EMISPHERE TECHNOLOGIES INC
Form S-3/A
March 03, 2005

Registration No. 333-117230

SECURITIES AND EXCHANGE COMMISSION

WASHINGTON, D.C. 20549

Amendment No. 2

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. ¨

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

CALCULATION OF REGISTRATION FEE

Title of Each Class of Securities To Be Registered	Amount To Be Registered	Proposed Maximum Aggregate Offering Price Per Share(1)	Proposed Maximum Aggregate Offering Price (1)	Amount of Registration Fee
Common Stock, par value $.01 per share	—	—	—	—
Warrants	—	—	—	—
Total	5,000,000	$ 4.85	$ 24,250,000	$ 2,855(2)

(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 January 28, 2005, which was $4.85 per share.

(2) A fee of $2,369 has previously been paid by registrant; a fee of $486 has been submitted herewith.

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 or until the Registration Statement shall become effective on such date as the Commission, acting pursuant to said Section 8(a), may determine.

THE INFORMATION IN THIS PROSPECTUS IS NOT COMPLETE AND MAY BE CHANGED. WE MAY NOT SELL THESE SECURITIES UNTIL THE REGISTRATION STATEMENT FILED WITH THE SECURITIES AND EXCHANGE COMMISSION IS EFFECTIVE. THIS PROSPECTUS IS NOT AN OFFER TO SELL THESE SECURITIES AND WE ARE NOT SOLICITING OFFERS TO BUY THESE SECURITIES IN ANY STATE WHERE THE OFFER OR SALE IS NOT PERMITTED.

Subject to Completion, Dated February 1, 2005

Prospectus

5,000,000 shares

Common Stock

Warrants

Emisphere Technologies, Inc. may offer shares of common stock, $.01 par value per share (Common Stock) or warrants to purchase shares of Common Stock from time to time in one or more offerings. The specific terms and number of shares of Common Stock or warrants so offered will be fully described in supplements to this prospectus. Please read any prospectus supplements and this prospectus carefully before you invest. This prospectus may not be used to sell securities unless accompanied by a prospectus supplement.

Our Common Stock is traded on the Nasdaq National Market under the symbol EMIS. On January 28, 2005, the last reported sale price for our Common Stock on the Nasdaq National Market was $4.76 per share.

Investing in our securities involves significant risks. See Risk Factors beginning on page 5.

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.

The securities may be sold directly by us to investors, through agents designated from time to time or to or through underwriters or dealers. See Plan of Distribution. If any underwriters are involved in the sale of any shares of any securities in respect of which this prospectus is being delivered, the names of such underwriters and any applicable commissions or discounts will be set forth in a prospectus supplement. The net proceeds we expect to receive from such sale also will be set forth in a prospectus supplement.

_____, 2005

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ABOUT THIS PROSPECTUS

This prospectus is part of a Registration Statement on Form S-3 that we filed with the Securities and Exchange Commission utilizing a shelf registration process. Under this shelf process, we may, over the next two years, offer Common Stock or warrants described in this prospectus in one or more offerings up to a total amount of 5,000,000 shares either as Common Stock or as warrants to purchase shares of Common Stock, in any combination thereof. Each time we use this prospectus to offer securities, we will provide a prospectus supplement that will contain specific information about the terms of that offering. The prospectus supplement may also add, update or change information contained in this prospectus. Additionally, in the event there is a material change to information contained in this prospectus, we will file a post-effective amendment setting forth an explanation of such change. You should read this prospectus, any post-effective amendment, and any prospectus supplement together with additional information described below under the heading Where You Can Find More Information.

In this prospectus, Emisphere, we, us and our 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 eligen® 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 September 30, 2004, we have 77 patents issued and 82 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 eligen® 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 eligen® 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 eligen® technology has competitive advantages, including:

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

Oral drug delivery using the eligen® 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 currently intend to seek FDA approval to begin Phase III testing in 2005. 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. Under the previous program, 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 eligen® 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 eligen® technology. Novartis will fully fund the program including all clinical studies.

Oral Small Molecule Compounds

On November 17, 2004, we entered into a licensing agreement with Hoffmann-La Roche Inc. (Roche Inc. and F. Hoffman-La Roche LTD (Roche LTD and, together with La Roche Inc., 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 eligen® technology to treat bone disease. Later stage trials may not support the findings of our pre-clinical or feasibility studies.

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 September 30, 2004, our accumulated deficit was approximately $324 million. For the first nine months of 2004, our net loss was $28.8 million and our cash outlays from operations and capital expenditures were $19.7 million. Our estimated cash outlays for the year ended December 31, 2004 were $26.2 million. Our net loss for 2003 and 2002 was $44.9 million and $71.3 million, respectively. Our stockholders equity decreased from $67.5 million as of December 31, 2002 to a stockholders deficit of $4.1 million as of September 30, 2004. We have also made substantial debt payments to Elan Pharmaceuticals, Inc. (Elan) and have commitments to make additional payments during 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.

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, will enable us to continue operations through the end of the second quarter of 2005. Should we be unable to raise needed capital by April 2005, we have developed a restructuring plan whereby we would significantly decrease operating costs by reducing our workforce and scaling back research and development efforts. These decreases would allow us to continue to operate through December 31, 2005. However, if our restructuring efforts as discussed herein are not sufficient due to unanticipated costs and expenses, we may be required to discontinue, shutdown, or cease operations. Even with a successful implementation of our restructuring effort, without raising additional capital or receiving substantial cash inflows our financial statements for the year ended December 31, 2004 will emphasize the existence of substantial doubt about our ability to continue as a going concern, and our independent registered public accounting firm will emphasize this going concern matter in their audit report for the year ending December 31, 2004 which may, in turn, adversely affect our ability to raise additional capital. If additional capital is raised through the sale of equity or convertible debt securities, the issuance of such securities could result in dilution to our existing stockholders.

On December 27, 2004, we entered into a Common Stock Purchase Agreement (the Common Stock Purchase Agreement) with Kingsbridge Capital Limited (Kingsbridge), 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 at an exercise price of $3.811 (representing a premium to the market price of shares of our common stock on the date of issuance of the warrant). Under the terms of the Common Stock Purchase Agreement, we may, at our election, draw funds from Kingsbridge in amounts up to 3% of our market capitalization at the time of the draw. The Company s market capitalization as of January 28, 2005 approximated $90 million. Only one draw down is permitted per draw down pricing period, which is a period of 15 days, with a minimum of 5 trading days between each draw down pricing period. In exchange for each draw, we will sell to Kingsbridge newly issued shares of our common stock priced at a discount of between 8-12% of the average trading price of our common stock during the financing period, with the reduced discount applying if the price of the common stock is equal or greater than $8.50 per share. We will set the minimum acceptable purchase price of any shares to be issued to Kingsbridge during the term of the Common Stock Purchase Agreement which, in no event, may be less than $2.00 per share. Our right to begin drawing funds will commence upon the SEC s declaring effective a registration statement to be filed by us. We are under no obligation to access any of the capital available under the Common Stock Purchase Agreement. Kingsbridge may terminate the agreement based on material adverse effects on the Company s business, operations, properties or financial condition excluding material adverse effects related to formation or dissolution of partnerships or the results of any clinical trials. In addition, we can effect other debt and equity financings without restriction, provided that such financings do not use any floating or other post-issuance adjustable discount to the market price of our common stock. Kingsbridge is precluded from short selling any of our common stock during the term of the Common Stock Purchase Agreement.

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 Company common stock outstanding, that at the time of such conversion no event of default under the 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 common stock of the Company, Novartis would have the right to require the Company 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.

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 and a 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, 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 approximately $29 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, we have the right to make a cash payment of $7 million and issue 323,077 shares on April 29, 2005 and a final cash payment of $6 million and the issuance of 276,923 shares of our common stock on June 30, 2005 in exchange for the remaining balance of the Modified Elan Note. Alternatively, prior to March 31, 2005, we have the right to make a cash payment of $13 million, and issue to Elan a warrant to purchase 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 date of issuance of such warrant) in exchange for the Modified Elan Note. We may also defer the cash payments and the common stock issuances to a date not later than September 30, 2005. If we exercise that right and elect to defer the $7 million installment due on April 29, 2005, we are required to issue to Elan an adjusted modified note (the Adjusted Note) equal to the outstanding balance of the Modified Elan Note plus approximately $2 million (the value of the 600,000 shares issued on December 27, 2004) in exchange for the Modified Elan Note and we will be obligated to pay Elan $250,000 per month for each month during which the Adjusted Note remains outstanding. If we do not complete the payments and the common

stock issuances by September 30, 2005, we will be obligated to continue the payment of $250,000 per month until the full repayment of the Adjusted Note any time between September 30, 2005 and the maturity date of the Original Elan Note (July 2, 2006).

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 September 30, 2004, our accumulated deficit was approximately $324 million. For the first nine months of 2004, our net loss was $28.8 million and our cash outlays from operations and capital expenditures were $19.7 million. Our estimated cash outlays for the year ended December 31, 2004 were $26.2 million. Our net loss for 2003 and 2002 was $44.9 million and $71.3 million, respectively. Our stockholders equity decreased from $67.5 million as of December 31, 2002 to a stockholders deficit of $4.1 million as of September 30, 2004. We have also made substantial debt payments to Elan and have commitments to make additional payments during 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.

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, will enable us to continue operations through the end of the second quarter of 2005. Should we be unable to raise needed capital by April 2005, we have developed a plan whereby we would decrease operating costs by reducing our workforce and scaling back research and development efforts. These decreases would allow us to continue to operate through December 31, 2005. However, if our restructuring efforts as discussed herein are not sufficient due to unanticipated costs and expenses, we may be required to discontinue, shutdown, or cease operations. Even with a successful implementation of our restructuring effort, without raising additional capital or receiving substantial cash inflows our financial statements for the year ended December 31, 2004 will emphasize the existence of substantial doubt about our ability to continue as a going concern, and our independent registered public accounting firm will emphasize this going concern matter in their audit report for the year ended December 31, 2004 which may in turn, adversely affect our ability to raise additional capital. If additional capital is raised through the sale of equity or convertible debt securities, the issuance of such securities could result in dilution to our existing stockholders.

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 and a 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, 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 approximately $29 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, we have the right to make a cash payment of $7 million and issue 323,077 shares on April 29, 2005 and a final cash payment of $6 million and the issuance of 276,923 shares of our common stock on June 30, 2005 in exchange for the remaining balance of the Modified Elan Note. Alternatively, prior to March 31, 2005, we have the right to make a cash payment of $13 million, and issue to Elan a warrant to purchase 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 date of issuance of such warrant) in exchange for the Modified Elan Note. We may also defer the cash payments and the common stock issuances to a date not later than September 30, 2005. If we exercise that right and elect to defer the $7 million installment due on April 29, 2005, we are required to issue to Elan an adjusted modified note (the Adjusted Note) equal to the outstanding balance of the Modified Elan Note plus approximately $2 million (the value of the 600,000 shares issued on December 27, 2004) in exchange for the Modified Elan Note and we will be obligated to pay Elan $250,000 per month for each month during which the Adjusted Note remains outstanding. If we do not complete the payments and the common stock issuances by September 30, 2005, we will be obligated to continue the payment of $250,000 per month until the full repayment of the Adjusted Note any time between September 30, 2005 and the maturity date of the Original Elan Note (July 2, 2006).

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 Company common stock outstanding, that at the time of such conversion no event of default under the 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 common stock of the Company, Novartis would have the right to require the Company 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 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%.

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, 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.

If we are unable to raise additional capital in the near term, our financial statements for the 2004 fiscal year will be subject to a going concern qualification by our independent registered public accounting firm, which may, in turn, 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 $14 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 2002, we recorded an impairment charge of $4.5 million. In 2003, we recorded an additional impairment charge of $5.4 million.

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 Pharmaceuticals, Inc. (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 case went to trial on January 31, 2005. An adverse determination in this litigation concerning our claim that Lilly has infringed upon our patents could limit our future ability to realize on the potential value of those patents. Although the costs of litigating this matter may be material, we anticipate that we will have sufficient financial resources to fund future costs, including trial costs, and we do not anticipate any significant impact on our ability to develop our product candidates. Through December 31, 2004, we have incurred approximately $1.4 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. We do not currently have a purchaser for this facility and we cannot be certain of when or if we will consummate a sale of the facility. A previously interested purchaser has terminated its interest in the facility and we may not find an alternate buyer. Also, 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, lawn care and real estate taxes) will require continued cash outlays. The carrying value of the Farmington facility as of September 30, 2004 was $3.6 million.

If we cannot adequately protect our patent and proprietary rights, our business will suffer.

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. Although 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 2002 and 2003, 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 the Company for fourteen years. We would be significantly disadvantaged if Dr. Goldberg were to leave the Company. 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 the Company. 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 December 31, 2004, our 52-week high and low market price for our common stock was $8.44 and $2.86, 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 December 31, 2004, there were outstanding options to purchase up to 4,410,688 shares of our common stock that are currently exercisable, and additional outstanding options to purchase up to 1,134,567 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 connection with the Common Stock Purchase Agreement with Kingsbridge described above, we entered into a Registration Rights Agreement with Kingsbridge (the Registration Rights Agreement). Under the terms of the Registration Rights Agreement, we granted registration rights to Kingsbridge concerning the resale by Kingsbridge of the 250,000 shares of our common stock that may be purchased by Kingsbridge pursuant to the warrant that was issued to Kingsbridge on December 27, 2004. The Registration Rights Agreement also grants registration rights to Kingsbridge for up to $20 million worth of common stock that we in our discretion choose to sell in the future to Kingsbridge under the Common Stock Purchase Agreement. The Registration Rights Agreement requires us to file a registration statement concerning such shares of our common stock with the SEC within sixty calendar days after December 27, 2004. We must use our commercially reasonable efforts to have the registration statement declared effective by the Securities and Exchange Commission within one hundred twenty calendar days after December 27, 2004.

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).

THE SECURITIES WE MAY OFFER

We may offer shares of Common Stock and/or warrants to purchase shares of Common Stock, in any combination thereof totaling 5,000,000 shares of Common Stock, from time to time under this prospectus at prices and on terms to be determined by market conditions at the time of offering. This prospectus provides you with a general description of the securities we may offer. Each time we offer a type or series of securities, we will provide a prospectus supplement that will describe the specific amounts, prices and other important terms of the securities.

The prospectus supplement also may add, update or change information contained in this prospectus or in documents we have incorporated by reference. However, no prospectus supplement shall fundamentally change the terms that are set forth in this prospectus or offer a security that is not registered and described in this prospectus at the time of its effectiveness.

This Prospectus May Not Be Used to Consummate a Sale of Securities Unless It Is Accompanied by a Prospectus Supplement.

We may sell the securities directly to or through agents, underwriters or dealers. We, and our agents or underwriters, reserve the right to accept or reject all or part of any proposed purchase of securities. If we do offer securities through agents or underwriters, we will include in the applicable prospectus supplement:

the names of those agents or underwriters;
applicable fees, discounts and commissions to be paid to them; and
the net proceeds to us.

Common Stock. We may issue shares of our Common Stock from time to time. Holders of Common Stock are entitled to one vote per share on all matters submitted to a vote of stockholders. Subject to any preferences of outstanding shares of preferred stock, holders of common stock are entitled to dividends when and if declared by our board of directors.

Warrants. We may issue warrants for the purchase of Common Stock. We may issue warrants independently or together with Common Stock, and the warrants may be attached to or separate from these securities. In this prospectus, we have summarized certain general features of the warrants. We urge you, however, to read the prospectus supplements related to the series of warrants being offered, as well as the warrant agreements that contain the terms of the warrants. We will file forms of any warrants being offered through a prospectus supplement.

We will evidence each series of warrants by warrant certificates that we will issue under a separate agreement. We may enter into the warrant agreements with a warrant agent. Any warrant agent will be a bank that we select that has its principal office in the United States and a combined capital and surplus of at least $50 million. We will indicate the name and address of the warrant agent in the applicable prospectus supplement relating to a particular series of warrants.

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 currently intend to use the net proceeds from the sale of shares of Common Stock offered by this prospectus 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. As of January 10, 2005, our aggregate existing indebtedness was $40.2 million. We will use a prospectus supplement in connection with the sale of shares of Common Stock offered by this prospectus to further specify how we intend to use any proceeds generated by such sale.

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 eligen® 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 eligen® Technology

The eligen® 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 eligen® 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 eligen® 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 cost 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 (i) the therapeutic areas for which we are developing product candidates, either alone or with corporate partners, (ii) the candidates currently in development, (iii) the present stage of clinical development, and (iv) 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	Pre-clinical[4]	Roche
Growth Disorders	Oral Recombinant Human Growth Hormone (somatropin; rhGH)	Phase I	Novartis Pharma AG [5]
Diabetes	Oral Insulin Oral Glucagon-Like Peptides (GLPs)	Phase I [6] Pre-clinical [4]	Self-developed 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]	
Anti-infectives	Oral Anthrax Antigen	Pre-clinical [4]	US Army Medical Research Institute of Infectious Diseases

(1) We previously were developing 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.

(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.

(4) Pre-clinical = 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 Eli Lilly and Company, 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.

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. Also, drug delivery companies 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 targeted by us.

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 eligen® 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 eligen® 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 eligen® TECHNOLOGY

Our oral drug delivery technology, the eligen® 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 eligen® 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 eligen® 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 eligen® 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 eligen® 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 U.S. Food and Drug Administration (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 eligen® 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 eligen® 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 eligen® 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.

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 the PROTECT Trial. Based on that study, 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 unfractionated heparin (UFH), an antithrombotic/anticoagulant, 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 a Phase III 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, and our liquid formulation. The new formulations consisted of tablets and soft-gel capsules. Each subject was also administered our liquid UFH formulation, previously tested in a Phase III clinical trial, 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 (aPTT) 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 previous Phase III trial that did not meet its efficacy endpoint, 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 PROTECT 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 study 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®. Retrospective statistical analysis indicates that a non-inferiority endpoint was achieved in the Protect trial.

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 study, and are evaluating the application of that safety database to supplement with additional efficacy data from the solid form of oral heparin for potential utility toward future regulatory submissions to the FDA. In 2003 and 2004, we conducted studies with various solid oral dosage forms of SNAC/UFH to examine different forms of the solid heparin and to optimize further the prototypes that were announced at the ASH conference in 2002.

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 SC 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 (ADA) 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 SC injection of 12 Unit short-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 10 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 (10 minutes before meals and at bedtime) 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 U insulin/160 mg EMISPHERE(R) delivery agent) or controlled treatment (two tablets containing a total of 200 mg EMISPHER (R) delivery agent), four times daily (10 minutes before breakfast, lunch and dinner, and once 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 announced that results from our the multiple-dose 13-patient Phase I clinical study were presented as a poster at the 64th Scientific Sessions of the American Diabetes Association. The study was conducted at PROFIL Institute, an internationally recognized diabetes research center in Neuss, Germany, and presented June 5, 2004 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(TM) 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(TM) 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(TM) oral insulin, postprandial (after meal) 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-termed 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(TM) 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 Pharma AG 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 and in that connection. In March 2000, Novartis paid us $2.5 million to obtain the license to our technology for calcitonin, and to obtain an option to use the eligen® technology for a second compound. Novartis rights to certain specified financial terms concerning a license of a second compound have since expired.

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 calcitonin 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 aggregate milestone payments and approximately $650,000 in accrued costs.

Novartis Pharma AG 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 Pharma AG 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.

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.

Under the terms of the new agreement, Novartis will pay us up to $34 million 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 Hoffmann-La Roche Inc. and F. Hoffmann-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 eligen® technology.

Under the terms of the agreement, Roche paid us an initial up-front fee, and will pay us future milestones of up to $18.5 million for each product 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.

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 parathyroid hormone (PTH 1-34 , or teriparatide) for the treatment of osteoporosis and a second product candidate, recombinant human growth hormone (rhGH , or somatropin), 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 Emisphere, 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 current 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 contigent on USAMRIID s developement 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 September 30, 2004, we had 77 issued patents in the United States and had other patents issued or applications pending in various countries around the world. Of our 77 U.S. issued patents, 9 were issued by the U.S. Patent and Trademark Office in 2003. 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 September 30, 2004, we had 82 patent applications relating to our drug delivery technology pending in the United States. We have pursued strategic international protection with approximately 43 patents and 224 patent applications pending internationally in a total of 37 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 18. 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 30 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 (i) physicians and patients prefer orally delivered forms of products over injectable forms, (ii) oral forms of products enable improved compliance, and (iii) 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 (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 December 31, 2004, we had 115 employees, 77 of whom are engaged in scientific research and technical functions and 38 of whom are performing information technology, engineering, facilities maintenance and administrative functions. Of the 115 employees, 31 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 Exchange Act). 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 the Annual Report or this Form 10-K.

DESCRIPTION OF CAPITAL STOCK

Our authorized capital stock consists of 40,000,000 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 December 31, 2004, there were 19,110,749 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.

DESCRIPTION OF WARRANTS

The following description, together with the additional information we may include in any applicable prospectus supplements, summarizes the material terms and provisions of the warrants that we may offer under this prospectus and the related warrant agreements and warrant certificates. While the terms summarized below will apply generally to any warrants that we may offer, we will describe the particular terms of any series of warrants in more detail in the applicable prospectus supplement. If we indicate in the prospectus supplement, the terms of any warrants offered under that prospectus supplement may differ from the terms described below. However, no prospectus supplement shall fundamentally change the terms that are set forth in this prospectus or offer a security that is not registered and described in this prospectus at the time of its effectiveness. Specific warrant agreements will contain additional important terms and provisions and will be incorporated by reference as an exhibit to the registration statement that includes this prospectus or as an exhibit to a current report on Form 8-K.

General

We will describe in the applicable prospectus supplement the terms of the series of warrants, including:

- the offering price and aggregate number of warrants offered;
- the currency for which the warrants may be purchased;
- if applicable, the date on and after which the warrants and the related Common Stock will be separately transferable;
- the number of shares of Common Stock purchasable upon the exercise of one warrant and the price at which these shares may be purchased upon such exercise;
- the effect of any merger, consolidation, sale or other disposition of our business on the warrant agreements and the warrants;
- the terms of any rights to redeem or call the warrants;
- any provisions for changes to or adjustments in the exercise price or amount of Common Stock issuable upon exercise of the warrants;
- the dates on which the right to exercise the warrants will commence and expire;
- the manner in which the warrant agreements and warrants may be modified;
- federal income tax consequences of holding or exercising the warrants; and
- any other specific terms, preferences, rights or limitations of or restrictions on the warrants.

Before exercising their warrants, holders of warrants will not have any of the rights of holders of the Common Stock purchasable upon such exercise, including the right to receive dividends, if any, or, payments upon our liquidation, dissolution or winding up or to exercise voting rights, if any.

Exercise of Warrants

Each warrant will entitle the holder to purchase the amount of Common Stock that we specify in the applicable prospectus supplement at the exercise price that we describe in the applicable prospectus supplement. Unless we otherwise specify in the applicable prospectus supplement, holders of the warrants may exercise the warrants at any time up to 5:00 P.M. New York time on the expiration date that we set forth in the applicable prospectus supplement. After the close of business on the expiration date, unexercised warrants will become void.

Holders of the warrants may exercise the warrants by delivering the warrant certificate representing the warrants to be exercised together with specified information, and paying the required amount to us (or the warrant agent, if applicable) in immediately available funds, as provided in the applicable prospectus supplement. We will set forth on the reverse side of the warrant certificate and in the applicable prospectus supplement the information that the holder of the warrant will be required to deliver to us (or the warrant agent, if applicable).

Upon receipt of the required payment and the warrant certificate properly completed and duly executed at the corporate trust office of the warrant agent or any other office indicated in the applicable prospectus supplement, we will issue and deliver the Common Stock purchasable upon such exercise. If fewer than all of the warrants represented by the warrant certificate are exercised, then we will issue a new warrant certificate for the remaining amount of warrants. If we so indicate in the applicable prospectus supplement, holders of the warrants may surrender securities as all or part of the exercise price for warrants.

Governing Law

The warrants and warrant agreements will be governed by and construed in accordance with the laws of the State of New York.

Enforceability of Rights by Holders of Warrants

Each warrant agent, if any, will act solely as our agent under the applicable warrant agreement and will not assume any obligation or relationship of agency or trust with any holder of any warrant. A single bank or trust company may act as warrant agent for more than one issue of warrants. A warrant agent will have no duty or responsibility in case of any default by us under the applicable warrant agreement or warrant, including any duty or responsibility to initiate any proceedings at law or otherwise, or to make any demand upon us. Any holder of a warrant may, without the consent of the related warrant agent or the holder of any other warrant, enforce by appropriate legal action its right to exercise, and receive the Common Stock purchasable upon exercise of, its warrants.

PLAN OF DISTRIBUTION

We may offer and sell shares of Common Stock:

through one or more underwriters or dealers in a public offering and sale by them,

directly to investors, or

through agents.

We may sell shares of Common Stock from time to time in one or more transactions at a fixed price or prices, which may be changed from time to time:

at market prices prevailing at the time of sale,

at prices related to such prevailing market prices, or

at negotiated prices.

We will describe the method of distribution of the shares of Common Stock in the applicable prospectus supplement. In the event there is a material change to our plan of distribution for shares offered pursuant to this prospectus, we will file a post-effective amendment to this prospectus setting forth an explanation of such change.

Underwriters, dealers or agents may receive compensation in the form of discounts, concessions or commissions from us or purchasers of our Common Stock (as their agents in connection with the sale of shares of Common Stock). These underwriters, dealers or agents may be considered to be underwriters under the Securities Act. As a result, discounts, commissions or profits on resale received by the underwriters, dealers or agents may be treated as underwriting discounts and commissions. The applicable prospectus supplement will identify any such underwriter, dealer or agent, and describe any compensation received by them from us.

Underwriters, dealers and agents may be entitled to indemnification by us against certain civil liabilities, including liabilities under the Securities Act, or to contribution with respect to payments made by the underwriters, dealers and agents.

We may grant underwriters who participate in the distribution of shares of Common Stock an option to purchase additional shares of Common Stock to cover over-allotments, if any, in connection with the distribution.

Underwriters or agents and their associates may be customers of, engage in transactions with or perform services for us in the ordinary course of business.

LEGAL MATTERS

Proskauer Rose LLP, New York, New York, will pass on the validity of the issuance of the shares of Common Stock offered in this prospectus.

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, 2003 have been incorporated in reliance on the report 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 for the fiscal year ended December 31, 2003;

2. Our Quarterly Reports on Form 10-Q for the fiscal quarters ended March 31, 2004, June 30, 2004 and September 30, 2004; and

3. Our Current Reports on Form 8-K dated January 27, 2004, February 3, 2004, July 9, 2004, August 9, 2004, September 29, 2004, November 23, 2004, December 7, 2004, December 30, 2004 and January 26, 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.

An estimate (other than the SEC registration fee) of the fees and expenses of issuance and distribution (other than discounts and commissions) of the Common Stock offered hereby (all of which will be paid by us) is as follows:

SEC registration fee	$	2,369
Legal fees and expenses	$	150,000
Accounting fees and expenses	$	75,000
Printing Costs and expenses	$	100,000
Total	$	327,369

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 exhibits listed in the Exhibit Index as filed as part of this Registration Statement.

Exhibit Number	Description
10.30	Research Collaboration License Agreement, dated and effective as of September 23, 2004 between Emisphere and Novartis Pharma AG (filed in redacted form pursuant to a Confidential Treatment Request; unredacted version filed separately with the SEC)
10.31	Development and License Agreement, dated and effective as of November 17, 2004 among Hoffmann-La Roche Inc., F. Hoffmann-La Roche LTD and Emisphere (filed in redacted form pursuant to Confidential Treatment Request; unredacted version filed separately with the SEC)
10.32	Research Collaboration Option and License Agreement dated December 1, 2004 by and between Emisphere and Novartis Pharma AG (filed in redacted form pursuant to a Confidential Treatment Request; unredacted version filed separately with the SEC)

10.33	Convertible Promissory Note due December 1, 2009 issued to Novartis Pharma AG (filed in redacted form pursuant to a Confidential Treatment Request; unredacted version filed separately with the SEC)
10.34	Registration Rights Agreement dated as of December 1, 2004 between Emisphere and Novartis Pharma AG
10.35	Common Stock Purchase Agreement by and between Kingsbridge Capital Limited and Emisphere dated as of December 27, 2004
10.36	Registration Rights Agreement by and between Kingsbridge Capital Limited and Emisphere dated December 27, 2004
10.37	Warrant issued by Emisphere to Kingsbridge Capital Limited dated December 27, 2004
10.38	Security Purchase Agreement dated as of December 27, 2004 by and between Elan International Services, Ltd. and Emisphere
10.39	Zero Coupon Note due 2006 issued by Emisphere in favor of Elan International Services, Ltd. dated December 27, 2004
10.40	Amendment to Employment Agreement by and between Emisphere and Michael M. Goldberg, M.D.
23.1	Consent of PricewaterhouseCoopers LLP
24.1	Power of Attorney (included in Signature Page)

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 AND POWER OF ATTORNEY

KNOW ALL MEN BY THESE PRESENTS, that each person whose signature appears below constitutes and appoints Michael M. Goldberg and Elliot M. Maza, and each of them, his true and lawful attorneys-in-fact and agents, with full power of substitution and resubstitution, for him and in his name, place and stead, in any and all capacities, to sign any and all amendments to this Registration Statement on Form S-3 and to file the same, with all exhibits thereto, and other documents in connection therewith, with the Securities and Exchange Commission, granting unto said attorneys-in-fact and agents, and each of them, full power and authority to do and perform each and every act and thing requisite and necessary to be done, as fully to all intents and purposes as he might or could do in person, hereby ratifying and confirming all that said attorneys-in-fact and agents or any of them, or their or his substitute or substitutes, may lawfully do or cause to be done by virtue thereof.

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 Registration Statement to be signed on its behalf by the undersigned, thereunto duly authorized, in the City of Tarrytown, State of New York on February 1, 2005.

EMISPHERE TECHNOLOGIES INC

By: /s/ MICHAEL M. GOLDBERG, M.D.

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, M.D. **Michael M. Goldberg, M.D.**	Director, Chairman of the Board and Chief Executive Officer (principal executive officer)	February 1, 2005
* **Howard M. Pack**	Director	February 1, 2005
* **Robert J. Levenson**	Director	February 1, 2005

*		
Arthur Dubroff	Director	February 1, 2005
*		
Stephen K. Carter, M.D.	Director	February 1, 2005
*		
Michael E. Black	Director	February 1, 2005
/s/ ELLIOT M. MAZA		
Elliot M. Maza, J.D., C.P.A.	Chief Financial Officer (principal financial and accounting officer)	February 1, 2005

* Executed by Attorney-in-Fact

INDEX TO EXHIBITS

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