingsbridge Capital Limited ( Kingsbridge ) described below, will enable us to continue operations through July of 2005. These circumstances may adversely affect our ability to raise additional capital. If we fail to raise additional capital or obtain substantial cash inflows from potential or existing partners, we will be forced to cease operations. If additional capital is raised through the sale of equity or convertible debt securities, the issuance of such securities would result in dilution to our existing stockholders. We are continuing to address our liquidity issues through various means including the financing matters discussed below.

On March 31, 2005, we entered into a Placement Agency Agreement (the Placement Agency Agreement ) with Harris Nesbitt Corp. (the Placement Agent ) pursuant to which the Placement Agent agreed to act as the exclusive placement agent, on a best efforts basis, for the issuance and sale by the Company of an aggregate of up to 4 million units (the Units ). Each Unit consisted of one share of our common stock and a warrant to purchase an additional 0.375 shares of common stock. The Placement Agency Agreement provided that the Placement Agent is entitled to receive 1.8% of the proceeds received by us from the sale of the Units completed on or prior to March 31, 2005. On March 31, 2005, we completed an offering and sale of 4 million Units at a price of $3.935 per Unit (the Offering ), resulting in net proceeds to the Company of $15.1 million. The initial exercise price of each warrant was set at $4.00 per share. The exercise price of each warrant contains anti-dilution protection with a floor at $3.81 (as adjusted for stock splits, stock combinations and similar events).

Under the terms of the warrant, we have an obligation to make a cash payment to the holders of the warrant for any gain that could have been realized if the holders exercise the warrants and we subsequently fail to deliver a certificate representing the shares to be issued upon such exercise by the third trading day after such shares have been exercised. Accordingly, the warrant has been accounted for as a liability. The fair value of the warrant at the date of issuance was $3.9 million. The warrant will be marked to market for each future period it remains outstanding. Pursuant to the Placement Agency Agreement, the Placement Agent received a fee of $0.3 million.

In 1996, we entered into a joint venture with Elan to develop oral heparin. In connection with the re-purchase of Elan s joint venture interest in 1999, we issued a zero coupon note (the Original Elan Note ) to Elan. The Original Elan Note had an issue price of $20 million and an original issue discount at maturity of $35,048,881 for a total amount of $55,048,881 due on the maturity date of July 2, 2006. On December 27, 2004, we entered into a Security Purchase Agreement (the Security Purchase Agreement ) with Elan, providing for our purchase of our indebtedness to Elan under the Original Elan Note. The value of the Original Elan Note plus accrued interest on December 27, 2004 was approximately $44 million. Pursuant to the Security Purchase Agreement, on December 27, 2004, we paid Elan $13 million and issued to Elan 600,000 shares of our common stock with a market value of approximately $2 million. Also, we issued to Elan a new zero coupon note with an issue price of $29.2 million (the Modified Elan Note ), representing the accrued value of the Original Elan Note minus the sum of the cash payment and the value of the 600,000 shares. Under the Security Purchase Agreement, prior to March 31, 2005, we had the right to make a cash payment of $13 million, and issue to Elan a warrant to purchase up to 600,000 shares of our common stock (with an exercise price equal to the volume weighted average price for our common stock for the period of twenty consecutive trading days ending on the trading day immediately preceding the issuance of such warrant) in exchange for the Modified Elan Note (an Accelerated Closing ). As of March 31, 2005, we issued to Elan a warrant to purchase 600,000 shares of our common stock with an initial exercise price of $3.88 per share. The warrants provide for adjustments to the exercise price upon the occurrence of certain events, including the issuance by Emisphere of common stock or common stock equivalents that have an effective price that is less than the exercise price of the warrants. On April 1, 2005, we made the $13 million payment to Elan, and Elan issued a letter to us acknowledging that an Accelerated Closing had occurred and that we were released from all outstanding indebtedness to Elan.

This transaction was accounted for as a troubled debt restructuring. The carrying amount of the debt was reduced to an amount equal to the total future cash payments, or $13 million. The fair value of the warrant issued, estimated using the Black-Scholes option pricing model, is $1.6 million. A gain of $14.7 million, calculated as the difference between the carrying value of approximately $29 million and the fair value of cash paid and warrants issued, was recognized in our condensed consolidated statement of operations for the quarter ended March 31, 2005. No interest expense was recorded during the quarter ended March 31, 2005.

On December 27, 2004, we entered into a structured secondary offering facility, (the SSO Facility ), with Kingsbridge, pursuant to a Common Stock Purchase Agreement (the Common Stock Purchase Agreement or the SSO Facility ), providing for the commitment of Kingsbridge to purchase up to $20 million of our common stock until December 27, 2006. In return for the commitment, we issued to Kingsbridge a warrant to purchase 250,000 shares of our common stock with an initial exercise price of $3.811 per share. Please see The Structured Secondary Offering Facility Arrangement beginning on page 19 of this prospectus for a more detailed description of the SSO Facility.

On December 1, 2004 we issued a $10 million convertible note (the Novartis Note ) to Novartis in connection with a new research collaboration option relating to the development of PTH 1-34. The Novartis Note bears interest at a rate of 3% prior to December 1, 2006, 5% from December 1, 2006 through December 1, 2008, and 7% from that point until maturity on December 1, 2009. We have the option to pay interest in cash on a current basis or accrue the periodic interest as an addition to the principal amount of the Novartis Note. We may convert the Novartis Note at any time prior to maturity into a number of shares of our common stock equal to the principal and accrued and unpaid interest to be converted divided by the

then market price of our common stock, provided certain conditions are met, including that the number of shares issued to Novartis, when issued, does not exceed 19.9% of the total shares of our common stock outstanding, that at the time of such conversion no event of default under the Novartis Note has occurred and is continuing, and that there is either an effective shelf registration statement in effect covering the resale of the shares issued in connection with such conversion or the shares may be resold by Novartis pursuant to SEC Rule 144(k). Under the Novartis Note, an event of default shall be deemed to have occurred if we default on the payment of the principal amount of, and accrued and unpaid interest on, the Novartis Note upon maturity, we suffer a bankruptcy or similar insolvency event or proceeding, we materially breach a representation or warranty, we fail to timely cure a default in the payment of any other indebtedness in excess of a certain material threshold, or there occurs an acceleration of indebtedness in excess of that threshold, we suffer and do not discharge in a timely manner a final judgment for the payment of a sum in excess of a certain material threshold, we become entitled to terminate the registration of our securities or the filing of reports under the Securities Exchange Act of 1934, our common stock will be delisted from Nasdaq, we experience a change of control (including by, among other things, a change in the composition of a majority of our board (other than as approved by the board) in any one-year period, a merger which results in our stockholders holding shares that represent less than a majority of the voting power of the merged entity, and any other acquisition by a third party of shares that represent a majority of the voting power of the company), we sell substantially all of our assets, or we are effectively unable to honor or perform our obligations under the new research collaboration option relating to the development of PTH 1-34. Upon the occurrence of any such event of default prior to conversion, any unpaid principal and accrued interest on the Novartis Note would become immediately due and payable. If the Novartis Note is converted into our common stock, Novartis would have the right to require us to repurchase the shares of common stock within six months after an event of default under the Novartis Note, for an aggregate purchase price equal to the principal and interest that was converted, plus interest from the date of conversion, as if no conversion had occurred.

## RISK FACTORS

*You should carefully consider the following risk factors, as well as the other information contained in this prospectus or any supplemental prospectus hereto or incorporated by reference in this prospectus, before purchasing any of our Common Stock.*

***We have incurred substantial losses since inception and as we expect to continue to incur development expenses for self-funded programs and partnered programs and for programs for which we are attempting to secure a partner, we are likely to require additional capital and if additional capital is not raised our ability to continue as a going concern is in substantial doubt.***

Since our inception in 1986, we have generated significant losses from operations and we anticipate that we will continue to generate significant losses from operations for the foreseeable future. As of March 31, 2005, our accumulated deficit was approximately $326 million. Our net loss was $37.5 million and $44.9 million for the years ended December 31, 2004, and 2003 respectively. Net income was $6.5 million for the quarter ended March 31, 2005 as a result of the $14.7 million gain on the extinguishment of the note payable. Our cash outlays from operations and capital expenditures were $23.5 million for 2004 and $7.4 million for the first quarter of 2005. Our stockholders equity decreased from $67.5 million as of December 31, 2002 to $8.4 million as of March 31, 2005. We have limited capital resources and operations to date have been funded with the proceeds from collaborative research agreements, public and private equity and debt financings and income earned on investments. These conditions raise substantial doubt about our ability to continue as a going concern. The audit report prepared by our independent registered public accounting firm relating to our consolidated financial statements for the year ended December 31, 2004 includes an explanatory paragraph expressing the substantial doubt about our ability to continue as a going concern.

As of March 31, 2005, we had cash, cash equivalents and investments totaling $23.3 million. On April 1, 2005, we paid $13 million of our cash balance to complete our repurchase of our indebtedness to Elan, leaving us with cash, cash equivalents and investments of $10.3 million. We anticipate that our existing capital resources, without implementing cost reductions, raising additional capital, or obtaining substantial cash inflows from potential partners for our products, and excluding potential proceeds of sales of shares of common stock under the SSO Facility will enable us to continue operations through July of 2005. These circumstances may adversely affect our ability to raise additional capital. If we fail to raise additional capital or obtain substantial cash inflows from potential or existing partners, we will be forced to cease operations. If additional capital is raised through the sale of equity or convertible debt securities, the issuance of such securities would result in dilution to our existing stockholders.

***We may not be able to make the payments we owe to Novartis.***

On December 1, 2004 we issued a $10 million convertible note (the Novartis Note ) to Novartis in connection with a new research collaboration option relating to the development of PTH 1-34. The Novartis Note bears interest at a rate of 3% prior to December 1, 2006, 5% from December 1, 2006 through December 1, 2008, and 7% from that point until maturity on December 1, 2009. We have the option to pay interest in cash on a current basis or accrue the periodic interest as an addition to the principal amount of the Novartis Note. In the event that interest accrues on the Novartis Note, the accretion to principal will cause future interest payments to increase. We may convert the Novartis Note at any time prior to maturity into a number of shares of our common stock equal to the principal and accrued and unpaid interest to be converted divided by the then market price of our common stock, provided certain conditions are met, including that the number of shares issued to Novartis, when issued, does not exceed 19.9% of the total shares of our common stock outstanding, that at the time of such conversion no event of default under the Novartis Note has occurred and is continuing, and that there is either an effective shelf registration statement in effect covering the resale of the shares issued in connection with such conversion or the shares may be resold to Novartis pursuant to SEC Rule 144(k). These conditions may not be met and we may be unable to convert the Novartis Note, in which case we would be required to continue to make interest payments and the rates of such interest payments will increase over time. Under the Novartis Note, an event of default shall be deemed to have occurred if we default on the payment of the principal amount of, and accrued and unpaid interest on, the Novartis Note upon maturity, we suffer a bankruptcy or similar

insolvency event or proceeding, we materially breach a representation or warranty, we fail to timely cure a default in the payment of any other indebtedness in excess of a certain material threshold, or there occurs an acceleration of indebtedness in excess of that threshold, we suffer and do not discharge in a timely manner a final judgment for the payment of a sum in excess of a certain material threshold, we become entitled to terminate the registration of our securities or the filing of reports under the Securities Exchange Act of 1934, our common stock will be delisted from Nasdaq, we experience a change of control (including by, among other things, a change in the composition of a majority of our board (other than as approved by the board) in any one-year period, a merger which results in our stockholders holding shares that represent less than a majority of the voting power of the merged entity, and any other acquisition by a third party of shares that represent a majority of the voting power of the company), we sell substantially all of our assets, or we are effectively unable to honor or perform our obligations under the new research collaboration option relating to the development of PTH 1-34. Upon the occurrence of any such event of default prior to conversion, any unpaid principal and accrued interest on the Novartis Note would become immediately due and payable. At such time, we may not be able to make the required payment, and if we are unable to pay the amount due under the Novartis Note, the resulting default would have a material adverse effect on our business and on the value of our stockholders investments in our common stock. If the Novartis Note is converted into our common stock, Novartis would have the right to require us to repurchase the shares of common stock within six months after an event of default under the Novartis Note, for an aggregate purchase price equal to the principal and interest that was converted, plus interest from the date of conversion, as if no conversion had occurred. If we are unable to make the repurchase, the resulting default would have a material adverse effect on our business and on the value of our stockholders investments in our common stock.

***If we are unable to generate sufficient revenue from potential partners or raise additional capital, we will be required to curtail our development efforts, which could have a material adverse effect on our ability to realize on the commercial potential of our products.***

If we fail to generate sufficient revenue or raise additional capital, we will have to undergo further restructuring and downsize our operations. Under those circumstances, our failure to restructure would have a material adverse effect on our ability to continue as a going concern. Historically, we have been able to implement cost reductions when necessary. In May 2002, we announced a plan for restructuring our operations, which included the discontinuation of our liquid oral heparin program and related initiatives, and a reduction of associated infrastructure. In the third quarter of 2002, we decided to dispose of our Farmington, Connecticut research facility. These actions reduced our full-time work force by approximately 50%. The sale of the Farmington facility may not occur in the near future and the costs associated with the facility (e.g., utilities, insurance, maintenance, and real estate taxes) will require continued cash outlays. Costs associated with maintaining the facility were approximately $0.5M in 2004 and will continue at the same level until the facility is sold.

If our current funding and any proceeds of sales of shares of common stock to Kingsbridge, if any, are not sufficient for our operations or our Common Stock Purchase Agreement with Kingsbridge terminates, we may be required to restructure and reduce spending, and the resultant curtailment of our development efforts could have a material adverse effect on our ability to realize the commercial potential of our products and achieve long-term profitability.

Our financial statements for the year ended December 31, 2004 emphasized the existence of substantial doubt about our ability to continue as a going concern, which may adversely affect our ability to raise additional capital.

***We are highly dependent on the clinical success of our oral heparin and insulin product candidates.***

Oral heparin and oral insulin are our two lead programs and are among our most advanced programs. To date, we have invested $90 million and $15.2 million, in oral heparin and oral insulin, respectively. We believe that, based on market size, these two products, if approved, could represent our largest sources of revenue. If we fail to obtain regulatory approval for either of these products, either solely through our own efforts or through collaborations with one or more major pharmaceutical companies, our ability to fund future operations from operating revenue or issuance of additional equity is likely to be adversely affected.

We are not dependent on successful culmination of clinical trials or regulatory approval of any particular one of our other product candidate programs because our investment in each such program and reward upon successful completion of each such program is substantially less significant to our long-term viability.

*Oral Heparin*

Heparin delivery is a highly competitive area. Other companies currently are developing spray (buccal) or alternate forms of heparin, and other anti-thrombotics have recently received European approval (e.g., AstraZeneca s EXANTA®). We are developing solid dosage forms of oral heparin and have commenced Phase III testing for the SNAC/heparin molecule combination.

We previously developed a liquid form of oral heparin and in 2000 conducted a Phase III clinical trial that was completed in early 2002. The trial did not meet its endpoint of superiority to LOVENOX®, a leading low molecular weight heparin. We believe that the trial failed to meet its endpoint of superiority possibly due in part to the poor taste of the liquid formulation. We subsequently restructured our operations, which included the discontinuation of our liquid oral heparin program and related initiatives, and a reduction of associated infrastructure. The resulting restructuring charge to earnings was approximately $1.5 million. In accordance with Statement of Financial Accounting Standards No. 144, Accounting for the Impairment or Disposal of Long-Lived Assets, in connection with the restructuring, we performed an evaluation of certain intangible and fixed assets to determine if their carrying amount exceeded their fair value. In 2003, we recorded an additional impairment charge of $5.4 million. In 2004, we did not record any impairment charges.

We cannot assure you that competitive heparin products will not have an adverse effect on our heparin product development efforts or that future clinical trials related to our solid form of oral heparin will meet targeted endpoints. If future clinical trials related to oral heparin fail to meet the targeted endpoints, we likely would discontinue our oral heparin program and write off any remaining oral heparin investment.

In 1996, we formed a joint venture with Elan to develop oral forms of heparin. In July 1999, we reacquired all product, marketing and technology rights for our heparin products from Elan. In accordance with the termination agreement with Elan, we will be required to pay Elan royalties on our sales of oral heparin, subject to an annual cap of $10 million.

*Oral Insulin*

Insulin delivery is a highly competitive area. Other companies currently are developing buccal or aerosol (pulmonary) forms of insulin (e.g., Aventis/Pfizer/Nektar s EXUBERA®). Our oral insulin product candidate has demonstrated favorable data in early patient studies in both Type 1 and Type 2 diabetics. However, we cannot assure you that future clinical trials related to our oral insulin will meet targeted endpoints, with the result that we may fail to obtain the necessary regulatory approval for sale of oral insulin, either alone or in collaboration with a major pharmaceutical company. If such circumstances were to occur, we likely would discontinue our oral insulin program and write off any remaining oral insulin investment.

***We are highly dependent upon collaborative partners to develop and commercialize compounds using our delivery agents.***

A key part of our strategy is to form collaborations with pharmaceutical companies that will assist us in developing, testing, obtaining government approval for and commercializing oral forms of therapeutic macromolecules using the *eligen*® technology. We have collaborative agreements for candidates in clinical development with Novartis and Roche, and as noted below, we are in litigation with Lilly and have given Lilly notice of termination of our agreements with it.

We negotiate specific ownership rights with respect to the intellectual property developed as a result of the collaboration with each partner. While ownership rights vary from program to program, in general we retain ownership rights to developments relating to our carrier and the collaborator retains rights related to the drug product developed.

Despite our existing agreements, we cannot assure you that:

- we will be able to enter into additional collaborative arrangements to develop products utilizing our drug delivery technology;
- any existing or future collaborative arrangements will be sustainable or successful;
- the product candidates in collaborative arrangements will be further developed by partners in a timely fashion;
- any collaborative partner will not infringe upon our intellectual property position in violation of the terms of the collaboration contract; or
- milestones in collaborative agreements will be met and milestone payments will be received.

If we are unable to obtain development assistance and funds from other pharmaceutical companies to fund a portion of our product development costs and to commercialize our product candidates, we may be unable to issue equity upon favorable terms to allow us to raise sufficient capital to fund clinical development of our product candidates. Lack of funding would cause us to delay, scale back or curtail clinical development of one or more of our projects. The determination of the specific project to curtail would depend upon the relative future economic value to us of each program.

***Our collaborative partners control the clinical development of the drug candidates and may terminate their efforts at will.***

Novartis controls the clinical development of oral calcitonin and oral rhGH. Pending the results of our litigation with Lilly, Novartis also has an option to control the clinical development of oral PTH. Roche controls the clinical development of the small molecule compound for which they have licensed our technology. Although we influence the clinical program through participation on a Steering Committee for each product, Novartis and Roche control the decision-making for the design and timing of their respective clinical studies. As noted below, we are in litigation with Lilly and have given Lilly notice of termination of our agreements with it.

Moreover, the agreements with Novartis and Roche provide that each may terminate its programs at will for any reason and without any financial penalty or requirement to fund any further clinical studies. We cannot assure you that Novartis or Roche will continue to advance the clinical development of the drug candidates subject to collaboration.

***Our collaborative partners are free to develop competing products.***

Aside from provisions preventing the unauthorized use of our intellectual property by our collaborative partners, there is nothing in our collaborative agreements that prevents our partners from developing competing products. If one of our partners were to develop a competing product, our collaboration could be substantially jeopardized.

***We are currently in litigation with one of our collaborative partners, and an adverse determination of our patent infringement claims in that case could limit our future ability to realize on the potential value of those patents.***

There is currently pending in the United States District Court for the Southern District of Indiana, Indianapolis Division, a lawsuit with Eli Lilly and Company. The suit results from a notice that we delivered to Lilly declaring that Lilly was in material breach of certain research and collaboration agreements entered into with Lilly with respect to the development of oral formulations of recombinant parathyroid hormone, PTH 1-34. Following receipt of the notice, Lilly filed a complaint seeking (i) a declaratory judgment declaring that Lilly is not in breach of its agreements with us concerning oral formulations of recombinant parathyroid hormone, PTH 1-34, and (ii) an order preliminarily and permanently enjoining us from terminating those agreements. On February 12, 2004, we served Lilly with an amended counterclaim, alleging that Lilly filed certain patent applications relating to the use of our proprietary technology in combination with another drug, in violation of our agreements with Lilly, and

that the activities disclosed in such applications infringe upon our patents. We are also alleging that Lilly has breached the agreements by failing to make a milestone payment of $3 million, as required upon the completion of oral PTH 1-34 product Phase I studies. Lilly has denied that the $3 million currently is due on the basis that the requisite Phase I studies have not been completed and that the patent applications that it filed relating to the use of our proprietary technology in combination with another drug is not in violation of our agreements with Lilly, and that the activities disclosed in such applications do not infringe upon our patents. On February 13, 2004, the court entered a case management plan and the parties commenced the exchange of discovery materials in March 2004. By notice dated August 23, 2004, the Company notified Lilly that in light of Lilly s ongoing, repeated and uncured violations of its PTH 1-34 license agreement, both its agreements with us were terminated. Thereafter, Lilly amended its complaint to seek a declaration that we are not entitled to terminate those agreements and also to seek declarations that Lilly has not infringed our patents. The trial has concluded and the judge is currently considering his decision. An adverse determination in this litigation concerning our claim that Lilly breached our agreements could limit our future ability to realize on the potential value of our oral PTH 1-34 assets. Although the costs of litigating this matter to its ultimate conclusion may be material, we anticipate that we will have sufficient financial resources to fund near-term costs, including trial costs, and we do not anticipate any significant impact on our ability to develop our product candidates. Through March 31, 2005, we incurred approximately $2.3 million in expenses relating to this litigation.

Although we are not currently involved in litigation with any of our other collaborative partners and have no reason to believe that such litigation will arise, it is possible that in the future this may not be the case. Were we to become involved in litigation with another of our collaborative partners, we would bear the additional expense of the litigation and we would likely suffer an adverse impact on both the program covered by the collaborative agreement and our relationship with the particular collaborative partner.

***Our product candidates are in various stages of development, and we cannot be certain that any will be suitable for commercial purposes.***

To be profitable, we must successfully research, develop, obtain regulatory approval for, manufacture, introduce, market and distribute our products under development, or secure a partner to provide financial and other assistance with these steps. The time necessary to achieve these goals for any individual product is long and uncertain. Before we or a potential partner can sell any of our products under development, we must demonstrate through preclinical (animal) studies and clinical (human) trials that such product is safe and effective for human use for each targeted indication. We have never successfully commercialized a drug candidate and we cannot be certain that we or our current or future partners will be able to begin, or continue, planned clinical trials for our product candidates, or if we are able, that the product candidates will prove to be safe and will produce their intended effects.

Even if safe and effective, the size of the solid dosage form, taste and frequency of dosage may impede their acceptance by patients.

A number of companies in the drug delivery, biotechnology and pharmaceutical industries have suffered significant setbacks in clinical trials, even after showing promising results in earlier studies or trials. We cannot assure you that favorable results in any preclinical study or early clinical trial will mean that favorable results will ultimately be obtained in future clinical trials. Nor can we assure you that results of limited animal and human studies are indicative of results that would be achieved in future animal studies or human clinical studies, all or some of which will be required in order to have our product candidates obtain regulatory approval. Similarly, we cannot assure you that any of our product candidates will be approved by the FDA.

For example, we initially set out to develop a liquid formulation of oral heparin. At the end of 1999, we initiated a Phase III study of our oral heparin liquid formulation. The multi-center, double-blind, double-dummy Phase III trial was referred to as the PROTECT trial (PRophylaxis with Oral SNAC/heparin against ThromboEmbolic Complications following Total hip replacement surgery).

The PROTECT trial enrolled 2,288 patients to evaluate the safety and efficacy of a solution oral heparin formulation using our *eligen*® oral drug delivery technology for the prevention of DVT in total hip replacement surgery patients (a surgical patient population that historically has had a high rate of DVT). The goal of the PROTECT trial was to demonstrate the superior efficacy and comparable safety of our oral heparin when dosed postoperatively for a 30-day regimen, as compared to injectable enoxaparin, when dosed postoperatively for a 10-day regimen. (A 10-day regimen of injectable enoxaparin, marketed by Aventis Pharma SA under the LOVENOX trademark, is the standard of care in the prevention of DVT, as determined by the American College of Chest Physicians Sixth Consensus Conference.)

The endpoint of the PROTECT trial was DVT occurrence in the 30 days following surgery, or pulmonary embolism or death. Investigators at more than 120 international sites evaluated a liquid form of heparin, consisting of the EMISPHERE delivery agent, SNAC (Sodium N-[8-(2 hydroxybenzoyl) Amino Caprylate), in combination with unfractionated heparin, when dosed orally in a 30-day regimen, compared to enoxaparin, when dosed subcutaneously (by injection) in a 10-day regimen. Total DVTs were determined by bilateral venogram, the FDA standard for measurement, measured at 30 days following surgery. A team of radiologists at Boston s Massachusetts General Hospital read all the venographies produced to determine the presence of a blood clot (thrombus).

On May 14, 2002, we announced initial results from the PROTECT study. Those initial results did not demonstrate the superiority of oral heparin, when dosed in a 30-day treatment regimen, compared to enoxaparin administered by injection in a 10-day dosing regimen in preventing DVTs.

Unless the clinical data has utility in other development programs or the safety data from the PROTECT trial is deemed useable, the termination of clinical trials for a product candidate may result in a loss of the Company s cumulative investment in the product candidate. These expenses are primarily costs of engaging clinical contract research organization and production of clinical supplies of the drug candidate.

***Our future business success depends heavily upon regulatory approvals, which can be difficult to obtain for a variety of reasons, including cost.***

Our preclinical studies and clinical trials, as well as the manufacturing and marketing of our product candidates, are subject to extensive, costly and rigorous regulation by various governmental authorities in the United States and other countries. The process of obtaining required approvals from the FDA and other regulatory authorities often takes many years, is expensive and can vary significantly based on the type, complexity and novelty of the product candidates. We cannot assure you that we, either independently or in collaboration with others, will meet the applicable regulatory criteria in order to receive the required approvals for manufacturing and marketing. Delays in obtaining United States or foreign approvals for our self-developed projects could result in substantial additional costs to us, and, therefore, could adversely affect our ability to compete with other companies. Additionally, delays in obtaining regulatory approvals encountered by others with whom we collaborate also could adversely affect our business and prospects. Even if regulatory approval of a product is obtained, the approval may place limitations on the intended uses of the product, and may restrict the way in which we or our partner may market the product.

The regulatory approval process presents several risks to us:

In general, preclinical tests and clinical trials can take many years, and require the expenditure of substantial resources, and the data obtained from these tests and trials can be susceptible to varying interpretation that could delay, limit or prevent regulatory approval.

Delays or rejections may be encountered during any stage of the regulatory process based upon the failure of the clinical or other data to demonstrate compliance with, or upon the failure of the product to meet, a regulatory agency s requirements for safety, efficacy and quality or, in the case of a product seeking an orphan drug indication, because another designee received approval first.

Requirements for approval may become more stringent due to changes in regulatory agency policy, or the adoption of new regulations or legislation.

The scope of any regulatory approval, when obtained, may significantly limit the indicated uses for which a product may be marketed and may impose significant limitations in the nature of warnings, precautions and contraindications that could materially affect the profitability of the drug.

Approved drugs, as well as their manufacturers, are subject to continuing and on-going review, and discovery of previously unknown problems with these products or the failure to adhere to manufacturing or quality control requirements may result in restrictions on their manufacture, sale or use or in their withdrawal from the market.

Regulatory authorities and agencies may promulgate additional regulations restricting the sale of our existing and proposed products.

Once a product receives marketing approval, the FDA may not permit us to market that product for broader or different applications, or may not grant us clearance with respect to separate product applications that represent extensions of our basic technology. In addition, the FDA may withdraw or modify existing clearances in a significant manner or promulgate additional regulations restricting the sale of our present or proposed products.

Additionally, we face the risk that our competitors may gain FDA approval for a product before us. Having a competitor reach the market before us would impede the future commercial success for our competing product because we believe that the FDA uses heightened standards of approval for products once approval has been granted to a competing product in a particular product area. We believe that this standard generally limits new approvals to only those products that meet or exceed the standards set by the previously approved product.

***We may not be able to sell our Farmington facility.***

In the third quarter of 2002, we decided to dispose of our Farmington, Connecticut research facility. In April 2005, we entered into a contract of sale for the Farmington facility. The purchase price for the property is $4.7 million. The contract provided, among other things, for a sixty day contingency period during which the purchaser may perform due diligence concerning the property, and during which the purchaser may terminate the contract for any reason or for no reason. The contingency period has been extended to June 17, 2005 and the closing date has been moved up to June 30, 2005. In January 2004, an adjoining landowner filed a notice of pendency on the property claiming certain rights under a right of way, and in addition filed suit in a matter captioned FARMINGTON AVENUE BAPTIST CHURCH, Plaintiff, vs. FARM TECH CORPORATION, Defendant, Superior Court of the State of Connecticut, Judicial District of Hartford . Depositions of the pastor and the attorney for the adjoining landowner have been completed. Our motion for summary judgment was argued in April 2005, and the plaintiff has been ordered to submit a similar motion by the middle of May 2005, which date has been extended to June 22, 2005. This litigation is ongoing and may have an adverse effect on our ability to sell the facility. Costs associated with maintaining the facility (e.g., utilities, insurance, maintenance and real estate taxes) were approximately $0.5 million in 2004 and will continue at approximately the same level until the facility is sold. The carrying value of the Farmington facility as of March 31, 2005 was $3.6 million. We evaluated the land, building and equipment available for sale as of March 31, 2005 based on the sale price in the contract and determined that an impairment loss on the carrying value of the land, building and equipment had not been incurred. In the event that we are not successful in selling the Farmington facility, we may need to record an impairment loss on the land, building and attached equipment.

***Our business will suffer if we cannot adequately protect our patent and proprietary rights.***

Although we have patents for some of our product candidates and have applied for additional patents, there can be no assurance that patents applied for will be granted, that patents granted to or acquired by us now or in the future will be valid and enforceable and provide us with meaningful protection from competition or that we will possess the financial resources necessary to enforce any of our patents. Also, we cannot be certain that any products that we (or a licensee) develop will not infringe upon any patent or other intellectual property right of a third party.

We also rely upon trade secrets, know-how and continuing technological advances to develop and maintain our competitive position. We maintain a policy of requiring employees, scientific advisors, consultants and collaborators to execute confidentiality and invention assignment agreements upon commencement of a relationship with us. We cannot assure you that these agreements will provide meaningful protection for our trade secrets in the event of unauthorized use or disclosure of such information.

Part of our strategy involves collaborative arrangements with other pharmaceutical companies for the development of new formulations of drugs developed by others and, ultimately, the receipt of royalties on sales of the new formulations of those drugs. These drugs are generally the property of the pharmaceutical companies and may be the subject of patents or patent applications and other rights of protection owned by the pharmaceutical companies. To the extent those patents or other forms of rights expire, become invalid or otherwise ineffective, or to the extent those drugs are covered by patents or other forms of protection owned by third parties, sales of those drugs by the collaborating pharmaceutical company may be restricted, limited, enjoined, or may cease. Accordingly, the potential for royalty revenues to us may be adversely affected.

***We may be at risk of having to obtain a license from third parties making proprietary improvements to our technology.***

There is a possibility that third parties may make improvements or innovations to our technology in a more expeditious manner than we do. Although we are not aware of any such circumstance related to our product portfolio, should such circumstances arise, we may need to obtain a license from such third party to obtain the benefit of the improvement or innovation. Royalties payable under such a license would reduce our share of total revenue. Such a license may not be available to us at all or on commercially reasonable terms. Although we currently do not know of any circumstances related to our product portfolio which would lead us to believe that a third party has developed any improvements or innovation with respect to our technology, we cannot assure you that such circumstances will not arise in the future. We cannot reasonably determine the cost to us of the effect of being unable to obtain any such license.

***We are dependent on third parties to manufacture and, in some cases, test our products.***

We have a facility to manufacture a limited quantity of clinical supplies containing EMISPHERE® delivery agents. Currently, we have no manufacturing facilities for production of any therapeutic compounds under consideration as products. We have no facilities for clinical testing. The success of our self-developed programs is dependent upon securing manufacturing capabilities and contracting with clinical service providers.

The availability of manufacturers is limited by both the capacity of such manufacturers and their regulatory compliance. Among the conditions for NDA approval is the requirement that the prospective manufacturer s quality control and manufacturing procedures continually conform with the FDA s current Good Manufacturing Practice ( GMP ) (GMP are regulations established by the FDA that govern the manufacture, processing, packing, storage and testing of drugs intended for human use). In complying with GMP, manufacturers must devote extensive time, money and effort in the area of production and quality control and quality assurance to maintain full technical compliance. Manufacturing facilities and company records are subject to periodic inspections by the FDA to ensure compliance. If a manufacturing facility is not in substantial compliance with these requirements, regulatory enforcement action may be taken by the FDA, which may include seeking an injunction against shipment of products from the facility and recall of products previously shipped from the facility. Such actions could severely delay our ability to obtain product from that particular source.

The success of our clinical trials and our partnerships is dependent on the proposed or current partner s capacity and ability to adequately manufacture drug products to meet the proposed demand of each respective market. Any significant delay in obtaining a supply source (which could result from, for example, an FDA determination that such manufacturer does not comply with current GMP) could harm our potential for success. Additionally, if a current manufacturer were to lose its ability to meet our supply demands during a clinical trial, the trial may be delayed or may even need to be abandoned.

***We may face product liability claims related to participation in clinical trials or future products.***

We have product liability insurance with a policy limit of $5 million per occurrence and in the aggregate. The testing, manufacture and marketing of products for humans utilizing our drug delivery technology may expose us to potential product liability and other claims. These may be claims directly by consumers or by pharmaceutical companies or others selling our future products. We seek to structure development programs with pharmaceutical companies that would complete the development, manufacturing and marketing of the finished product in a manner that would protect us from such liability, but the indemnity undertakings for product liability claims that we secure from the pharmaceutical companies may prove to be insufficient.

***We are subject to environmental, health and safety laws and regulations for which we incur costs to comply.***

We use some hazardous materials in our research and development activities and are subject to environmental, health and safety laws and regulations governing the use of such materials. For example, our operations involve the controlled use of chemicals, biologicals and radioactive materials and we bear the costs of complying with the various regulations governing the use of such materials. Costs of compliance have not been material to date. While we believe we are currently in compliance with the federal, state and local laws governing the use of such materials, we cannot be certain that accidental injury or contamination will not occur. Should we be held liable or face regulatory actions regarding an accident involving personal injury or an environmental release, we potentially could incur costs in excess of our resources or insurance coverage, although, to date, we have not had to deal with any such actions. During each of 2003 and 2004, we incurred costs of approximately $200,000 in our compliance with environmental, health and safety laws and regulations.

***We face rapid technological change and intense competition.***

Our success depends, in part, upon maintaining a competitive position in the development of products and technologies in an evolving field in which developments are expected to continue at a rapid pace. We compete with other drug delivery, biotechnology and pharmaceutical companies, research organizations, individual scientists and non-profit organizations engaged in the development of alternative drug delivery technologies or new drug research and testing, as well as with entities developing new drugs that may be orally active. Many of these competitors have greater research and development capabilities, experience, and marketing, financial and managerial resources than we have, and, therefore, represent significant competition.

Our products, when developed and marketed, may compete with existing parenteral or other versions of the same drug, some of which are well established in the marketplace and manufactured by formidable competitors, as well as other existing drugs. For example, our oral heparin product candidate, if successful, would compete with intravenous heparin, injectable low molecular weight heparin and oral warfarin, as well as the recently approved injectable pentasaccharide and oral melagatran products. These products are marketed throughout the world by leading pharmaceutical companies such as Aventis Pharma SA, Pfizer, Inc. and Bristol Myers Squibb Company. Similarly, our salmon calcitonin product candidate, if developed and marketed, would compete with a wide array of existing osteoporosis therapies, including a nasal dosage form of salmon calcitonin, estrogen replacement therapy, selective estrogen receptor modulators, bisphosphonates and other compounds in development.

Our competitors may succeed in developing competing technologies or obtaining government approval for products before we do. Developments by others may render our product candidates, or the therapeutic macromolecules used in combination with our product candidates, noncompetitive or obsolete. For example, Nobex Corporation has an oral insulin formulation being developed and at least one competitor has notified the FDA that it is developing a competing formulation of salmon calcitonin. We cannot assure you that, if our products are marketed, they will be preferred to existing drugs or that they will be preferred to or available before other products in development.

If a competitor announces a successful clinical study involving a product that may be competitive with one of our product candidates or an approval by a regulatory agency of the marketing of a competitive product, such announcement may have a material adverse effect on our operations or future prospects resulting from reduced sales of future products that we may wish to bring to market or from an adverse impact on the price of our common stock or our ability to obtain regulatory approval for our product candidates.

***We are dependent on our key personnel and if we cannot recruit and retain leaders in our research, development, manufacturing, and commercial organizations, our business will be harmed.***

We are highly dependent on our executive officers. Our Chairman and CEO, Michael Goldberg, M.D., has been with Emisphere for fifteen years. We would be significantly disadvantaged if Dr. Goldberg were to leave Emisphere. The loss of other officers could have an adverse effect as well, given their specific knowledge related to our proprietary technology and personal relationships with our pharmaceutical company partners. If we are not able to retain our executive officers, our business may suffer. None of our key officers are nearing retirement age or have announced any intention to leave Emisphere. We have an employment contract with Dr. Goldberg that extends through August of 2005. We do not maintain key-man life insurance policies for any of our executive officers.

There is intense competition in the biotechnology industry for qualified scientists and managerial personnel in the development, manufacture, and commercialization of drugs. We may not be able to continue to attract and retain the qualified personnel necessary for developing our business. Additionally, because of the knowledge and experience of our scientific personnel and their specific knowledge with respect to our drug carriers the continued development of our product candidates could be adversely affected by the loss of any significant number of such personnel.

***Provisions of our corporate charter documents, Delaware law and our stockholder rights plan may dissuade potential acquirors, prevent the replacement or removal of our current management and may thereby affect the price of our common stock.***

Our Board of Directors has the authority to issue up to 1,000,000 shares of preferred stock and to determine the rights, preferences and privileges of those shares without any further vote or action by our stockholders. Of these 1,000,000 shares, 200,000 are currently designated Series A Junior Participating Cumulative Preferred Stock ( A Preferred Stock ) in connection with our stockholder rights plan, and the remaining 800,000 shares remain available for future issuance. Rights of holders of common stock may be adversely affected by the rights of the holders of any preferred stock that may be issued in the future.

We also have a stockholder rights plan, commonly referred to as a poison pill, in which Preferred Stock Purchase Rights (the Rights ) have been granted at the rate of one one-hundredth of a share of A Preferred Stock at an exercise price of $80 for each share of the Company s common stock. The Rights are not exercisable or transferable apart from the common stock, until the earlier of (i) ten days following a public announcement that a person or group of affiliated or associated persons have acquired beneficial ownership of 20% or more of our outstanding common stock or (ii) ten business days (or such later date, as defined) following the commencement of, or announcement of an intention to make a tender offer or exchange offer, the consummation of which would result in the beneficial ownership by a person, or group, of 20% or more of our outstanding common stock. If we enter into consolidation, merger, or other business combinations, as defined, each Right would entitle the holder upon exercise to receive, in lieu of shares of A Preferred Stock, a number of shares of common stock of the acquiring company having a value of two times the exercise price of the Right, as defined. By potentially diluting the ownership of the acquiring company, our rights plan may dissuade prospective acquirors of our company.

The A Preferred Stockholders will be entitled to a preferential cumulative quarterly dividend of the greater of $1.00 per share or 100 times the per-share dividend declared on our stock and are also entitled to a liquidation preference, thereby hindering an acquiror s ability to freely pay dividends or to liquidate the company following an acquisition. Each A Preferred Stock share will have 100 votes and will vote together with the common shares, effectively preventing an acquiror from removing existing management. The Rights contain anti-dilutive provisions, are redeemable at our option, subject to certain defined restrictions for $.01 per Right, and expire on February 23, 2006.

Additional provisions of our certificate of incorporation and by-laws could have the effect of making it more difficult for a third party to acquire a majority of our outstanding voting common stock. These include provisions that classify our Board of Directors, limit the ability of stockholders to take action by written consent, call special meetings, remove a director for cause, amend the by-laws or approve a merger with another company.

We are subject to the provisions of Section 203 of the Delaware General Corporation Law which prohibits a publicly-held Delaware corporation from engaging in a business combination with an interested stockholder for a period of three years after the date of the transaction in which the person became an interested stockholder, unless the business combination is approved in a prescribed manner. For purposes of Section 203, a business combination includes a merger, asset sale or other transaction resulting in a financial benefit to the interested stockholder, and an interested stockholder is a person who, either alone or together with affiliates and associates, owns (or within the past three years, did own) 15% or more of the corporation s voting stock.

***Our stock price has been and may continue to be volatile.***

The trading price for our common stock has been and is likely to continue to be highly volatile. The market prices for securities of drug delivery, biotechnology and pharmaceutical companies have historically been highly volatile. Factors that could adversely affect our stock price include:

fluctuations in our operating results; announcements of partnerships or technological collaborations,

innovations or new products by us or our competitors;

governmental regulation;

developments in patent or other proprietary rights;

public concern as to the safety of drugs developed by us or others;

the results of preclinical testing and clinical studies or trials by us, our partners or our competitors;

litigation;

general stock market and economic conditions;

number of shares available for trading (float);

inclusion in or dropping from stock indexes.

As of May 13, 2005, our 52-week high and low closing market price for our common stock was $5.92 and $2.78, respectively.

***Future sales of common stock or warrants, or the prospect of future sales, may depress our stock price.***

Sales of a substantial number of shares of common stock or warrants, or the perception that sales could occur, could adversely affect the market price of our common stock. As of March 31, 2005, there were outstanding options to purchase up to 4,489,363 shares of our common stock that are currently exercisable, and additional outstanding options to purchase up to 1,030,132 shares of common stock that are exercisable over the next several years. The holders of these options have an opportunity to profit from a rise in the market price of our common stock with a resulting dilution in the interests of the other. The existence of these options may adversely affect the terms on which we may be able to obtain additional financing.

In addition, currently, 20,000 shares of our common stock (and outstanding options to purchase an additional 30,000 shares of our common stock) are subject to piggyback registration rights, at the option of the option holder, in the event we register any of our common stock for the account of any person other than the Company (other than a registration statement on Form S-4 or S-8 or an offering to our existing security holders or pursuant to a dividend reinvestment plan, or any other registration which is not appropriate for the registration of these particular options).

***We may not be able to access the SSO Facility***

Our ability to access financing under the SSO Facility is contingent on a number of conditions. If we are unable to access financing under the SSO Facility, we may be required to restructure and reduce spending, and the resultant curtailment of our development efforts could have a material adverse effect on our ability to realize the commercial potential of our products and achieve long-term profitability. In addition, our failure to satisfy the conditions necessary for us to access financing under the SSO Facility may adversely affect the terms on which we may be able to obtain additional financing.

***The Kingsbridge SSO Facility may have a dilutive impact on our stockholders and may encourage short sales. The SSO Facility imposes certain limitations on our ability to issue equity or equity linked securities.***

There are 3,803,039 shares of our common stock that are reserved for issuance under the SSO Facility, that we entered into with Kingsbridge, 250,000 shares of which are related to a warrant that we issued to Kingsbridge. In certain circumstances where the registration statement covering these shares, of which this prospectus is a part, is not effective or available to Kingsbridge, additional shares may be issuable to Kingsbridge under the agreement. The issuance of shares under the SSO Facility at a discount to the market price of the common stock, and upon exercise of the warrant, will have a dilutive impact on other shareholders, and the issuance or even potential issuance of such shares, if any, could have a negative effect on the market price of our common stock. If we sell stock to Kingsbridge when our share price is decreasing, such issuance will have a more dilutive effect and may further decrease our stock price.

To the extent that Kingsbridge sells shares of our common stock issued under the SSO Facility to third parties, our stock price may decrease due to the additional selling pressure in the market. The perceived risk of dilution from sales of stock to or by Kingsbridge may cause holders of our common stock to sell their shares or encourage short sales. This could contribute to a decline in our stock price.

During the two-year term of the SSO Facility, we are subject to certain restrictions on our ability to engage in certain equity or equity-linked financings without the consent of Kingsbridge. These restrictions primarily relate to non-fixed future-priced securities. We may not issue securities that are, or may become, convertible or exchangeable into shares of common stock where the purchase, conversion or exchange price for such common stock is determined using a floating or otherwise adjustable discount to the market price of the common stock during the two year term of our agreement with Kingsbridge. However, the agreement does not prohibit us from conducting most other kinds of debt or equity financings, including private investments in public equity ( PIPEs ), shelf offerings, and other follow-on offerings.

**THE STRUCTURED SECONDARY OFFERING FACILITY ARRANGEMENT**

On December 27, 2004, we entered into a structured secondary offering facility arrangement, (the SSO Facility ), with Kingsbridge, pursuant to a Common Stock Purchase Agreement dated as of December 27, 2004, which we sometimes refer to as the Common Stock Purchase Agreement. The Common Stock Purchase Agreement entitles us to sell and obligates Kingsbridge to purchase, from time to time over a period of two years, shares of our common stock for cash consideration up to an aggregate of $20 million, subject to several conditions and restrictions. At the same time, we entered into a related Registration Rights Agreement with Kingsbridge, and we issued a warrant to Kingsbridge. Pursuant to the Common Stock Purchase Agreement, we have (i) filed a registration statement of which this prospectus is a part, covering the possible resale by Kingsbridge of any shares that we may issue to Kingsbridge under the Common Stock Purchase Agreement, and (ii) issued a warrant to Kingsbridge, which we will sometimes refer to as the Warrant, to purchase 250,000 shares of our common stock at an initial exercise price of $3.811 per share. The Warrant may be exercised from June 27, 2005 through June 27, 2010. Through this prospectus, the selling shareholder may offer to the public for resale shares of our common stock that we may issue to the selling shareholder pursuant to the Common Stock Purchase Agreement, or that the selling shareholder may acquire upon exercise of the Warrant.

For a period of 24 months from the date of the Common Stock Purchase Agreement, we may, from time to time, at our discretion, but subject to certain conditions that we must satisfy in order to sell to Kingsbridge or draw down funds under the SSO Facility, sell shares of our common stock to Kingsbridge at a purchase price having a discount of up to 12% from the volume weighted average of the price of our common stock for each of the 15 trading days following our election to sell shares. The discount will be determined as follows:

| VWAP* | PERCENT OF VWAP (APPLICABLE DISCOUNT) | |
|---|---|---|
| Greater than or equal to $8.50 per share | 92% | (8)% |
| Greater than or equal to $4.00 per share but less than $8.50 per share | 90% | (10)% |
| Greater than $2.00 per share but less than $4.00 per share | 88% | (12)% |

* As set forth in the Common Stock Purchase Agreement, VWAP means the volume weighted average price of our common stock during a trading day as reported by Bloomberg, L.P. using the AQR function.

The maximum number of shares of common stock that we can issue pursuant to the SSO Facility arrangement is 3,553,039 shares. An additional 250,000 shares of common stock are issuable with respect to a Warrant that we issued to Kingsbridge in connection with our entering into the SSO Facility. We intend to exercise our right to draw down amounts under the SSO Facility, if and to the extent available, at such times as there is a need for additional capital and when we believe that sales of stock under the SSO Facility provide the most effective means of raising capital.

Our ability to require Kingsbridge to purchase our common stock is subject to various limitations. We can make draw downs in amounts ranging from a minimum of $250,000 to a maximum of 3.0% of our market capitalization at the time of the draw down. Unless Kingsbridge agrees otherwise, a minimum of five trading days must elapse between the expiration of any draw down pricing period and the beginning of the next draw down pricing period. Kingsbridge is not obligated to purchase shares at prices below $2.00 per share.

During the term of the SSO Facility, without the prior written consent of Kingsbridge we may not issue securities that are, or may become, convertible or exchangeable into shares of common stock where the purchase, conversion or exchange price for such common stock is determined using a floating discount or other post-issuance adjustable discount to the market price of the common stock, including pursuant to an equity line or other financing that is substantially similar to the arrangement provided for in the SSO Facility.

The issuance of our common stock under the SSO Facility or upon exercise of the Warrant will have no effect on the rights or privileges of existing holders of common stock except that the economic and voting interests of each shareholder will be diluted as a result of such issuance. Although the number of shares of common stock that shareholders presently own will not decrease, such shares will represent a smaller percentage of our total shares that will be outstanding after such events. If we draw down amounts under the SSO Facility when our share price is decreasing, we will need to issue more shares than if our stock price was higher. Such issuances will have a dilutive effect and may further decrease our stock price.

Kingsbridge agreed in the Common Stock Purchase Agreement that during the term of the SSO Facility, neither Kingsbridge nor any of its affiliates, nor any entity managed by Kingsbridge, will (i) be in a short position with respect to shares of our common stock in any accounts directly or indirectly managed by Kingsbridge or any of its affiliates or any entity managed by Kingsbridge or (ii) engage in any transaction that is intended to reduce the economic risk of ownership of shares of our common stock (including the purchase of any option or contract to sell) that would, directly or indirectly, have an effect substantially equivalent to selling short such shares of common stock that are subject to, underlie or may be deliverable in satisfaction of such transaction or that otherwise may be reasonably be expected to adversely affect the market price of the common stock.

Before Kingsbridge is obligated to buy any shares of our common stock pursuant to a draw down, the following conditions, none of which is in the control of Kingsbridge, must be met:

Each of our representations and warranties in the Common Stock Purchase Agreement shall be true and correct in all material respects as of the date when made and as of the draw down exercise date as though made at that time, except for representations and warranties that are expressly made as of a particular date.

We shall have performed, satisfied and complied in all material respects with all covenants, agreements and conditions required by the Common Stock Purchase Agreement, the Registration Rights Agreement and the Warrant to be performed, satisfied or complied with by us.

We shall have complied in all material respects with all applicable federal, state and local governmental laws, rules, regulations and ordinances in connection with the execution, delivery and performance of the Common Stock Purchase Agreement and the consummation of the transactions contemplated by such agreement.

The registration statement, which includes this prospectus, shall have previously become effective and shall remain effective.

We shall not have knowledge of any event that could reasonably be expected to have the effect of causing the registration statement applicable to the resale of shares of our common stock by Kingsbridge to be suspended or otherwise ineffective (which event is more likely than not to occur within fifteen trading days after the trading day on which we deliver a draw down notice under the SSO Facility).

Trading in our common stock shall not have been suspended by the Securities and Exchange Commission, the Nasdaq Stock Market or the National Association of Securities Dealers and trading in securities generally on the Nasdaq Stock Market shall not have been suspended or limited.

No statute, rule, regulation, executive order, decree, ruling or injunction shall have been enacted, entered, promulgated or endorsed by any court or governmental authority which prohibits the consummation of any of the transactions contemplated by the Common Stock Purchase Agreement.

No action, suit or proceeding before any arbitrator or any governmental authority shall have been commenced, and no investigation by any governmental authority shall have been threatened, against us or any of our officers, directors or affiliates seeking to enjoin, prevent or change the transactions contemplated by the Common Stock Purchase Agreement.

We shall have sufficient shares of common stock, calculated using the closing trade price of the common stock as of the trading day immediately preceding a draw down, registered under the registration statement to issue and sell such shares in accordance with such draw down.

In addition, Kingsbridge is not obligated to buy any shares of our common stock pursuant to a draw down which would result in the number of shares of our common stock beneficially owned by Kingsbridge, together with those shares that we propose to sell to Kingsbridge in connection with a draw down, to exceed 9.9% of the total amount of our common stock that would be outstanding upon completion of the draw down. There is no guarantee that we will be able to meet the foregoing conditions or any other conditions under the Common Stock Purchase Agreement or that we will be able to draw down any portion of the amounts available under the SSO Facility.

We also entered into a Registration Rights Agreement with Kingsbridge. Pursuant to the Registration Rights Agreement, we have filed a registration statement, which includes this prospectus, with the Securities and Exchange Commission relating to the resale by Kingsbridge of any shares of common stock purchased by Kingsbridge under the Common Stock Purchase Agreement or issued to Kingsbridge as a result of the exercise of the Warrant. The effectiveness of such registration statement is a condition precedent to our ability to sell common stock to Kingsbridge under the Common Stock Purchase Agreement. We are entitled in certain circumstances, including the existence of certain kinds of nonpublic information, to deliver a blackout notice to Kingsbridge, suspend the use of this prospectus and prohibit Kingsbridge from selling shares, until an appropriate prospectus supplement has been filed or an amendment to the registration statement has been filed and declared effective. If we impose a blackout notice in circumstances not permitted by the Registration Rights Agreement, or if the registration statement of which this prospectus is a part is not effective in circumstances not permitted by the agreement, then we must pay amounts to Kingsbridge, calculated by means of a varying percentage of an amount based on the number of shares held by Kingsbridge and the change in the market price of our common stock between the date the blackout notice is imposed (or the registration statement is not effective) and the date the prospectus again becomes available.

The foregoing summary of the SSO Facility does not purport to be complete and is qualified by reference to the Common Stock Purchase Agreement, the Registration Rights Agreement and the Warrant, copies of which have been filed as exhibits to the registration statement of which this prospectus is a part.

## THE SELLING SHAREHOLDER

This prospectus relates to the possible resale by the selling shareholder of shares of common stock that we may issue pursuant to the Common Stock Purchase Agreement or upon exercise of the Warrant. We are filing the registration statement of which this prospectus is a part pursuant to the provisions of the Registration Rights Agreement.

The selling shareholder may from time to time offer and sell pursuant to this prospectus any or all of the shares that it acquires under the Common Stock Purchase Agreement or upon exercise of the Warrant. Because the selling shareholder is not obligated to sell shares of common stock, and because the selling shareholder may also acquire or dispose of publicly traded shares of our common stock, we cannot estimate how many shares of common stock the selling shareholder will beneficially own after this offering.

The following table sets forth certain information regarding beneficial ownership of our common stock by Kingsbridge as of May 3, 2005. The selling shareholder has not, within the past three years, had any position, office or other material relationship with us or any of our predecessors or affiliates, except as a result of entering into the SSO Facility arrangement described herein.

| | Shares of Common Stock Beneficially Owned (1) Prior to the Offering | | Number of Shares Being Offered | Shares of Common Stock Beneficially Owned After the Offering (2) | |
|---|---|---|---|---|---|
| **Selling Shareholder** | **Number** | **Percent** | | **Number** | **Percent** |
| Kingsbridge Capital Limited (3) | 3,803,039 | 16.33% (4) | 3,803,039 | 0 | 0% |

(1) Assumes the Company s exercise in full of its draw down rights under the SSO Facility, and includes 3,553,039 shares issuable under the Common Stock Purchase Agreement and 250,000 shares that are issuable upon exercise of the Warrant. The address of Kingsbridge is 3rd Floor, Barclays House, P.O. Box 3340, Road Town, Tortola, British Virgin Islands.

(2) Assumes that all of the offered shares are sold, that no other shares shown in the table as beneficially owned by the selling shareholder are sold, and that the selling shareholder does not acquire any other shares of our common stock.

(3) We have been advised by Kingsbridge that it is controlled by Valentine O Donoghue and does not accept third party investments. Accordingly, Mr. O Donoghue is also regarded as a beneficial owner of the shares of common stock acquired by Kingsbridge.

(4) Based on the number of issued and outstanding shares of common stock as of May 5, 2005.

## FORWARD-LOOKING STATEMENTS

Certain statements contained or incorporated by reference in this prospectus are forward-looking statements concerning our business, financial condition, results of operations, economic performance and financial condition. Forward-looking statements within the meaning of Section 27A of the Securities Act of 1933 and within the meaning of Section 21E of the Securities Exchange Act of 1934 are included, for example, in the discussions about:

our strategy;

new product development or product introduction;

product sales, royalties and contract revenues;

expenses and net income; and

our liquidity.

These and other forward-looking statements involve risks and uncertainties. Actual results may differ materially from those expressed or implied in those statements. Factors that could cause such differences include, but are not limited to, those discussed under the preceding section entitled Risk Factors.

**USE OF PROCEEDS**

We will not receive any of the proceeds from the sale of shares of our common stock by Kingsbridge pursuant to this prospectus. Any proceeds from the sale of the shares by us to Kingsbridge under the Common Stock Purchase Agreement or received in connection with the exercise of the Warrant will be used for general corporate purposes, including further development of our lead clinical programs, capital expenditures and to meet working capital needs and the prepayment or payment at maturity of all or any portion of existing indebtedness. General corporate purposes may also include, without limitation, repayment of debt, possible acquisitions, investments, repurchase of our capital stock and any other purposes that we may specify in any prospectus supplement.

**OUR BUSINESS**

**OVERVIEW OF EMISPHERE**

**Introduction**

Emisphere Technologies, Inc. ( Emisphere , Our , Us or We ) is seeking to overcome one of the most challenging technical hurdles in the pharmaceutical industry the oral delivery of medicines not currently available in oral form. We have product candidates in development across a broad range of therapeutic areas, including cardiovascular disease, diabetes, osteoporosis, growth disorders, asthma and allergies, obesity and infectious diseases. We have not yet obtained regulatory approval for sales of any of our product candidates.

**History**

Emisphere was originally founded as Clinical Technologies Associates, Inc. in 1986. We conducted an initial public offering in 1989, and were listed on NASDAQ under the ticker symbol CTAI . In 1990 we decided to focus on our oral drug delivery technology, now known as the *e*lig*e*n® technology. In 1991, we changed our name to Emisphere Technologies, Inc., and we continued to be listed on NASDAQ, under the new ticker symbol, EMIS .

**The *e*lig*e*n® Technology**

The *e*lig*e*n® technology is a broadly applicable proprietary oral drug delivery technology based on the use of proprietary, synthetic chemical compounds known as EMISPHERE® delivery agents, or carriers. These delivery agents facilitate and/or enable the transport of therapeutic macromolecules (such as proteins, peptides, and polysaccharides) across biological membranes such as the small intestine. We believe that our *e*lig*e*n® technology makes it possible to orally deliver a therapeutic macromolecule without altering its chemical composition or compromising the integrity of biological membranes.

**Business Strategy**

Our core business strategy is to develop oral forms of parenteral drugs, either alone or with corporate partners, by applying the *e*lig*e*n® technology to those drugs. Typically, the parenteral drugs that we target (i) have received regulatory approval, (ii) have demonstrated safety and efficacy, and (iii) are currently available on the market. We believe that focusing on the oral delivery of these types of product candidates increases our probability of successfully executing our business strategy.

As part of our business strategy, we often collaborate with pharmaceutical companies in Phase I studies to determine if one or more of our carriers will facilitate the oral delivery of a particular drug candidate. Our direct costs of such studies are often reimbursed to us by our collaborative partner. Occasionally we conduct such studies on our own with the anticipation that we will secure a partner upon successful completion of such studies. Since our inception, we have progressed nine different drug candidates through such feasibility studies. Later stage clinical trials may not support the findings of these early stage studies. The amount of additional time and money required to obtain regulatory approval for sale of these drug candidates is difficult to determine but is often at least several years, and millions of dollars.

**Product Candidates in Development**

The following table sets forth the therapeutic areas for which we are developing product candidates, either alone or with corporate partners, the candidates currently in development, the present stage of clinical development, and the identity of our corporate partner for partnered programs, as previously reported by Emisphere or the partner.

| THERAPEUTIC AREA | DRUG CANDIDATES | STAGE OF DEVELOPMENT | PARTNER |
|---|---|---|---|
| Cardiovascular | Oral Unfractionated ( UF ) Heparin | Phase III [1] | Self-developed |
| | Oral Low Molecular Weight Heparin ( LMWH[2]) | Phase I | Self-developed |
| Osteoporosis | Oral Salmon Calcitonin ( sCT ) | Phase IIa | Novartis Pharma AG |
| | Oral Recombinant Parathyroid Hormone (teriparatide; PTH 1-34 ) | Phase I | Novartis Pharma AG [3] |
| Bone-related diseases | Partner proprietary small molecule compounds | Phase I | Roche |
| Growth Disorders | Oral Recombinant Human Growth Hormone (somatropin; rhGH ) | Phase I | Novartis Pharma AG [5] |
| Diabetes | Oral Insulin | Phase I [6] | Self-developed |
| | Oral Glucagon-Like Peptides ( GLPs ) | Pre-clinical [4] | Self-developed |
| Asthma/Allergies | Oral Cromolyn Sodium | Phase I | Self-developed |
| Obesity | Oral Ciliary Neutrophic Growth Factor ( CNTF ) | Pre-clinical [4] | Self-developed |
| | Oral $PYY_{3-36}$ | Pre-clinical [4] | Self-developed |
| Anti-infectives | Oral Anthrax Antigen | Pre-clinical [4] | US Army Medical Research Institute of Infectious Diseases |

(1) We previously developed a liquid form of oral heparin and in 2000 conducted a Phase III clinical trial that was completed in early 2002. The trial did not meet its endpoint of superiority to LOVENOX®, a leading low molecular weight heparin. Current development involves solid forms of oral heparin.

(2) We have an agreement with a producer of LMWH to supply us a proprietary LMWH and in 2003 we conducted a Phase I study with this producer. Either party may terminate this agreement with or without cause on sixty days notice to the other party. While our development of an oral LMWH product is dependent on having a source of LMWH, we believe that we could secure a replacement supplier of LMWH if our current supply arrangement were to be terminated. In 1991 we conducted a Phase I study with a different LMWH product.

(3) As noted elsewhere in this prospectus, we had previously partnered this program with Lilly. We are currently in litigation with Lilly and have given Lilly a notice of termination of our agreements with them. On December 1, 2004, we entered into a new arrangement with Novartis to develop this product candidate, should we be successful in fully reacquiring our rights from Lilly for this candidate.

(4) Pre-clinical is defined as investigating safety of a product candidate in a controlled laboratory environment and establishing activity in standard animal models. We have not filed an IND with the FDA for product candidates described as Pre-clinical .

(5) Originally partnered with Lilly. We reacquired all rights in 2003 and have partnered with Novartis to develop the candidate.

(6) We conducted a 13-patient clinical trial to investigate safety and confirm efficacy of the EMISPHERE oral insulin tablet using a multiple dose regimen. A clinical trial that includes human testing and predetermined endpoints qualifies as a Phase II trial, however, the limited number of patients in the trial could cause the trial to be viewed as a Phase I trial.

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**OVERVIEW OF THE DRUG DELIVERY INDUSTRY**

The drug delivery industry develops technologies for the improved administration of therapeutic macromolecules with the goal of expanding markets for existing products and extending drug franchises. Drug delivery companies also seek to develop products on their own that would be patent protected by applying proprietary technologies to off-patent pharmaceutical products. Primarily, drug delivery technologies are focused on improving safety, efficacy, ease of patient use and patient compliance. Pharmaceutical and biotechnology companies consider improved drug delivery as a means of gaining competitive advantage over their peers.

Therapeutic macromolecules, of which proteins are the largest sub-class, are prime targets for the drug delivery industry for two reasons. First, therapeutic macromolecules address large markets for which there is an established medical need. These drugs are widely used, as physicians are familiar with them and are accustomed to prescribing them. Second, therapeutic molecules are significantly enhanced through alternative delivery. These medicines are comprised of proteins and other large or highly charged molecules that, if orally administered under traditional oral delivery methods, would degrade in the stomach or intestine before they are absorbed into the bloodstream. Therefore, they are administered parenterally. Parenteral administration is undesirable, however, for many reasons, including patient discomfort, inconvenience and risk of infection. Poor patient acceptance of, and compliance with, parenteral therapies can lead to medical complications. In addition, parenteral therapies can often require incremental costs associated with administration in hospitals or doctors offices.

Previously published research indicates that patient acceptance of and adherence to a dosing regimen is higher for orally delivered medications than it is for non-orally delivered medications. Our business strategy is based upon our belief that the development of an efficient and safe oral delivery system for therapeutic macromolecules represents a significant commercial opportunity. We believe that more patients will take orally delivered drugs more often, spurring market expansion.

**LEADING CURRENT APPROACHES TO DRUG DELIVERY**

*Transdermal (via the skin) and Needleless Injection*

The size of most macromolecules makes penetration of the skin inefficient or ineffective. Some peptides and proteins can be transported across the skin barrier into the bloodstream using high-pressure needleless injection devices. The devices, which inject proteins through the skin into the body, have been available for many years. We believe these devices have not been well accepted due to patient discomfort, relatively high cost, and the inconvenience of placing the drugs into the device.

*Nasal (via the nose)*

The nasal route (through the membranes of the nasal passage) of drug administration has been limited by low and variable bioavailability for proteins and peptides. As a result, penetration enhancers often are used with nasal delivery to increase bioavailability. These enhancers may cause local irritation to the nasal tissue and may result in safety concerns with long-term use. A limited number of peptides using nasal delivery have been approved for marketing in the United States including MIACALCIN®, developed by Novartis as an osteoporosis therapy, a therapeutic area we have targeted.

*Pulmonary (via the lung)*

Pulmonary delivery (through the membranes of the lungs) of drugs is emerging as a delivery route for large molecules. Although local delivery of respiratory drugs to the lungs is common, the systemic delivery (i.e., delivery of the drugs to the peripheral vasculature) of macromolecule drugs is less common because it requires new formulations and delivery technologies to achieve efficient, safe and reproducible dosing.

*Intraoral (via the membranes in the mouth)*

Intraoral delivery is also emerging as a delivery route for large molecules. Buccal delivery (through the membrane of the cheek) and sublingual delivery (through the membrane under the tongue) are forms of intraoral delivery.

*Oral (via the mouth)*

We believe that the oral method of administration is the most patient-friendly option, in that it offers convenience, is a familiar method of administration, enables increased compliance and, for some therapies, is considered the most physiologically appropriate. We and other drug delivery and pharmaceutical companies have developed or are developing technologies for oral delivery of drugs. We believe that our *e*lig*e*n® technology, however, provides an important competitive advantage in the oral drug delivery route of administration because it does not alter the chemical composition of the therapeutic macromolecules. We have conducted over 100,000 human dosings and have witnessed no serious adverse events that can be attributed to the EMISPHERE® delivery agents dosed or the mechanism of the *e*lig*e*n® technology.

In general, we believe that oral administration will be preferred to other methods of administration. However, such preference may be offset by possible negative attributes of orally administered drugs such as the quantity or frequency of the dosage, the physical size of the capsule or tablet being swallowed or the taste. For example, in the PROTECT trial, patient compliance was hindered by patients distaste for the liquid being administered.

**THE *e*lig*e*n® TECHNOLOGY**

Our oral drug delivery technology, the *e*lig*e*n® technology, is based upon proprietary, synthetic chemical compounds known as EMISPHERE® delivery agents (or carriers ) that facilitate or enable the transport of therapeutic macromolecules across biological membranes, such as the membranes of the small intestine. We have orally delivered in early stage testing the following therapeutic macromolecules: heparin, insulin, PTH 1-34, rhGH, and salmon calcitonin in humans, and over 40 other compounds in laboratory animals. In addition, we have demonstrated oral delivery in humans of other compounds that are not macromolecules but are poorly absorbed, such as cromolyn sodium. We have not successfully completed a Phase III trial with respect to any of our product candidates nor have we received any regulatory approvals for sales of any of our product candidates.

We believe based on our testing to date, including animal studies and early-stage clinical trials, that the EMISPHERE® delivery agents use a natural transport process in the body (passive transcellular transport) that enables therapeutic macromolecules to cross membranes. Also, we believe that the *e*lig*e*n® technology changes only the shape of the therapeutic macromolecule and not its chemical composition. Under physiological conditions, protein molecules naturally exist in many different shapes, or conformations. Some of these conformations can be transported across the cell membranes. Our hypothesis is that once the therapeutic macromolecule crosses the membrane, the delivery agent separates from the macromolecule and the drug reestablishes its natural shape, thereby allowing it to remain therapeutically active.

We have designed and synthesized a library of over 3,000 delivery agents and continue to evaluate our delivery agents for their ability to facilitate the delivery of therapeutic macromolecules across biological membranes.

**Key Characteristics of the *e*lig*e*n® Technology**

Based on our testing to date, including animal studies and early-stage clinical trials, we believe that our oral drug delivery technology has competitive advantages, including:

- EMISPHERE® delivery agents are applicable across a diverse group of molecules such as proteins, peptides, carbohydrates, polar organics, and other compounds;

Oral drug delivery using the *e*lig*e*n® technology does not rely upon the addition of other agents that can have adverse effects on the intestinal membranes or digestion;

We have created various types of oral formulations, including solutions, suspensions, tablets and capsules;

We believe our *e*lig*e*n® technology is applicable to controlled release dosage forms; and

We believe that the technology and manufacturing equipment required to produce EMISPHERE® delivery agent material in commercial quantities is readily available based on discussions with multiple manufacturers and based on such manufacturers current capacities to produce similar material.

**THERAPEUTIC INDICATIONS**

**Cardiovascular (Anti-thrombosis)**

Unfractionated heparin ( UFH ) and low molecular weight heparin ( LMWH ) are widely used anti-thrombotics/anti-coagulants. These agents are primarily indicated for treating and preventing post-surgical deep vein thrombosis (blood clots following major surgery) ( DVT ) and more severe sequelae, e.g., pulmonary embolism. Also, these drugs are frequently prescribed for acute myocardial infarction, graft surgery, stroke and unstable angina. The most common indications for heparin therapy are the prevention of venous thrombosis (blood clots) following surgical procedures lasting longer than 30 minutes (especially orthopedic, pelvic, abdominal, trauma, angioplasty or heart surgery). According to the website www.dvt.org (maintained by the University of Massachusetts Medical School), the risk of developing DVT following major surgery can range as high as seventy percent. DVT treatment generally includes about five to ten days of heparin treatment, continued by months of orally administered warfarin. Currently, all forms of heparin are administered as either a continuous intravenous infusion or a subcutaneous injection.

According to published reports in *The Lancet* and the *Journal of Bone and Joint Surgery*, recent studies indicate that a longer prophylaxis regimen (extending the duration of heparin preventative therapy from the current standard of practice) would benefit patients following major surgery. We believe that compliance would be improved if a commercially viable oral form of UFH or LMWH was available because patients could be more inclined to comply with this type of dosage compared to parenteral forms. Preventative therapy is typically recommended for at least 10 to 14 days post-surgery. However, several studies indicate that longer heparin prophylaxis (preferably for 30 days) is optimal because the risk of DVT remains high throughout this period. We believe our oral heparin product candidate would be a desirable therapy in this 30-day period. Without DVT prophylaxis, the incidence of DVT in certain post surgical states is often greater than 50%. Heparin is often considered the anti-coagulant of choice for the prevention and treatment of cardiovascular complications, such as DVT or blood clots and pulmonary embolism in high-risk, hospitalized patients. Typically, heparin is favored by clinicians over warfarin because heparin is more effective, produces a rapid onset of anti-coagulation activity, has a shorter physiological half-life, and is indicated in fewer drug-drug interactions than many FDA approved drugs. In addition, warfarin requires frequent patient monitoring. A major disadvantage of heparin therapy is the requirement for subcutaneous administration.

We believe that our solid oral heparin and LMWH candidates could penetrate and expand existing heparin markets. We anticipate that new markets for the heparins will be created based on recently reported studies published by the American Heart Association and the *New England Journal of Medicine* indicating that UFH may have utility for indications other than anti-coagulation and anti-thrombosis. These indications include: unstable angina, arterial fibrillation, acute myocardial infarction, angioplasty, stent placement, coronary artery bypass graft, pulmonary embolism and stroke. In addition, a growing body of pre-clinical and clinical data indicates that heparin has potent anti-inflammatory and anti-cancer properties and the studies mentioned above indicate that heparin has been shown to be beneficial as a treatment for inflammatory bowel disease, rheumatoid arthritis, asthma, psoriasis, transplant rejection and proteinurias.

We believe that oral heparin could be considered a more convenient and patient-friendly therapy than injectable heparin by both patients and physicians, and could open the at-home market to heparin by replacing warfarin and injectable LMWH use. Also, we believe that our oral heparin product candidates ultimately could enable an extended dosing regimen and be applicable for a wide range of anti-coagulant/anti-thrombotic uses.

*Our Oral Heparin Program*

We are evaluating solid oral heparin prototypes, including capsule and tablet forms of UFH and LMWH, using our delivery agent, SNAC. SNAC was administered as Heparin/SNAC Oral solution in a Phase III study of over 2,000 patients that we refer to as the PROTECT trial .

Heparin, a polysaccharide, represents a significant formulation challenge for our *e*lig*e*n® technology because the potency of heparin is significantly lower than most existing macromolecule drugs, requiring a large dose of heparin, which combined with the carrier SNAC, results in both a large solid dosage form and a large number of tablets or capsules per dose. Since 2002, we have significantly reduced the necessary dose by using both traditional formulation techniques and *e*lig*e*n® technology-specific techniques. We believe that reducing the size of the dosage form and the number of tablets or capsules per dose would provide the most patient-preferred and commercially viable solid dosage form. We are continuing our efforts to optimize a solid oral UFH dosage form and have produced improved solid formulations with additional performance enhancements.

In December 2002, at the American Society of Hematology ( ASH ) Annual Meeting, we presented positive outcomes from a Phase I clinical study evaluating two solid oral UFH formulations, in tablet and capsule forms. For each solid dosage form which made use of our *e*lig*e*n® technology, the data demonstrated that an effect on blood coagulation was achieved consistent with therapeutic levels that are acceptable in known heparin indications, without any tolerability issues. In addition, the total quantity of material was significantly reduced in both formulations from the oral liquid formulation and the physical blend in a capsule used in previous studies.

In the first quarter of 2004, we selected prototype formulations in the forms of a tablet and capsule for production and Phase I clinical testing in the United States. That testing was completed in June 2004, and in August 2004, we announced that we selected a soft gelatin capsule formulation of UFH that achieved clinically significant delivery of heparin. This formulation was chosen after the evaluation of results from a Phase I clinical trial comparing various oral dosage formulations of EMISPHERE® Heparin/SNAC to our liquid UFH formulation, which was previously tested in the PROTECT trial.

The randomized, open label, cross-over placebo controlled single blind study, conducted in 15 healthy volunteers, evaluated anti-coagulant activity before and after the administration of four new oral dosage forms of UFH. The new formulations consisted of tablets and soft-gel capsules. Each subject was also administered our liquid UFH formulation and SNAC (Emisphere s proprietary delivery agent) alone, as a control arm.

Following each dose, subjects were evaluated for anticoagulation activity, by measurement of anti-Factors Xa and IIa and activated partial thromboplastin time that demonstrate the presence of pharmacologically active heparin in blood. Three of the four new formulations delivered heparin as well or better than the liquid formulation. Subjects treated with SNAC alone showed no change from baseline in anti-coagulant activity. No serious adverse events considered to be related to Heparin/SNAC were reported in the study.

Both soft-gel capsule formulations contained less UFH and SNAC per dose than the previously tested liquid formulation yet consistently demonstrated significant improvements over the liquid dose in delivering UFH.

With an established database on safety from our PROTECT trial, we believe we are well positioned to rapidly bring our new formulation forward into late-stage clinical trials.

*Our PROTECT Phase III Trial (Discontinued Liquid Dosage Form)*

We discontinued our liquid oral heparin program in 2002 following confirmed failure of the trial to meet its predetermined endpoints. We conducted a multinational Phase III program with a liquid formulation of oral heparin. We refer to the multi-center, double-blind, double-dummy Phase III trial as the PROTECT (PRophylaxis with Oral SNAC/heparin against ThromboEmbolic Complications following Total hip replacement surgery) trial.

The PROTECT trial enrolled 2,288 patients to evaluate the safety and efficacy of a solution oral heparin formulation using our *eligen*® oral drug delivery technology for the prevention of DVT in total hip replacement surgery patients (a surgical patient population that historically has had among the highest rate of DVT). The goal of the PROTECT trial was to demonstrate the superior efficacy and comparable safety of our oral heparin when dosed postoperatively for a 30-day regimen, as compared to injectable enoxaparin, when dosed postoperatively for a 10-day regimen. A 10-day regimen of injectable enoxaparin, marketed by Aventis Pharma SA under the LOVENOX trademark, is the standard of care in the prevention of DVT, as determined by the American College of Chest Physicians Sixth Consensus Conference.

The endpoint of the PROTECT trial was DVT occurrence in the 30 days following surgery, or pulmonary embolism or death. Investigators at more than 120 international sites evaluated a liquid form of heparin, consisting of the EMISPHERE® delivery agent SNAC in combination with unfractionated heparin, when dosed orally in a 30-day regimen, compared to enoxaparin, when dosed subcutaneously (by injection) in a 10-day regimen. Total DVTs were determined by bilateral venogram, the standard measurement for clinical trials evaluating agents designed to prevent DVTs, measured at 30 days following surgery. A team of radiologists at Boston s Massachusetts General Hospital read all the venographies produced to determine the presence of a blood clot (thrombus).

On May 14, 2002, we announced initial results from the PROTECT trial which did not demonstrate the superiority of oral liquid heparin, when dosed in a 30-day treatment regimen, compared to enoxaparin administered by injection in a 10-day dosing regimen in preventing DVTs. However, the data from the study suggested that the lower than expected efficacy net result may have been due to the poor taste of the liquid dosage form, and that a more tolerable dosage form (e.g., capsule or tablet) would result in higher patient acceptability. The trial sought to demonstrate clinical superiority of oral liquid heparin over injectable LOVENOX® by demonstrating at least an absolute 10% reduction in DVT events as a result of extended oral liquid heparin dosing as compared to ten days of dosing of injectable LOVENOX®.

In December 2002, we presented an analysis of the study at the 44th annual meeting of the American Society of Hematology. The data demonstrated for the first time that the macromolecule heparin could be delivered into the bloodstream of a patient following dosing in an oral form. However, a liquid formulation of oral heparin in a 30-day treatment regimen was deemed to have poor tolerability due to its taste.

We hope to leverage the extensive safety database that we now have for SNAC, the EMISPHERE® delivery agent that was used in the PROTECT trial. We are evaluating the application of that safety database to supplement with additional efficacy data from planned Phase III trials for the solid form of oral heparin for potential utility toward future regulatory submissions to the FDA for the Heparin/SNAC product. We are currently seeking FDA approval to begin Phase III testing.

**Diabetes**

According to statistics provided by the World Health Organization and the American Diabetes Association, approximately 177 million people worldwide are afflicted by diabetes, with approximately 18 million of those afflicted residing in the United States. Nearly one-third of all individuals in the United States suffering from diabetes are unaware that they have this chronic disease. There are two principal types of diabetes:

*Type 1* - An autoimmune disease in which the body does not produce any insulin. Type 1 diabetes typically appears initially in children and young adults. Type 1 diabetics must receive multiple daily insulin injections to stay alive. Type 1 diabetes accounts for approximately 5-10% of total diabetes cases.

*Type 2* - A metabolic disorder resulting from the body s inability to properly utilize or produce adequate amounts of insulin. Type 2 diabetics account for approximately 90-95% of diabetes cases. Reportedly, the incidence of Type 2 diabetes is rising rapidly as a result of an aging population, greater prevalence of obesity, and a more sedentary lifestyle. Type 2 diabetes is also being diagnosed in younger patients as compared to historical observations.

According to the publicly filed annual reports of leading insulin manufacturers, worldwide sales of insulin exceeded $5.8 billion in 2003. Although diet, exercise and non-insulin medications are often used to control the disease, approximately 40% of all Type 2 diabetics use insulin to control the disease, accounting for approximately 50% of total insulin use. Although many more Type 2 diabetics could benefit from insulin therapy, use of the drug has been limited because it is administered by injection. We believe that a successful oral insulin therapy could, depending on factors such as the quantity and frequency of the dosage, the physical size of the tablet or capsule being swallowed or the taste, facilitate compliance for diabetic patients who are not diligent with their prescribed injection regimens, and enable those patients adverse to injections to adopt insulin therapy at an earlier stage of the disease.

Based on previously published research, we believe that oral insulin delivery is consistent with the physiology of natural secretion of insulin from the pancreas, which travels to the liver prior to being distributed to the peripheral circulation. We believe that our orally delivered insulin likewise travels to the liver prior to being distributed to the peripheral circulation. In comparison, also based on previously published research, we believe that injected insulin, like other non-oral insulin therapies, is administered into the general (systemic) circulatory system first and then to the liver. We believe that as a result, injectable insulin results in higher circulating insulin levels than oral insulin. Chronic excess insulin in the general circulation (known as hyperinsulinemia) is thought to contribute to certain diabetic patient complications.

Furthermore, we believe that the pharmacological profile of our oral insulin to date, namely, the onset and duration of action, has been consistent with the physiological profile of naturally secreted insulin from the pancreas, especially under fed conditions. For the foregoing reasons, we believe that, aside from the convenience benefits, orally delivered insulin, with the appropriate clinical attributes, may provide an alternative therapy with fewer complications when compared to existing medical diabetes treatments.

*Our Oral Insulin Program*

In June 2001, we entered an oral unformulated dosage of insulin using an EMISPHERE® delivery agent into proof-of-concept Phase I clinical testing. There were 29 treatment-emergent adverse events during this study, of which 14 were considered to be related to medication. The most frequent related adverse event was hypoglycemia which occurred once in each of four subjects. Overall, the treatments were safe and well tolerated.

In October 2001, we completed a Phase I study using the most promising EMISPHERE® delivery agent selected for insulin. The resulting data were used to support the testing of this unformulated dosage in early-stage Type 2 diabetic patients. Overall the safety profiles for combined treatments were good; however, 3 subjects following 150 unit dosings required food and drink due to hypoglycemia. All 8 subjects required rescue treatments due to hypoglycemia following 10 unit subcutaneous insulin dosings.

In November 2001, we completed a Phase I trial testing oral insulin in Type 2 diabetic patients upon completing a euglycemic clamp study (a study in which insulin and glucose are infused intravenously at different doses to see what levels of insulin control different levels of glucose). No adverse events were observed in this study and the results were found to be statistically significant.

In June 2002, in an oral presentation and media briefing at the Annual Meeting of the American Diabetes Association in San Francisco, we presented proof-of-concept preliminary clinical results from a Phase I study conducted in Europe, which showed that an early capsule prototype of oral insulin using the *eligen*® technology resulted in absorption from the gastrointestinal tract. The data also demonstrated significant reductions in blood glucose levels. Although not directly compared in this trial, the reductions in blood glucose levels were consistent with reductions in glucose seen with injectable insulin. No serious adverse events were reported.

The double-blind, placebo-controlled study consisted of the administration of insulin with an EMISPHERE® delivery agent in capsule form to a total of 20 healthy human volunteers in the fasted state who received five different dose regimens, ranging from 100 to 150 units of insulin and 100 mg to 600 mg of delivery agent, and a subcutaneous control, with another two subjects who received placebo. Nine subjects received only the delivery agent. The study demonstrated that the orally delivered insulin had favorable pharmacokinetic and pharmacodynamic profiles, in that systemic blood insulin levels peaked within 25 minutes. Such favorable profiles are considered to be significant by physicians, in general, because the primary potential use of oral insulin would be before meals, and the more rapid the delivery, the better patients can time their medication to their meal. We believe that this data and the data from the 2001 studies provide proof-of-concept for our oral drug delivery technology with insulin as evaluated in healthy, fasted volunteers.

In March 2003, we announced completion of a Phase I study in early-stage Type 2 diabetic patients designed to demonstrate the pharmacokinetics and absorption of insulin, and subsequent effects on blood glucose of this product candidate following a standardized meal. The placebo controlled, crossover study evaluated two oral doses of insulin. Patients received one capsule containing 5.6 mg (150 units) of insulin and 200 mg of EMISPHERE® delivery agent or two capsules containing a total of 11 mg (300 units) of insulin and 400 mg of EMISPHERE® delivery agent. The study compared the two oral unformulated dosages to a fast-acting injectable insulin in fourteen patients with Type 2 diabetes who had received a standardized solid meal (722 kcal). The study also included a placebo group. For the 11 mg dose, the data demonstrated that unformulated oral insulin dosages, when administered 30 minutes prior to the standardized meal, reduced post-prandial glucose excursion (the rise in blood sugar following a meal) and produced a marked increase in systemic insulin levels and a concomitant reduction in C-peptide (a marker of endogenous insulin production) as compared to the placebo. In addition, plasma insulin concentrations peaked faster using our oral unformulated dosage as compared to fast-acting injectable insulin (30 minutes with oral versus approximately 45 minutes typically seen with injectable formulations). Similar results were observed in certain patients given the 5.6 mg dose, who received the same standardized meal. The study produced evidence that one or two capsules could impact post-prandial blood glucose in certain early-stage Type 2 diabetic patients and demonstrated favorable pharmacokinetics. No serious adverse events were reported. All study treatments were safe and well tolerated with few hypoglycemic episodes occurring mainly after subcutaneous injection of 12 unit fast-acting insulin.

In June of 2003, we presented preliminary data at the Annual Meeting of the American Diabetes Association from two EMISPHERE® oral insulin capsule Phase I studies. The first study ( the overnight study ), presented in a poster session, was conducted to determine if the administration of the EMISPHERE® oral insulin prototype capsules at bedtime could exert effects on overnight-fasting glucose homeostasis and insulin secretion in early-stage Type 2 diabetics. The overnight study summary conclusion was that the amount of oral insulin delivered reduced fasting glucose levels the following morning. The prototype of oral insulin was well-tolerated and no serious adverse events were reported. The second study ( the glucose clamp study ), presented in a plenary session, was a proof-of-concept study conducted in early-stage Type 2 diabetics to assess insulin secretion and resistance following the administration of two oral insulin prototype capsules containing a total of 11 mg insulin (300 units) when a simultaneous infusion of glucose was administered. The data demonstrated that relative biopotency of oral insulin was 32% (mean) in the first hour after administration, which is the most critical time period when the first-phase insulin response should be replicated in a Type 2 diabetic. No serious adverse events were observed in this study. All 24 subjects who passed screening completed the study. The safety profiles conducted following administration of the EMISPHERE® delivery agent oral/4-CNAB were excellent, with only one minor adverse event. There were no hypoglycemic events.

In November 2003, we announced preliminary data from a Phase I study evaluating a tablet prototype of EMISPHERE® oral insulin. These data were presented at the Fifth Annual Diabetes Technology Meeting. Data from the study demonstrated that a practical tablet dosage form totaling 11 mg (300 units) of insulin and 160 mg of EMISPHERE® delivery agent could reduce post-prandial glucose excursion when administered in the pre-prandial state ten minutes prior to a standard, American Diabetes Association breakfast.

In the fourth quarter of 2003, we completed the clinical dosing portion of our first multiple dosing with the EMISPHERE® oral insulin tablet prototype when dosed in Type 2 diabetics. The 13-patient Phase I study, consisting of seven treated patients and six control patients, evaluated the safety, effect and tolerability of the oral insulin tablets when administered four times daily over a two-week period. The study was conducted at PROFIL Institute, an internationally recognized diabetes research center in Neuss, Germany. The study enrolled Type 2 diabetic patients treated with diet alone (HbA1C<8.0%). After baseline assessments, patients were randomized to active treatment (two tablets containing a total of 300 units of insulin/160 mg EMISPHERE® delivery agent) or controlled treatment (two tablets containing a total of 200 mg EMISPHERE® delivery agent), four times daily (10 minutes before meals and at bedtime).

In January 2004, we announced that the preliminary data indicated that repeated administration of our oral insulin was not associated with clinically relevant hypoglycemic events, an adverse complication that is often associated with injected insulin and other anti-diabetic treatments while the oral insulin did impact positively on a number of clinically relevant diabetic endpoints.

In June 2004, we presented results from our multiple-dose 13-patient Phase I clinical study at the 64th Scientific Sessions of the American Diabetes Association. The results were presented in a late-breaker session (abstract #8-LB) by lead investigator, Tim Heise, M.D. of PROFIL Institute. The study s results indicated that treatment with EMISPHERE® oral insulin over 14 days was well-tolerated, led to improvements in post-prandial blood glucose concentrations both under oral glucose tolerance test (OGTT) and standardized meal conditions, and tended to improve fasting blood glucose concentrations and insulin resistance.

Patients receiving EMISPHERE® oral insulin tablets for two weeks showed improvement when compared to baseline levels on key testing parameters, including fasting blood glucose (-27 mg/dl; p< 0.1); two-hour, post-load blood glucose following an oral glucose tolerance test (OGTT) (-57mg/dl; p<0.05), a standard clinical marker for assessing a diabetic s disease state; and, serum fructosamine levels (an indicator of average glycemic control over approximately the previous two weeks). Improvement was also seen in indices of insulin sensitivity (i.e. the Homeostasis Model Assessment, or HOMA, index). Specifically, the data demonstrated that after a two week treatment with EMISPHERE® oral insulin, postprandial blood glucose concentrations were significantly reduced by 19% (p<0.05 vs. baseline). Blood glucose excursions were also significantly reduced. Overall metabolic control was also improved, indicated by a 9% decrease in fructosamine concentrations.

The control group also experienced improvements in certain parameters; however, most of these improvements were not statistically significant. Improvements in Type 2 diabetics are typically observed within the first two weeks of studies, presumably due to lifestyle modifications. A longer study could address this observation. The study was not powered to demonstrate statistical significance between the active and control groups. A larger sample size would be required to evaluate statistically significant differences between the active and control groups.

Safety and tolerability findings among patients receiving treatment with the EMISPHERE® oral insulin indicated that the study drug was well tolerated with no serious adverse events. Only two adverse events occurred in the oral insulin group (one patient reported moderate joint pain, another patient suffered from mild headaches that were of short duration). Six adverse events occurred in the control group.

Despite the tight diabetes control and the frequent blood glucose self-monitoring of the subjects, no hypoglycemic episodes were observed in this study.

We will continue to develop our oral insulin candidate while seeking a partner for this program. We are continuing a toxicology study that we initiated in late 2003 and Phase I studies related to dosage form development designed to optimize efficiency of delivery. We are also planning a Phase II study that would include exposure to a larger patient population and a longer duration of dosing. Later stage clinical trials may not support the findings of our early stage trials.

**Bone-related Disease**

Osteoporosis is a disease characterized by low bone mass and structural deterioration of bone tissue, leading to bone fragility and an increased susceptibility to fractures. It is a common condition among the elderly both men and women. The most common consequence of osteoporosis is greatly increased risk of broken bones, especially in the hip region. According to the website www.emedicine.com, Osteoporosis is estimated to affect over 10 million Americans, and it is predicted that 1 in 2 women and 1 in 8 men older than 50 years will have an osteoporosis-related fracture in their lifetimes. Several medicines are available to either delay the onset of, or reverse, bone loss. We believe that new therapies currently under development should foster greater patient compliance, and ultimately improve the market penetration rate.

*Novartis and Lilly Relationships*

Novartis Pharma AG ( Novartis ) and Eli Lilly and Company ( Lilly ) are seeking to commercialize oral forms of their existing nasal and injectable therapies. Roche is seeking to commercialize various treatments in the field as well. We believe that oral forms of therapy or improved oral forms of therapy would be considered more patient-friendly, and would ensure better compliance, especially among the elderly, for the treatment and prevention of osteoporosis. For information on our product candidates addressing the osteoporosis patient population, see Ongoing Collaborative Agreements below.

**Growth Disorders**

Growth hormone is necessary to stimulate growth in children by promoting the growth of muscle and bone. In adults, growth hormone maintains muscle and bone quality. Children that suffer from growth hormone deficiency fail to grow normally without supplemental growth hormone.

Recombinant human growth hormone ( rhGH ) has been available for many years. rhGH must be administered by injection, and therefore, compliance is particularly difficult in pediatric patients. rhGH therapy requires a long-term commitment by the patient and his or her family to achieve the best results. The prescribed dosing ranges between three and seven injections per week. Treatment continues for several years until the child has completed puberty or has stopped responding. rhGH is approved for pediatric growth hormone deficiency, adult growth hormone deficiency, pre-kidney transplantation, and short stature due to chronic kidney disease and Turner s syndrome.

*Our Oral Recombinant Human Growth Hormone Program*

From 1998 through August 2003, we developed oral rhGH in collaboration with Lilly. In August 2002, Emisphere and Lilly advanced an oral form of rhGH, the largest protein ever evaluated with the *eligen*® technology, into human testing. In 2003, an early stage clinical study was successfully completed. Results from the study indicated that the oral prototype achieved the desired blood levels and physiological profile of growth hormone. With this study, we demonstrated the utility and acute safety profile of our sixth EMISPHERE® delivery agent to be tested in humans.

As of August 2003, Lilly returned to us all rights to the oral rhGH program pursuant to the terms of our license agreement. We were not required to provide any consideration to Lilly in exchange for reacquiring the rights to the program.

On September 23, 2004 we announced a new partnership with Novartis to develop our oral rhGH program. Under this collaboration, we will work with Novartis to initiate clinical trials of a convenient oral human growth hormone product using the *eligen*® technology. Novartis will fully fund the program including all clinical studies.

**Asthma/Allergies**

An allergy is an immune response by the body to certain stimuli in the environment. One of the most common forms of allergy is hay fever, which is estimated to affect as many as 36 million people in the United States. Asthma is a chronic inflammatory disorder of the airways caused by allergens and viral respiratory infections leading to bronchial hyper responsiveness and obstruction of airways. According to the American Academy of Allergies, Asthma and Immunology, more than 20 million Americans have asthma.

*Our Oral Cromolyn Sodium Program*

Cromolyn sodium mitigates allergic reactions by the inhibition of the release of histamine and other chemical mediators from the mast cells. Cromolyn sodium is marketed as an aerosol formulation, eye solution and nasal spray for the treatment of asthma and allergies.

Cromolyn sodium is a charged organic molecule that has not otherwise been developed in an oral form due to its low oral bioavailability. As such, there is no proof that an oral version would have the same effect as non-oral forms delivered via the nasal, pulmonary, or ocular routes to the systemic circulation. In November 2001, we announced proof-of-concept Phase I data for this product candidate using an EMISPHERE® delivery agent. The data demonstrated that the drug was absorbed in less than 30 minutes in healthy human subjects. We have conducted additional Phase I dose-ranging studies since 2001 and have found the data to be consistent. In 2002, oral cromolyn sodium entered into proof-of-concept patient testing. We continue to explore improved delivery of cromolyn sodium.

**Obesity**

Obesity is a major health problem in all developed countries. The prevalence of obesity in the United States has increased substantially during the past decade. Nearly two-thirds of adults in the United States are overweight, and nearly one-third are obese, according to data from the 1999-2000 National Health and Nutrition Examination Survey. A 1998 National Institutes of Health report confirmed that obesity significantly increases a number of health risks, including Type II diabetes. The most recent report commissioned by the American Obesity Association estimated that total costs related to overweight and obesity conditions total $102 billion in the United States. Obesity-related conditions such as stroke and myocardial infarction are estimated to contribute to hundreds of thousands of deaths annually. Current treatment of obesity consists of diet, exercise and other life-style changes, and a limited number of drugs.

*Our Oral $PYY_{3-36}$ Program*

$PYY_{3-36}$, an experimental substance, is a peptide with 34 amino acids. Clinical research experiments are currently underway by academic institutions to evaluate $PYY_{3-36}$ relative to the condition of obesity. A factor that would limit the adoption of this therapy, even if proven successful, is the requirement for intravenous delivery of this compound, which will require frequent dosings over long periods of time.

We have demonstrated that $PYY_{3-36}$ can be delivered orally at pharmacologically relevant levels in non-human primate animal models and are developing a solid dosage prototype for testing in humans.

**ONGOING COLLABORATIVE AGREEMENTS**

We are a party to collaborative agreements with corporate partners to provide development and commercialization services relating to the products under collaboration. These agreements are in the form of research and development collaborations and licensing agreements. Under these agreements, we have granted licenses or the rights to obtain licenses to our oral drug delivery technology. In return, we are entitled to receive certain payments upon the achievement of milestones and royalties on the sales of the products should a product ultimately be commercialized. We also are entitled to be reimbursed for research and development costs that we incur.

All of our collaborative agreements are subject to termination by our corporate partners, but not by us, without significant financial penalty to them. Under the terms of these agreements, upon a termination we are entitled to reacquire all rights in our technology at no cost and are free to re-license the technology to other collaborative partners.

**Novartis Pharma AG Oral Salmon Calcitonin ( sCT ) Program**

In December 1997, we entered into a collaboration agreement with Novartis to develop an oral form of sCT, currently used to treat osteoporosis. sCT is a hormone that inhibits the bone-tissue resorbing activity of specialized bone cells called osteoclasts, enabling the bone to retain more of its mass and functionality. sCT has demonstrated efficacy in increasing lumbar spine bone mineral density and in reducing vertebral fractures. sCT is estimated to be about 30 times more potent than the human version. Synthetic sCT, which is identical to the naturally occurring one, currently is available only as a nasal spray or injectable therapy. Novartis markets synthetic sCT in the United States as MIACALCIN® nasal spray, which is indicated for the treatment of postmenopausal osteoporosis in women greater than five years post menopause with low bone mass.

Treatment with sCT has been shown to increase bone mineral density in the spine and reduce the risk of new vertebral fractures in post-menopausal women with osteoporosis. It is also used to treat Paget s disease, a disease that results in, among other things, bone pain and breakdown. sCT is currently available as an injection or nasal spray. In its nasal spray forms, it is believed that sCT s major advantages are its efficacy resulting from a lack of serious side effects, excellent long-term safety profile and ease of administration. Some studies even suggest that sCT produces an analgesic effect. Annual worldwide sales of sCT marketed in nasal spray form were approximately $389 million in 2003, of which the U.S. accounts for an estimated $240 million.

In October 1999, Novartis completed a Phase I clinical study in the United Kingdom, testing a capsule form of sCT utilizing the *eligen*® technology. The study results, released in January 2000, indicated that Novartis achieved its targeted endpoint of therapeutic sCT blood levels, following oral administration of capsules containing sCT and an EMISPHERE® delivery agent. We believe that these results demonstrate the successful oral delivery of a protein macromolecule from a solid oral dosage form without chemical modification of the molecule or damage to the biological membrane. In February 2000, Novartis exercised its option to acquire an exclusive license to develop and commercialize oral sCT.

In February 2003, we announced favorable results of a Phase IIa study conducted by Novartis evaluating the performance in post-menopausal women of an oral tablet form of sCT. The purpose of the study was to assess the efficacy and safety of various doses of an oral tablet of sCT in post-menopausal women and to confirm the activity of sCT when given orally, as reflected by changes in markers of bone formation or resorption. Oral sCT was dosed for 90 days in the study, the longest time period that the *eligen*® technology has been dosed in human testing. The study demonstrated activity on bone markers over a three month dosing period when the peptide was delivered in combination with the EMISPHERE® delivery agent. Only two serious adverse events were reported, neither of which were related to the EMISPHERE® delivery agent or to sCT. The side effects (mainly gastrointestinal in nature) seen with the highest doses of sCT were consistent with those normally seen with high plasma levels of sCT when administered by injection. These results were presented by Novartis at the American Society of Bone and Mineral Research in September of 2003.

We are entitled to receive an additional milestone payment (the amount of which is confidential) for oral sCT upon the initiation of Phase III studies by Novartis. Further development of the oral program will be guided by Novartis.

Under the sCT agreements, Novartis has an option to an exclusive worldwide license to develop in conjunction with us, make, have made, use and sell products developed under this program. Novartis also has the right to exercise an option to commence a research collaboration with us on a second compound under this agreement. Novartis rights to certain specified financial terms concerning a license of a second compound have since expired. We have no payment obligations with respect to this program; we are, however, obligated to collaborate with Novartis by providing access to our technology that is relevant to this program. We are also obligated to help to manage this program through a joint steering committee with Novartis.

To date, we have received $9.7 million in payments from Novartis under this program. Under the terms of the agreement, we may receive up to $7 million in additional milestone payments and approximately $500,000 in direct reimbursements for related costs.

**Novartis Pharma AG Oral Recombinant Human Growth Hormone Program**

From 1998 through August 2003, we developed oral rhGH in collaboration with Lilly. As of August 2003, Lilly returned to us all rights to the oral rhGH program pursuant to the terms of our license agreement. On September 23, 2004 we announced a new partnership with Novartis to develop our oral rhGH program. Under this collaboration, we will work with Novartis to initiate clinical trials of a convenient oral human growth hormone product using the *eligen*® technology.

Under this agreement, Novartis has an exclusive worldwide license to develop, make, have made, use and sell products developed under this program. We have no payment obligations with respect to this program; we are, however, obligated to collaborate with Novartis by providing access to our technology that is relevant to this program. We are also obligated to help to manage this program through a joint steering committee with Novartis.

To date, we have received $1 million in non-refundable payments from Novartis under this program. Under the terms of the new agreement, Novartis was granted a twelve-month license to utilize our *eligen*® technology. At the end of this twelve-month license period, Novartis may elect to commence development or terminate the agreement. If they elect to commence development, we may receive up to $33 million in additional milestone payments during the course of product development and royalties based on sales.

**Roche Small Molecules for Bone-Related Diseases**

On November 17, 2004, we entered into a licensing agreement with Roche to develop oral formulations of undisclosed small molecule compounds approved for use in the field of bone-related diseases. The agreement follows successful pre-clinical studies, and a human feasibility study incorporating our *eligen*® technology.

Under the terms of the agreement, Roche paid us an initial non-refundable up-front fee of $2.5 million and may pay us future milestones of up to $18.5 million for each product, if any, developed using our *eligen*® technology. We will also receive royalties based on product sales. Roche will fund all necessary preclinical, clinical and manufacturing costs for all products. We have no payment obligations with respect to this program; we are, however, obligated to collaborate with Roche by providing access to our technology that is relevant to this program. We are also obligated to help to manage this program through a joint steering committee with Roche. Roche may terminate the agreement upon 90 days notice for any reason and without financial penalty or requirement to fund any further clinical studies.

**Eli Lilly and Company; Novartis Pharma AG Oral PTH 1-34 Program**

In February 1997, we formed a strategic alliance with Lilly for the development of an oral recombinant PTH 1-34 for the treatment of osteoporosis and a second product candidate, rhGH, for treatment of growth disorders. PTH 1-34 is a bone anabolic/formation compound currently marketed by Lilly as a once daily injectable for the treatment of osteoporosis. In contrast to sCT that reduces bone loss, PTH 1-34 stimulates new bone formation.

In March 1998, Lilly and Emisphere entered into license agreements for PTH 1-34 and rhGH and Lilly paid us a $4 million milestone payment. In June 2000, the parties executed a follow-on agreement for both proteins and Lilly paid Emisphere a $2 million milestone payment in connection with the selection of the EMISPHERE® delivery agent to be used with PTH 1-34. In August 2001, Emisphere and Lilly issued a joint publication on the oral delivery of PTH 1-34 in the American Association of Pharmaceutical Scientists July issue of Pharmaceutical Research (Vol. 18, No. 7, 2001), setting forth the first reproducible, oral delivery of biologically active PTH 1-34 in a preclinical model of osteoporosis. In late 2001, Emisphere and Lilly entered an oral unformulated solid dosage of parathyroid hormone into the clinic.

The oral PTH 1-34 program is currently in Phase I testing. Lilly is responsible for managing any trials and for all related costs. For information concerning our pending litigation with Lilly related to the agreement for the oral PTH 1-34 program and our termination of those agreements, see Risk Factors *We are currently in litigation with one of our collaborative partners, and an adverse determination of our patent infringement claim in that case could limit our future ability to realize on the potential future value of those patents.* In August of 2003, Emisphere and Lilly announced that Lilly would return all rights and data generated on an oral form of rhGH to us, and would continue to develop the oral PTH 1-34 program. We are currently in litigation with Lilly and have given Lilly a notice of termination of our agreements with them regarding PTH 1-34. We have agreed to continue to provide technical support to Lilly pending resolution of the litigation.

To date we have received $13.1 million in payments from Lilly under these programs. Until resolution of our litigation with Lilly, we do not expect to receive any additional milestone payments under these programs.

On December 1, 2004, we entered into a Research Collaboration Option and License Agreement with Novartis whereby Novartis obtained an option to license our existing technology to develop oral forms of PTH 1-34 should we be successful in fully reacquiring our rights from Lilly pertaining to PTH 1-34. Contemporaneously with the entering of this new agreement, Novartis purchased from us a $10 million convertible note maturing December 1, 2009 that we may repay, at our option, in either stock or cash. If Novartis exercises its option to the license, we are eligible for milestone payments totaling up to a maximum of $30 million, plus royalties on sales of product developed using our *eligen*® technology. Novartis will fund all necessary preclinical, clinical and manufacturing costs for all products.

**U.S. Army Medical Research Institute of Infectious Diseases ( USAMRIID ) Oral Vaccines Against Anthrax and Other Biological Pathogens**

In June 2003, we announced that we entered into a cooperative research and development agreement ( CRADA ) with the USAMRIID, the U.S. Department of Defense s lead medical research laboratory for the U.S. Biological Defense Research Program. USAMRIID is evaluating the use of our eligen® technology to create oral vaccines against anthrax and other biological pathogens using a new recombinant protein antigen. The Institute plays a key role in infectious disease research, and its mission is to conduct basic and applied research on biological threats resulting in medical solutions (such as vaccines, drugs and diagnostics) to protect the war fighter. USAMRIID is a subordinate laboratory of the U.S. Army Medical Research and Materiel Command. USAMRIID has agreed to grant us an exclusive license to each U.S. patent application or issued patent as a result of the work performed under the CRADA. We will be eligible to receive royalties under a license agreement with the ultimate vaccine developer should an oral anthrax vaccine ultimately be developed. There are no material financial commitments under this agreement and any revenue that may be generated is contingent on USAMRIID s development of a vaccine that does not currently exist.

**PATENTS AND OTHER FORMS OF INTELLECTUAL PROPERTY**

Our patent strategy is designed to maximize our patent portfolio, proprietary rights and any future licensing opportunities we might pursue. We seek patent protection on various aspects of our proprietary chemical and pharmaceutical delivery technologies, including, but not limited to, the delivery agent compounds themselves, the combination of our compounds with a pharmaceutical or chemical agent and for generic structures that encompass EMISPHERE® delivery agents. We also seek to patent the processes utilized in manufacturing EMISPHERE® delivery agents and the methods of use of EMISPHERE® delivery agents. We concentrate our efforts in the key pharmaceutical markets of the United States, Europe, and Japan, and file in additional countries on a case-by-case basis.

We have patents, or patent applications pending, for delivery agents that we currently use in conjunction with insulin, heparin, LMWH, calcitonin, PTH 1-34, rhGH, cromolyn sodium and numerous other compounds. As of March 31, 2005, we had 78 issued patents in the United States and had other patents issued or applications pending in various countries around the world. Of our 78 U.S. issued patents, three were issued by the U.S. Patent and Trademark Office in 2004 and one was issued in 2005. Of our patents issued in the United States, one will expire in 2007, and the others including those which cover our product candidates will begin to expire in 2012. The disclosed patent expiration dates do not include any potential patent term restoration under 35 USC §156 that might be sought in the future. As of March 31, 2005, we had 74 patent applications relating to our drug delivery technology pending in the United States. We have pursued strategic international protection with approximately 58 patents and 230 patent applications pending internationally in a total of 41 different countries. The majority of the filings are made in Australia, Canada, the European Patent Office, Japan and Mexico.

Emisphere has US-issued patents and/or pending patent applications with claims to the potential products listed in the table under *Product Candidates in Development* on page 25. Emisphere s US-issued patents that claim such products begin to expire in the year 2012. Currently pending applications, should they mature into patents, will expire 20 years from the filing date of the earliest US utility or national patent application, subject to potential shortening of patent term due to terminal disclaimers, and subject to possible patent term extension under 35 USC §154 and /or patent term restoration under 35 USC §156 if such is sought.

**MANUFACTURING**

The primary raw materials used in making the delivery agents for our product candidates are readily available in large quantities from multiple sources. We internally manufacture delivery agents on a small scale for research purposes and for early stage clinical supplies. We believe that our manufacturing capabilities comply with the FDA s current GMP. In 2003, we manufactured early stage clinical supplies under GMP conditions for the oral insulin tablet prototype studies and heparin multiple arm studies.

Currently, we purchase EMISPHERE® delivery agents from third parties in accordance with GMP regulations in batch sizes greater than 10 kilograms. We have identified other commercial manufacturers meeting the FDA s GMP regulations that have the capability of producing EMISPHERE® delivery agents and do not rely on any particular manufacturer to supply us with needed quantities of our EMISPHERE® delivery agent.

**COMPETITION**

Our success depends in part upon maintaining a competitive position in the development of product candidates and technologies in an evolving field in which developments are expected to continue at a rapid pace. We compete with other drug delivery, biotechnology and pharmaceutical companies, research organizations, individual scientists and non-profit organizations engaged in the development of alternative drug delivery technologies or new drug research and testing, and with entities developing new drugs that may be orally active. Our product candidates compete against alternative therapies or alternative delivery systems for each of the medical conditions our product candidates address, independent of the means of delivery. Many of our competitors have substantially greater research and development capabilities, experience, and marketing, financial and managerial resources than we have.

Our competitors may succeed in developing competing technologies and obtaining governmental approval for products before we can do so, alone or with partners. We cannot assure you that developments by other drug delivery innovators will not render our product candidates, or the therapeutic macromolecules used in combination with our product candidates, noncompetitive or obsolete.

**Oral Heparin Competition**

AstraZeneca PLC has reported European approval for EXANTA , a pro-drug form of melagatran that is a direct thrombin inhibitor. While this product was rejected for approval by the FDA in the United States, this product could compete with our oral heparin product candidates outside of the United States. Organon Sanofi-Synthelabo LLC has reported approval of an injectable pentasaccharide product, ARIXTRA®, injectable form of a synthetic anti-clotting agent. A number of other companies reportedly are currently testing direct thrombin or Xa inhibitors, some of which may eventually be indicated for the prevention of DVT in patients undergoing surgery for hip fracture, hip replacement or knee replacement.

Other technologies use micro-encapsulation to orally deliver heparin. We believe our oral heparin delivery technology is distinguished from other announced technologies, in that it demonstrates the preservation of the chemical integrity of the drug and the integrity of the intestinal membrane.

**Oral Insulin Competition**

Other private and public companies, as well as academic institutions are developing oral insulin analogues. One such company is Nobex Corp. We believe these analogues differ from our product, in that insulin is chemically modified, creating a new chemical entity. In May 2002, Nobex entered into a partnership agreement with GlaxoSmithKline ( GSK ) for the development and potential marketing of their product candidate. In November 2003, Nobex announced that GSK would return the product candidate rights to Nobex, and that GSK would no longer collaborate to develop the candidate. Other alternative insulin delivery systems include Aventis/Pfizer/Nektar s EXUBERA® a pulmonary reportedly in Phase III testing. We believe our oral insulin delivery technology is distinguished from other announced technologies as it demonstrates the preservation of both the biological effects of the drug and the integrity of the intestinal membrane.

**Oral Osteoporosis Candidate Competition**

An injectable form of PTH 1-34, a bone anabolic, is manufactured and sold by Lilly, as FORTEO®. PTH 1-34 is a bone anabolic that decreases bone loss and builds new bone. Unigene Laboratories, Inc. has reported that, in collaboration with GSK, it is developing an oral form of PTH 1-34. Unigene also reported that it is developing an oral salmon calcitonin. Both candidates are in early stage clinical testing.

Novartis currently offers a nasal dosage form of sCT, MIACALCIN®. Other osteoporosis therapies include estrogen replacement therapy, selective estrogen receptor modulators, bisphosphonates and several new biologics that are under development.

**Competition Summary**

Although we believe that our oral formulations, if successful, will likely compete with well established injectable versions of the same drugs, we believe that we will enjoy a competitive advantage because physicians and patients prefer orally delivered forms of products over injectable forms, oral forms of products enable improved compliance, and for many programs, the oral form of products enable improved therapeutic regimens.

**GOVERNMENT REGULATION**

Our operations and product candidates under development are subject to extensive regulation by the FDA, other governmental authorities in the United States and governmental authorities in other countries.

The duration of the governmental approval process for marketing new pharmaceutical substances, from the commencement of preclinical testing to receipt of governmental approval for marketing a new product, varies with the nature of the product and with the country in which such approval is sought. For new chemical entities, the approval process could take eight to ten years or more. For reformulations of existing drugs, typically the process is shorter. In either case, the procedures required to obtain governmental approval to market new drug products will be costly and time-consuming to us, requiring rigorous testing of the new drug product. Even after such time and effort, regulatory approval may not be obtained for our products.

The steps required before we can market or ship a new human pharmaceutical product commercially in the United States include, in part, preclinical testing, the filing of an Investigational New Drug Application ( IND ), the conduct of clinical trials and the filing with the FDA of either a New Drug Application ( NDA ) for drugs or a Biologic License Application ( BLA ) for biologics.

In order to conduct the clinical investigations necessary to obtain regulatory approval in the US, we must file an IND with the FDA to permit the shipment and use of the drug for investigational purposes. The IND sets forth, in part, the results of preclinical (laboratory and animal) toxicology testing and the applicant s initial Phase I plans for clinical (human) testing. Unless notified that testing may not begin, the clinical testing may commence 30 days after filing an IND. As indicated on the table above in the section entitled Product Candidates in Development, many of our product candidates have passed this initial stage.

Under FDA regulations, the clinical testing program required for marketing approval of a new drug typically involves three clinical phases. In Phase I, safety studies are generally conducted on normal, healthy human volunteers to determine the maximum dosages and side effects associated with increasing doses of the substance being tested. In Phase II, studies are conducted on small groups of patients afflicted with a specific disease to gain preliminary evidence of efficacy and to determine the common short-term side effects and risks associated with the substance being tested. Phase III involves large-scale trials conducted on disease-afflicted patients to provide statistical evidence of efficacy and safety and to provide an adequate basis for product labeling. Frequent reports are required in each phase and, if unwarranted hazards to patients are found, the FDA may request modification or discontinuance of clinical testing until further studies have been conducted. Phase IV testing is sometimes conducted, either to meet FDA requirements for additional information as a condition of approval, or to gain post-approval market acceptance of the pharmaceutical product. Our product candidates are and will be subjected to each step of this lengthy process from conception to market and many of those candidates are still in the early phases of testing.

Once clinical testing has been completed pursuant to an IND, the applicant files an NDA or BLA with the FDA seeking approval for marketing the drug product. The FDA reviews the NDA or BLA to determine whether the drug is safe and effective, and adequately labeled, and whether the applicant can demonstrate proper and consistent manufacture of the drug. The time required for FDA action on an NDA or BLA varies considerably, depending on the characteristics of the drug, whether the FDA needs more information than is originally provided in the NDA or BLA and whether the FDA has concerns with the evidence submitted. Once our product candidates reach this stage, we will be subjected to these additional costs of time and money.

The facilities of each company involved in the commercial manufacturing, processing, testing, control and labeling of pharmaceutical products must be registered with and approved by the FDA. Continued registration requires compliance with GMP regulations and the FDA conducts periodic establishment inspections to confirm continued compliance with its regulations. We are subject to various federal, state and local laws, regulations and recommendations relating to such matters as laboratory and manufacturing practices and the use, handling and disposal of hazardous or potentially hazardous substances used in connection with our research and development work. We believe that we are in compliance with these laws and regulations in all material respects.

While we do not currently manufacture any product ourselves, if we did, we would bear additional cost of FDA compliance.

**EMPLOYEES**

As of March 31, 2005, we had 118 employees, 81 of whom are engaged in scientific research and technical functions and 37 of whom are performing information technology, engineering, facilities maintenance and administrative functions. Of the 118 employees, 33 hold Ph.D. or M.D. degrees. We believe our relations with our employees are good.

**LEGAL PROCEEDINGS**

For information concerning the pending litigation between Emisphere and Eli Lilly and Co., and our termination of our agreements with Lilly, see *Risk Factors We are currently in litigation with one of our collaborative partners, and an adverse determination of our patent infringement claim in that case could limit our future ability to realize on the potential future value of those patents.*

**AVAILABLE INFORMATION**

We file annual, quarterly, and current reports, proxy statements, and other documents with the Securities and Exchange Commission, (the SEC ), under the Securities Exchange Act of 1934. The public may read and copy any materials that we file with the SEC at the SEC s Public Reference Room at 450 Fifth Street, NW, Washington, DC 20549. The public may obtain information on the operation of the Public Reference Room by calling the SEC at 1-800-SEC-0330. Also, the SEC maintains an Internet website that contains reports, proxy and information statements, and other information regarding issuers, including our company, that file electronically with the SEC. The public can obtain any documents that we file with the SEC at http://www.sec.gov.

We also make available free of charge on or through our Internet website (http://www.emisphere.com) our Annual Report on Form 10-K, Quarterly Reports on Form 10-Q, Current Reports on Form 8-K, Section 16 filings, and, if applicable, amendments to those reports filed or furnished pursuant to Section 13(a) or Section 16 of the Exchange Act as soon as reasonably practicable after we or the reporting person electronically files such material with, or furnishes it to, the SEC. Our Internet website and the information contained therein or connected thereto are not intended to be incorporated into this prospectus.

Our Board of Directors has adopted a Code of Business Conduct and Ethics which is posted on our website at http://www.emisphere.com/ovr_cgcoe.asp.

## DESCRIPTION OF CAPITAL STOCK

Our authorized capital stock consists of 50,000,000 shares of common stock, par value $.01 per share, and 1,000,000 shares of preferred stock, par value $.01 per share, of which 200,000 shares have been designated Series A Junior Participating Cumulative Preferred Stock. As of March 31, 2005, there were 23,201,519 shares of common stock outstanding and no shares of preferred stock outstanding.

**Common Stock**

Holders of common stock are entitled to one vote for each share held on all matters submitted to a vote of stockholders, and do not have cumulative voting rights. Holders of common stock are entitled to receive ratably such dividends, if any, as may be declared by our board of directors out of funds legally available therefor, and subject to any preferential dividend rights of any then outstanding preferred stock. Upon our liquidation, dissolution or winding-up, the holders of common stock are entitled to receive ratably our net assets available after the payment of all debts and other liabilities and subject to any liquidation preference of any then outstanding preferred stock. Holders of common stock have no preemptive, subscription or conversion rights. There are no redemption or sinking fund provisions applicable to the common stock. The outstanding shares of common stock are, and the shares offered by us in this offering will be when issued and paid for, fully paid and non-assessable.

**Preferred Stock**

Our board of directors has the authority, subject to certain restrictions, without further stockholder approval, to issue, at any time and from time to time, shares of preferred stock in one or more series. Each such series shall have such number of shares, designations, preferences, voting powers, qualifications, and special or relative rights or privileges as shall be determined by our board of directors, which may include, among others, dividend rights, voting rights, redemption and sinking fund provisions, liquidation preferences, conversion rights and preemptive rights, to the full extent now or hereafter permitted by the laws of the State of Delaware.

The rights of the holders of common stock will be subject to, and may be adversely affected by, the rights of holders of any preferred stock that may be issued in the future. Such rights may include voting and conversion rights which could adversely affect the holders of the common stock. Satisfaction of any dividend preferences of outstanding preferred stock would reduce the amount of funds available, if any, for the payment of dividends on common stock. Holders of preferred stock would typically be entitled to receive a preference payment.

**Stockholder Rights Plan**

Our board of directors has adopted a stockholder rights plan. The stockholder rights plan was adopted to give the board of directors increased power to negotiate in our best interests and to discourage appropriation of control of our Company at a price that is unfair to our stockholders. It is not intended to prevent fair offers for acquisition of control determined by our board of directors to be in our best interests and the best interests of our Company s stockholders, nor is it intended to prevent a person or group from obtaining representation on or control of our board of directors through a proxy contest, or to relieve our board of directors of its fiduciary duty concerning any proposal for our acquisition in good faith.

The stockholder rights plan involves the distribution of one right as a dividend on each outstanding share of our common stock to all holders of record on March 16, 1996, and an ongoing distribution of one right with respect to each share of our common stock issued subsequently. Each right shall entitle the holder to purchase one one-hundredth of a share of Series A Junior Participating Cumulative Preferred Stock. The rights trade in tandem with the common stock until, and become exercisable upon, the occurrence of certain triggering events, and the exercise price is based on the estimated long-term value of our common stock. The exercise of these rights becomes economically attractive upon the triggering of certain flip-in or flip-over rights which work in conjunction with the stockholder rights plan s basic provisions. The flip-in rights will permit the preferred stock s holders to purchase shares of common stock at a discounted rate, resulting in substantial dilution of an acquiror s voting and economic interests in our company.

The flip-over element of the stockholder rights plan involves certain mergers or significant asset purchases, which trigger certain rights to purchase shares of the acquiring or surviving company at a discount. The stockholder rights plan contains a permitted offer exception which allows offers determined by our board of directors to be in our best interests and the best interests of our stockholders to take place free of the diluting effects of the stockholder rights plan s mechanisms.

Our board of directors retains the right, at all times prior to acquisition of 20% of our voting common stock by an acquiror, to discontinue the stockholder rights plan through the redemption of all rights, or to amend the stockholder rights plan in any respect.

**Delaware Law and Certain By-Law Provisions**

Certain provisions of our by-laws are intended to strengthen our board of directors position in the event of a hostile takeover attempt. These by-law provisions have the following effects:

- they provide that only persons who are nominated in accordance with the procedures set forth in the by-laws shall be eligible for election as directors, except as may be otherwise provided in the by-laws;
- they provide that only business brought before the annual meeting by our board of directors or by a stockholder who complies with the procedures set forth in the by-laws may be transacted at an annual meeting of stockholders; and
- they establish a procedure for our board of directors to fix the record date whenever stockholder action by written consent is undertaken.

Furthermore, our Company is subject to the provisions of Section 203 of the Delaware General Corporation Law, an anti-takeover law. In general, the statute prohibits a publicly held Delaware corporation from engaging in a business combination with an interested stockholder for a period of three years after the date of the transaction in which the person became an interested stockholder, unless the business combination is approved in a prescribed manner. For purposes of Section 203, a business combination includes a merger, asset sale or other transaction resulting in a financial benefit to the interested stockholder, and an interested stockholder is a person who, together with affiliates and associates, owns, or within three years prior, did own, 15% or more of the corporation s voting stock.

**Transfer Agent and Registrar**

Our transfer agent and registrar is Mellon Investor Services, whose offices are located at 85 Challenge Road, Ridgefield Park, New Jersey 07660, and its telephone number is 800-851-9677.

**PLAN OF DISTRIBUTION**

We are registering 3,803,039 shares of common stock under this prospectus on behalf of Kingsbridge. Except as described below, to our knowledge, the selling shareholder has not entered into any agreement, arrangement or understanding with any particular broker or market maker with respect to the shares of common stock offered hereby, nor, except as described below, do we know the identity of the brokers or market makers that will participate in the sale of the shares. As used in this prospectus, the term selling shareholder includes donees, pledges, transferees or other successors-in-interest selling shares received after the date of this prospectus from a selling shareholder as a gift, pledge, or other non-sale related transfer.

*Who May Sell; How Much; Applicable Restrictions*. The selling shareholder may decide not to sell any shares. The selling shareholder may from time to time offer some or all of the shares of common stock through brokers, dealers or agents who may receive compensation in the form of discounts, concessions or commissions from the selling shareholder and/or the purchasers of the shares of common stock for whom they may act as agent. In effecting sales, broker-dealers that are engaged by the selling shareholder may arrange for other broker-dealers to participate. Kingsbridge is an underwriter within the meaning of the Securities Act of 1933, as amended (the Securities Act ). Any brokers, dealers or agents who participate in the distribution of the shares of common stock may also be deemed to be underwriters, and any profits on the sale of the shares of common stock by them and any discounts, commissions or concessions received by any such brokers, dealers or agents may be deemed to be underwriting discounts and commissions under the Securities Act. Kingsbridge has advised us that it may effect resales of our common stock through any one or more registered broker-dealers. To the extent the selling shareholder may be deemed to be an underwriter, the selling shareholder will be subject to the prospectus delivery requirements of the Securities Act and may be subject to certain statutory liabilities of, including but not limited to, Sections 11, 12 and 17 of the Securities Act and Rule 10b-5 under the Securities Exchange Act of 1934, as amended, (the Exchange Act ). We have agreed to indemnify Kingsbridge with respect to the shares offered hereby against certain liabilities, including, without limitation, certain liabilities under the Securities Act, or, if such indemnity is unavailable, to contribute toward amounts required to be paid in respect of such liabilities.

*Manner of Sales and Applicable Restrictions*. The selling shareholder will act independently of Emisphere in making decisions with respect to the timing, manner and size of each sale. Such sales may be made over the NASDAQ Stock Market, on the over-the-counter market, otherwise, or in a combination of such methods of sale, at then prevailing market prices, at prices related to prevailing market prices or at negotiated prices. The shares of common stock may be sold according to one or more of the following methods:

(a) a block trade in which the broker or dealer so engaged will attempt to sell the shares of common stock as agent but may position and resell a portion of the block as principal to facilitate the transaction;

(b) purchases by a broker or dealer as principal and resale by such broker or dealer for its account pursuant to this prospectus;

(c) an over-the-counter distribution in accordance with the NASDAQ rules;

(d) ordinary brokerage transactions and transactions in which the broker solicits purchasers; or

(e) privately negotiated transactions.

Any shares covered by this prospectus which qualify for sale pursuant to Rule 144 of the Securities Act may be sold under Rule 144 rather than pursuant to this prospectus. In addition, the selling shareholder may transfer the shares by other means not described in this prospectus.

Any broker-dealer participating in such transactions as agent may receive commissions from Kingsbridge (and, if they act as agent for the purchaser of such shares, from such purchaser). Broker-dealers may agree with Kingsbridge to sell a specified number of shares at a stipulated price per share, and, to the extent such a broker-dealer is unable to do so acting as agent for Kingsbridge, to purchase as principal any unsold shares at the price required to fulfill the broker-dealer commitment to Kingsbridge. Broker-dealers who acquire shares as principal may thereafter resell such shares from time to time in transactions (which may involve crosses and block transactions and which may involve sales to and through other broker-dealers, including transactions of the nature described above) on the NASDAQ National Market, on the over-the-counter market, in privately-negotiated transactions or otherwise at market prices prevailing at the time of sale or at negotiated prices, and in connection with such resales may pay to or receive from the purchasers of such shares commissions computed as described above. To the extent required under the Securities Act, a supplemental prospectus will be filed, disclosing:

the name of any such broker-dealers;

the number of shares involved;

the price at which such shares are to be sold;

the commission paid or discounts or concessions allowed to such broker-dealers, where applicable;

that such broker-dealers did not conduct any investigation to verify the information set out or incorporated by reference in this prospectus, as supplemented; and

other facts material to the transaction.

Underwriters and purchasers that are deemed underwriters under the Securities Act may engage in transactions that stabilize, maintain or otherwise affect the price of the securities, including the entry of stabilizing bids or syndicate covering transactions or the imposition of penalty bids. Kingsbridge and any other persons participating in the sale or distribution of the shares will be subject to the applicable provisions of the Exchange Act and the rules and regulations thereunder including, without limitation, Regulation M. These provisions may restrict certain activities of, and limit the timing of, purchases by the selling shareholder or other persons or entities. Furthermore, under Regulation M, persons engaged in a distribution of securities are prohibited from simultaneously engaging in market making and certain other activities with respect to such securities for a specified period of time prior to the commencement of such distributions, subject to special exceptions or exemptions. Regulation M may restrict the ability of any person engaged in the distribution of the securities to engage in market-making and certain other activities with respect to those securities. In addition, the anti-manipulation rules under the Exchange Act may apply to sales of the securities in the market. All of these limitations may affect the marketability of the shares and the ability of any person to engage in market-making activities with respect to the securities.

*Expenses Associated With Registration*. We have agreed to pay the expenses of registering the shares of common stock under the Securities Act, including registration and filing fees, printing expenses, administrative expenses and certain legal and accounting fees, as well as certain fees of counsel for the selling shareholder incurred in the preparation of the SSO Facility agreements and the registration statement of which this prospectus forms a part. The selling shareholder will bear all discounts, commissions or other amounts payable to underwriters, dealers or agents, as well as transfer taxes and certain other expenses associated with the sale of securities.

*Indemnification*. Under the terms of the Common Stock Purchase Agreement and the Registration Rights Agreement, we have agreed to indemnify the selling shareholder and certain other persons against certain liabilities in connection with the offering of the shares of common stock, including liabilities arising under the Securities Act.

*Prospectus Updates*. At any time a particular offer of the shares of common stock is made, a revised prospectus or prospectus supplement, if required, will be distributed. Such prospectus supplement or post-effective amendment will be filed with the Securities and Exchange Commission, to reflect the disclosure of required additional information with respect to the distribution of the shares of common stock. We may suspend the sale of shares by the selling shareholder pursuant to this prospectus for certain periods of time for certain reasons, including if the prospectus is required to be supplemented or amended to include additional material information.

## LEGAL MATTERS

Certain legal matters with respect to the securities will be passed on by Proskauer Rose LLP, New York, New York.

## EXPERTS

The financial statements incorporated by reference in this prospectus by reference to the Annual Report on Form 10-K for the year ended December 31, 2004 and Quarterly Report on Form 10-Q for the quarter ended March 31, 2005 have been incorporated in reliance on the report, which includes an explanatory paragraph relating to our ability to continue as a going concern, of PricewaterhouseCoopers LLP, an independent registered public accounting firm, given on the authority of said firm as experts in accounting and auditing.

## WHERE YOU CAN FIND MORE INFORMATION

We file reports with the Securities and Exchange Commission on a regular basis that contain financial information and results of operations. You may read or copy any document that we file with the SEC at the SEC s Public Reference Room at 450 Fifth Street, N.W., Washington, D.C. 20549. You may obtain information about the Public Reference Room by calling the SEC for more information at 1-800-SEC-0330. Our SEC filings are also available at the SEC s website at http://www.sec.gov and at our website at http://www.emisphere.com.

Our common stock is listed on the Nasdaq National Market and we are required to file reports, proxy statements and other information with Nasdaq. You may read any document we file with Nasdaq at the offices of the Nasdaq Stock Market, Inc. which is located at 1735 K Street, N.W., Washington, D.C. 20006.

## INCORPORATION BY REFERENCE

The SEC allows companies to incorporate by reference information filed with the SEC, which means that we can disclose important information to you by referring you to those documents. The information incorporated by reference is considered to be part of this prospectus, and information that we file later with the SEC will automatically update and supersede this information. We incorporate by reference the documents listed below and any future filings that we will make with the SEC under Sections 13(a), 13(c), 14 or 15(d) of the Securities Exchange Act of 1934 and under our Commission File Number 1-10615.

1. Our Annual Report on Form 10-K and Form 10-K/A for the fiscal year ended December 31, 2004.

2. Our Quarterly Report on Form 10-Q for the quarter ended March 31, 2005.

3. Our Current Reports on Form 8-K dated January 26, 2005, March 3, 2005, April 6, 2005, May 4, 2005, and May 27, 2005.

You may request a copy of these filings, at no cost, by writing or telephoning our Secretary at our principal executive offices at the following address:

Emisphere Technologies, Inc.
765 Old Saw Mill River Road
Tarrytown, New York 10591
(914) 347-2220

You may also request information through our website at http://www.emisphere.com. The reference to our website does not constitute incorporation by reference of the information contained at the site and you should not consider it part of this prospectus.

This prospectus is part of a registration statement we have filed with the SEC. You should rely only on the information or representations provided in this prospectus. We have authorized no one to provide you with different information. We are not making an offer of these shares of common stock in any state where the offer is not permitted. You should not assume that the information in this prospectus is accurate as of any date other than the date on the front of the document.

**PART II**

**INFORMATION NOT REQUIRED IN PROSPECTUS**

**Item 14. Other Expenses of Issuance and Distribution.**

The following table sets forth the various expenses payable by the Registrant in connection with the sale and distribution of the securities being registered hereby. All expenses of the offering, other than selling discounts, commissions and certain legal fees incurred by securityholders, will be paid by the Registrant. All amounts are estimated except the Securities and Exchange Commission registration fee.

| | | |
|---|---|---|
| SEC registration fee | $ | 1,559 |
| Legal fees and expenses | | 30,000 |
| Accounting fees and expenses | | 35,000 |
| Printing costs and expenses | | 20,000 |
| Total | $ | 86,559 |

**Item 15. Indemnification of Directors and Officers.**

The General Corporation Law of the State of Delaware ( DGCL ) permits us and our stockholders to limit directors exposure to liability for certain breaches of the directors fiduciary duty, either in a suit on behalf of us or in an action by our stockholders.

Our Certificate of Incorporation (the Charter ) eliminates the liability of directors to stockholders or our Company for monetary damages arising out of the directors breach of their fiduciary duty of care. The Charter also authorizes us to indemnify our directors, officers, incorporators, employees and agents with respect to certain costs, expenses and amounts incurred in connection with an action, suit or proceeding by reason of the fact that such person was serving as our director, officer, incorporator, employee or agent. In addition, the Charter permits us to provide additional indemnification rights to our officers and directors and to indemnify them to the greatest extent possible under the DGCL.

We maintain a standard form of officers and directors liability insurance policy which provides coverage to our officers and directors for certain liabilities, including certain liabilities which may arise out of this Registration Statement.

**Item 16. Exhibits.**

The following exhibits are filed with or incorporated by reference into this registration statement.

| Exhibit Number | Description |
|---|---|
| 5.1 | Opinion of Proskauer Rose LLP |
| 10.1 | Common Stock Purchase Agreement (the Common Stock Purchase Agreement ), dated as of December 27, 2004, between Emisphere Technologies, Inc. and Kingsbridge Capital Limited (Incorporated by reference to Exhibit 10.26(a) to the 2004 Form 10-K) |
| 10.2 | Registration Rights Agreement (the Registration Rights Agreement ), dated as of December 27, 2004, between Emisphere Technologies, Inc. and Kingsbridge Capital Limited ( Kingsbridge ) (Incorporated by reference to Exhibit 10.26(b) to the 2004 Form 10-K) |

| | |
|---|---|
| 10.3 | Letter Agreement between Kingsbridge and Emisphere dated March 22, 2005* |
| 10.4 | Warrant, dated December 27, 2004, issued to Kingsbridge (Incorporated by reference to Exhibit 10.26(c) to the 2004 Form 10-K) |
| 23.1 | Consent of PricewaterhouseCoopers LLP |
| 23.2 | Consent of Proskauer Rose LLP (incorporated by reference to Exhibit 5.1) |

* Filed as an exhibit to the Registration Statement on Form S-3 filed by the Company on May 24, 2005.

**Item 17. Undertakings.**

The undersigned Registrant hereby undertakes:

(1) To file, during any period in which offers or sales are being made, a post-effective amendment to this Registration Statement: (i) to include any prospectus required by Section 10(a)(3) of the Securities Act of 1933; (ii) to reflect in the prospectus any facts or events arising after the effective date of the Registration Statement (or the most recent post-effective amendment thereof) which, individually or in the aggregate, represent a fundamental change in the information set forth in the Registration Statement. Notwithstanding the foregoing, any increase or decrease in volume of shares of common stock offered (if the total dollar value of shares of common stock offered would not exceed that which was registered) and any deviation from the low or high end of the estimated maximum offering range may be reflected in the form of prospectus filed with the Commission pursuant to Rule 424(b) if, in the aggregate, the changes in volume and price represent no more than a 20% change in the maximum aggregate offering price set forth in the Calculation of Registration Fee table in the effective registration statement; and (iii) to include any material information with respect to the plan of distribution not previously disclosed in the Registration Statement or any material change to such information in the Registration Statement; provided, however, that (i) and (ii) do not apply if the Registration Statement is on Form S-3 or Form S-8, and the information required to be included in a post-effective amendment by (i) and (ii) is contained in periodic reports filed with or furnished to the Commission by the Registrant pursuant to Section 13 or Section 15(d) of the Securities Exchange Act of 1934 that are incorporated by reference in the Registration Statement.

(2) That, for the purpose of determining any liability under the Securities Act of 1933, each such post-effective amendment shall be deemed to be a new registration statement relating to the shares of common stock offered therein, and the offering of such shares of common stock at that time shall be deemed to be the initial bona fide offering thereof.

(3) To remove from registration by means of a post-effective amendment any of the shares of common stock being registered which remain unsold at the termination of the offering.

Insofar as indemnification for liabilities arising under the Securities Act may be permitted to directors, officers and controlling persons of the Registrant pursuant to the foregoing provisions, or otherwise, the Registrant has been advised that in the opinion of the Securities and Exchange Commission such indemnification is against public policy as expressed in the Securities Act of 1933 and is, therefore, unenforceable. In the event that a claim for indemnification against such liabilities (other than the payment by the Registrant of expenses incurred or paid by a director, officer or controlling person of the Registrant in the successful defense of any action, suit or proceeding) is asserted by such director, officer or controlling person in connection with the shares of common stock being registered, the Registrant will, unless in the opinion of its counsel the matter has been settled by controlling precedent, submit to a court of appropriate jurisdiction the question whether such indemnification by it is against public policy as expressed in the Securities Act of 1933 and will be governed by the final adjudication of such issue.

The undersigned Registrant hereby undertakes that, for purposes of determining any liability under the Securities Act of 1933, each filing of the Registrant s annual report pursuant to Section 13(a) or Section 15(d) of the Securities Exchange Act of 1934 that is incorporated by reference in the Registration Statement shall be deemed to be a new registration statement relating to the shares of common stock offered therein, and the offering of such shares of common stock at that time shall be deemed to be the initial bona fide offering thereof.

The undersigned Registrant hereby undertakes that:

(1) For purposes of determining any liability under the Securities Act of 1933, the information omitted from the form of prospectus filed as part of this Registration Statement in reliance upon Rule 430A and contained in a form of prospectus filed by the Registrant pursuant to Rule 424(b)(1) or (4) or 497(h) under the Securities Act of 1933 shall be deemed to be part of this Registration Statement as of the time it was declared effective.

(2) For the purpose of determining any liability under the Securities Act of 1933, each post-effective amendment that contains a form of prospectus shall be deemed to be a new registration statement relating to the shares of common stock offered therein, and the offering of such shares of common stock at that time shall be deemed to be the initial bona fide offering thereof.

The undersigned Registrant hereby undertakes to file an application for the purpose of determining the eligibility of the trustee to act under subsection (a) of Section 310 of the Trust Indenture Act in accordance with the rules and regulations prescribed by the Commission under Section 305(b)(2) of the Act.

**SIGNATURES**

Pursuant to the requirements of the Securities Act of 1933, the Registrant certifies that it has reasonable grounds to believe that it meets all of the requirements for filing on Form S-3 and has duly caused this Amendment No. 1 to the Registration Statement to be signed on its behalf by the undersigned, thereunto duly authorized, in the City of Tarrytown, State of New York on June 16, 2005.

EMISPHERE TECHNOLOGIES INC

By: /s/ MICHAEL M. GOLDBERG

**Michael M. Goldberg,**
**M.D. Chairman of the Board and Chief Executive Officer**

Pursuant to the requirements of the Securities Act of 1933, this Registration Statement has been signed below by the persons whose signatures appear below, which persons have signed such Registration Statement in the capacities indicated:

| NAME AND SIGNATURE | TITLE | DATE |
|---|---|---|
| /s/ MICHAEL M. GOLDBERG<br>**Michael M. Goldberg, M.D.** | Director, Chairman of the Board and Chief Executive Officer (principal executive officer) | June 16, 2005 |
| *<br>**Howard M. Pack** | Director | June 16, 2005 |
| *<br>**Robert J. Levenson** | Director | June 16, 2005 |
| *<br>**Arthur Dubroff** | Director | June 16, 2005 |
| *<br>**Stephen K. Carter, M.D.** | Director | June 16, 2005 |
| *<br>**Michael E. Black** | Director | June 16, 2005 |
| /s/ ELLIOT MAZA<br>**Elliot M. Maza, J.D., C.P.A.** | Chief Financial Officer (principal financial and accounting officer) | June 16, 2005 |

* Executed on June 16, 2005 by Elliot Maza as attorney-in-fact under power of attorney granted in the Registration Statement previously filed on May 24, 2005.

**INDEX TO EXHIBITS**

The following exhibits are filed with or incorporated by reference into this registration statement.

| Exhibit Number | Description |
|---|---|
| 5.1 | Opinion of Proskauer Rose LLP |
| 10.1 | Common Stock Purchase Agreement (the Common Stock Purchase Agreement ), dated as of December 27, 2004, between Emisphere Technologies, Inc. and Kingsbridge Capital Limited (Incorporated by reference to Exhibit 10.26(a) to the 2004 Form 10-K) |
| 10.2 | Registration Rights Agreement (the Registration Rights Agreement ), dated as of December 27, 2004, between Emisphere Technologies, Inc. and Kingsbridge Capital Limited (Kingsbridge ) (Incorporated by reference to Exhibit 10.26(b) to the 2004 Form 10-K) |
| 10.3 | Letter Agreement between Kingsbridge and Emisphere dated March 22, 2005* |
| 10.4 | Warrant, dated December 27, 2004, issued to Kingsbridge (Incorporated by reference to Exhibit 10.26(c) to the 2004 Form 10-K) |
| 23.1 | Consent of PricewaterhouseCoopers LLP |
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