NEOSE TECHNOLOGIES INC
Form 10-K
March 16, 2007

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UNITED STATES SECURITIES AND EXCHANGE COMMISSION
Washington, D.C. 20549
FORM 10-K

(Mark One)

þ **ANNUAL REPORT PURSUANT TO SECTION 13 OR 15(D) OF THE SECURITIES EXCHANGE ACT OF 1934**
for the fiscal year ended December 31, 2006 or

o **TRANSITION REPORT PURSUANT TO SECTION 13 OR 15(D) OF THE SECURITIES EXCHANGE ACT OF 1934**
for the transition period from _____ to _____

Commission File Number 0-27718
NEOSE TECHNOLOGIES, INC.
(Exact name of registrant as specified in its charter)

Delaware	**13-3549286**
(State or other jurisdiction of incorporation or organization)	(I.R.S. Employer Identification No.)
102 Rock Road **Horsham, Pennsylvania**	**19044**
(Address of principal executive offices)	(Zip Code)

Registrant s telephone number, including area code: **(215) 315-9000**
Securities registered pursuant to Section 12(b) of the Act:

Common Stock, par value $0.01 per share	**The NASDAQ Stock Market LLC**
(Title of each class)	(Name of each exchange on which registered)

Securities registered pursuant to Section 12(g) of the Act:
Preferred Share Purchase Rights

(Title of class)

Indicate by check mark if the registrant is a well-known seasoned issuer, as defined in Rule 405 of the Securities Act. Yes o No þ
Indicate by check mark if the registrant is not required to file reports pursuant to Section 13 or Section 15(d) of the Act. Yes o No þ
Indicate by check mark whether the registrant (1) has filed all reports required to be filed by Section 13 or 15(d) of the Securities Exchange Act of 1934 during the preceding 12 months (or for such shorter period that the registrant was required to file such reports), and (2) has been subject to such filing requirements for the past 90 days. Yes þ No o
Indicate by check mark if disclosure of delinquent filers pursuant to Item 405 of Regulation S-K is not contained herein, and will not be contained, to the best of registrant s knowledge, in the definitive proxy statement or information statements incorporated by reference in Part III of this Form 10-K or any amendment to this Form 10-K. þ
Indicate by check mark whether the registrant is a large accelerated filer, an accelerated filer, or a non-accelerated filer. See definition of accelerated filer and large accelerated filer in Rule 12b-2 of the Exchange Act. (Check one):

Large accelerated filer o Accelerated filer þ Non-accelerated filer o

Indicate by check mark whether the registrant is a shell company (as defined in Rule 12b-2 of the Act). Yes o No þ

As of June 30, 2006, the aggregate market value of the registrant s Common Stock held by non-affiliates of the registrant was approximately $76,818,298 based on the last sale price of the Common Stock on such date as reported by The NASDAQ Stock Market LLC. This calculation excludes 13,861,139 shares held on June 30, 2006 by directors, executive officers, and two holders of more than 10% of the registrant s Common Stock.

As of March 15, 2007, there were 54,387,843 shares of the registrant s Common Stock outstanding.

DOCUMENTS INCORPORATED BY REFERENCE

The registrant s definitive proxy statement to be filed in connection with solicitation of proxies for its Annual Meeting of Stockholders to be held on May 4, 2007, is incorporated by reference into Part III of this Annual Report on Form 10-K.

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NEOSE, GlycoAdvance, GlycoPEGylation and GlycoConjugation are trademarks of Neose Technologies, Inc. This Annual Report on Form 10-K also includes trademarks and trade names of other companies.

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PART I

ITEM 1. BUSINESS.

Overview

We are a clinical stage biopharmaceutical company focused on the development of next-generation therapeutic proteins, which we believe will be competitive with best-in-class protein drugs currently on the market. Our lead therapeutic protein candidates are GlycoPEG-EPO (NE-180) and GlycoPEG-GCSF. In 2005, the EPO and G-CSF drug categories had aggregate worldwide sales of approximately $11.2 billion and $4.0 billion, respectively.

NE-180 is a long-acting version of erythropoietin (EPO) produced in insect cells. EPO is prescribed to stimulate production of red blood cells, and is approved for sale in major markets around the world for treatment of chemotherapy-induced anemia and anemia associated with chronic renal failure. NE-180 is being developed for the treatment of anemia in adult cancer patients with non-myeloid malignancies receiving chemotherapy and for the treatment of anemia associated with chronic kidney disease, including patients on dialysis and patients not on dialysis. During 2006, we completed a Phase I clinical trial for NE-180 in Switzerland. In January 2007, we received approval from Swissmedic, the Swiss Agency for Therapeutic Products, for the initiation of a Phase II human trial to evaluate the safety, tolerability and dose response of NE-180 in cancer patients receiving platinum-based chemotherapy. In March 2007, we received approval from the U.S. Food and Drug Administration (FDA) to initiate clinical trials in the U.S. in response to our amended Investigational New Drug application (IND).

Our second proprietary protein, GlycoPEG-GCSF, is a long-acting version of granulocyte colony stimulating factor (G-CSF) that we are co-developing with BioGeneriX AG, a company of the ratiopharm Group. G-CSF is prescribed to stimulate production of neutrophils (a type of white blood cell) and is approved for sale in major markets around the world for treatment of neutropenia associated with myelosuppressive chemotherapy. In November 2006, BioGeneriX initiated the first of two planned Phase I clinical trials for GlycoPEG-GCSF. We expect BioGeneriX to initiate and complete the second Phase I trial during 2007.

We believe that our enzymatic pegylation technology, GlycoPEGylation , can improve the drug properties of therapeutic proteins by building out, and attaching polyethylene glycol (PEG) to, carbohydrate structures on the proteins. We are using our technology to develop proprietary versions of protein drugs with proven safety and efficacy and to improve the therapeutic profiles of proteins being developed by our partners. We expect these modified proteins, such as NE-180 and GlycoPEG-GCSF, to offer significant advantages, including less frequent dosing and possibly improved efficacy, over the original versions of the drugs now on the market, as well as to meet or exceed the pharmacokinetic profile of next-generation versions of the drugs now on the market. We believe this strategy of targeting drugs with proven safety and efficacy allows us to lower the risk profile of our proprietary development portfolio as compared to *de novo* protein drug development. We intend to continue to focus our research and development resources on therapeutic proteins that we believe have the highest probability of clinically meaningful therapeutic profile improvements from our technology and are in commercially attractive categories.

Opportunities in the Therapeutic Protein Market

Worldwide sales of protein drugs in 2006 have been reported at over $47 billion, and by some estimates are expected to grow to over $55 billion by 2011. We believe that many of the proteins now on the market will lose the protection of certain patent claims over the next 15 years. In addition, many marketed proteins are facing increased competition from next-generation versions or from other drugs approved for the same disease indications. Although not every protein drug is a candidate for the use of our technologies, we believe our technologies can be applied to many of these marketed drugs to create products with improved clinical profiles. We are pursuing opportunities in this field through our own proprietary drug development portfolio, our exploratory research program and our partnering and licensing program. We will continue our efforts to build a portfolio of commercially attractive partnerships in a blend of co-developments and licenses. Where possible, we will seek partnerships that allow us to participate significantly in the commercial success of each of the compounds.

Our Technology

Our GlycoPEGylation technology involves the use of enzymes to attach PEG to carbohydrate structures that we have introduced or modified on proteins. We have developed a special expertise and an extensive intellectual property position in this area. Our technologies may permit the development of therapeutic proteins with improved clinical

profiles. In

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some cases, these improvements to therapeutic proteins may also allow us to create new intellectual property relating to our core technologies, as well as new compositions of matter. In addition, our technology can be applied to proteins produced in a variety of cell expression systems, including Chinese hamster ovary (CHO) cells, *E. coli*, and insect cells. We continue to make significant investments in research and development and legal services to protect and expand our intellectual property position. We believe our core technologies have broad application to protein drug development and can be extended to provide an opportunity for sustainable growth. We are using our GlycoPEGylation technology in our drug development portfolio, in our partnering and licensing program, and in our exploratory research.

Improved Clinical Profiles. Common protein drug delivery problems include poor solubility and stability, proteolysis (rapid degradation), rapid clearance, and immunogenicity. For some proteins, one approach to these problems has been conventional chemical pegylation the attachment of the large, water-soluble polymer, PEG, directly to the amino acid backbone of the protein. Pegylation may improve the solubility, stability, half-life and immunogenicity profile of a protein drug. Pegylation has been used in marketed drugs, such as PEG-INTRON®, PEGASYS® and Neulasta®.

For some protein drugs, it has been difficult to achieve the benefits of pegylation by the conventional approach of attaching PEG directly to the protein backbone. A possible explanation is that the sites for the attachment of PEG occur at positions where the bulky PEG molecules block access to the active site on the protein or alter the conformation of the protein. This may diminish or eliminate drug activity.

By employing GlycoPEGylation, we are able to attach PEG efficiently and selectively to the carbohydrate structures on proteins, rather than attaching PEG directly to the protein backbone. By linking PEG to carbohydrate structures that are remote from the protein s active site, GlycoPEGylation may preserve the bioactivity of the drug and extend its half-life. We believe that significant clinical benefits may be achieved through the application of our GlycoPEGylation technology to proteins. By using our GlycoPEGylation technology, we have been able to demonstrate with several drug candidates a prolonged drug effect in animals, including drug candidates that have not shown biological activity following chemical pegylation.

Enabling Multiple Expression Systems. In addition to attaching PEG to carbohydrate structures, our enzymes also modify or introduce carbohydrate structures on proteins. We refer to this as our GlycoAdvance® technology. Currently, recombinant glycoprotein drugs are often produced in mammalian cell culture expression systems, primarily Chinese hamster ovary (CHO) cells. Generally, carbohydrates are added to proteins during the process of expression. CHO cells, and many other expression systems used for commercial manufacturing of proteins, tend to produce protein molecules with incomplete or inconsistent carbohydrate structures. In the human body, these incompletely glycosylated proteins may be cleared too rapidly, thus compromising the half-life and effectiveness of these proteins.

Our technology addresses these problems by employing enzymes to modify the carbohydrate structures on proteins that have inadequate carbohydrate structures and to introduce carbohydrate structures on proteins that have none. Proteins may have inadequate carbohydrate structures as a result of the cell expression systems used, or may have no carbohydrate structures in their native state. Our ability to modify or introduce carbohydrate structures allows our GlycoPEGylation technology to be applied to proteins produced in a variety of cell expression systems, including CHO cells, *E. coli*, and insect cells.

GlycoPEGylated Products in Development

There are currently three next-generation therapeutic protein candidates in development using our GlycoPEGylation technology: NE-180, GlycoPEG-GCSF, and a long-acting version of Factor VIIa (GlycoPEG-FVIIa).

NE-180. We are developing NE-180, a long-acting version of EPO that is produced in insect cells. NE-180 is being developed for the treatment of anemia in adult cancer patients with non-myeloid malignancies receiving chemotherapy and for the treatment of anemia associated with chronic kidney disease, including patients on dialysis and patients not on dialysis. During 2006, we completed a Phase I clinical trial for NE-180 in Switzerland. We concluded from that trial that single doses of NE-180, up to 1.5 µg/kg, were generally well-tolerated with no serious adverse events and demonstrated potent, dose-dependent erythropoietic activity. The results from the Phase I study

support a Phase II program in patients with anemia associated with chronic kidney disease, dosed every four weeks, and in cancer patients receiving chemotherapy, dosed every three weeks.

In January 2007, we received approval from Swissmedic, the Swiss Agency for Therapeutic Products, for the initiation of a Phase II human trial. The Phase II trial is designed as an open label, sequential, ascending dose study to evaluate the safety, tolerability and dose response of NE-180 in cancer patients receiving platinum-based chemotherapy. In

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March 2007, we received clearance from the U.S. Food and Drug Administration (FDA) to initiate clinical trials in the U.S. in response to our amended Investigational New Drug application (IND).

EPO is prescribed to stimulate production of red blood cells, and is approved for sale in major markets around the world for the treatment of chemotherapy-induced anemia and anemia associated with chronic renal failure. EPO accounts for more sales worldwide than any other glycoprotein drug. Worldwide sales in the EPO category in 2005 were approximately $11.2 billion. Of these sales, approximately $6.8 billion were in the U.S. and approximately $4.4 billion were outside the U.S.

We believe that the expiration of key patents covering EPO will provide commercial opportunities in time frames consistent with our development timeline. While we expect to pursue early entry opportunities in the U.S., we expect to pursue regulatory and marketing approval first in Europe, where the key patents, along with those in Japan, have expired.

In the U.S., we believe that the key patents surrounding EPO expressed in non-vertebrate systems will expire by the end of 2013, and that the remaining key patents will expire by the end of 2015. Accordingly, we believe that our use of an insect cell expression system will allow NE-180 to enter the U.S. market sooner than EPO products expressed in vertebrate or mammalian cells. In addition, we believe that the use of an insect cell expression system may allow us to enter the U.S. market before even the non-vertebrate patents expire. Some of the issues relevant to the analysis of our freedom to operate in the U.S. are the subject of ongoing litigation between other parties. We continue to monitor these matters, as well as evaluate whether the applicable patent claims would block our entry into the U.S. market prior to expiration. In the meantime, we expect to continue development in the U.S. of NE-180 under the protection of a statutory safe harbor.

GlycoPEG-GCSF. We are developing GlycoPEG-GCSF, a long-acting version of G-CSF, in collaboration with our partner BioGeneriX. In November 2006, BioGeneriX initiated in a Western European jurisdiction the first of two planned Phase I clinical trials for GlycoPEG-GCSF. We expect BioGeneriX to initiate and complete the second Phase I trial during 2007. G-CSF is prescribed to stimulate production of neutrophils (a type of white blood cell), and is approved for sale in major markets around the world for treatment of neutropenia associated with myelosuppressive chemotherapy. Worldwide sales in the G-CSF category in 2005 were approximately $4.0 billion. Of these sales, approximately $2.7 billion were in the U.S. and approximately $1.3 billion were outside the U.S.

We believe that the expiration of key patents covering G-CSF will provide commercial opportunities in a time frame consistent with our development timeline. We expect that regulatory approval for GlycoPEG-GCSF will be sought both in and outside the U.S. We believe that key patents covering G-CSF have expired in Europe, and will expire in the U.S. in late 2013 and in other jurisdictions between these times. We expect BioGeneriX to pursue regulatory and marketing approval for GlycoPEG-GCSF first in Europe.

GlycoPEG-FVIIa (Long-acting rFVIIa). A long-acting form of recombinant Factor VIIa is being developed by our partner, Novo Nordisk, utilizing our GlycoPEGylation technology. In 2006, we successfully completed technical transfer of the process to Novo Nordisk, who performed preclinical pharmacokinetic and pharmacodynamic studies, and conducted other preclinical activities. Novo Nordisk has announced that they plan to initiate Phase I clinical studies in 2007. Factor VIIa is used in the treatment of bleeding episodes and for the prevention of bleeding during surgery or invasive procedures in patients with congenital hemophilia with inhibitors to coagulation factors VIII or IX. The worldwide market for recombinant Factor VIIa was approximately $1 billion in 2006, with all of the sales being generated by Novo Nordisk. Novo Nordisk is also investigating other applications for Factor VIIa, including its use in hemophilia prophylaxis, intracerebral hemorrhage, trauma, traumatic brain injury, and spinal and cardiac surgery.

Partnering And Licensing Program

Currently we have the following collaborations:

BioGeneriX. In 2004, we entered into an agreement with BioGeneriX to use our proprietary GlycoAdvance and GlycoPEGylation technologies to develop a long-acting version of G-CSF. In October 2006, we entered into an amendment of this agreement. Under the agreement, as amended, we and BioGeneriX shared the expenses of preclinical development. BioGeneriX is responsible for supplying the protein and funding the clinical development program and we are responsible for supplying enzyme reagents and sugar nucleotides. As of January 1, 2007, BioGeneriX is responsible for the cost of reagent supply. If we and BioGeneriX proceed to commercialization, we

will have commercial rights in the U.S., Canada, Mexico and Japan, and BioGeneriX will have commercial rights in Europe and the rest of the world. Each company has the ability to search for its own marketing partner for its territories and will receive significant royalties on product sales in the other company s territory. Each party has the right, in various circumstances, to terminate the agreement by giving the required

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notice to the other party, subject to the other party s right to continue working on the development and commercialization of a long-acting version of G-CSF, as provided in the agreement. In addition, we have immediate termination rights, in which case we will have all rights to the product candidate, including supply of protein from BioGeneriX or its contract manufacturer, in the event BioGeneriX does not meet certain Phase I and Phase II diligence requirements. In November 2006, BioGeneriX initiated a Phase I clinical trial for GlycoPEG-CGSF in a Western European jurisdiction, and we expect BioGeneriX to conduct a second Phase I trial during 2007.

In 2005, we entered into a research, co-development and commercialization agreement with BioGeneriX for a GlycoPEGylated erythropoietin made in CHO cells (GlycoPEG-CHO-EPO). We received a non-refundable payment in connection with the execution of this agreement. The agreement provided for us to conduct research on behalf of BioGeneriX for up to 12 months and grant BioGeneriX the right to obtain an exclusive, worldwide license to use our enzymatic technologies to develop and commercialize a long-acting version of the target protein. Under an amendment to the agreement entered into in October 2006, BioGeneriX had until December 31, 2006 to exercise the option. BioGeneriX did not exercise the option and all rights to Neose s GlycoPEGylation technology as it applies to GlycoPEG-CHO-EPO reverted to Neose.

Novo Nordisk. In 2003, we entered into two agreements with Novo Nordisk A/S to use our GlycoPEGylation technology to develop and commercialize next-generation versions of Factors VIIa, VIII and IX, one of which, Factor VIIa, is currently marketed by Novo Nordisk. Under these agreements, we received a $4.3 million upfront fee, and Novo Nordisk funds our research and development activities for these three proteins. We may also receive up to $52 million in development milestones under these agreements, as amended, as well as significant royalties on sales of the licensed products.

In October 2006, we entered into an amended and restated agreement with Novo Nordisk, which supersedes one of the original agreements entered into in November 2003. The amended and restated agreement incorporates the prior amendments to the original agreement and further amends the original agreement to clarify certain terms and conditions related to intellectual property. Under these agreements, as amended, Novo Nordisk s license with respect to each protein continues until the expiration of the last Neose patent covering a licensed product, or until the earlier termination of the applicable agreement. Novo Nordisk has the right to terminate each of the agreements without cause. We have the right to terminate the agreement with respect to Factors VIII and IX if there are no commercial sales of licensed products within a specified period, subject to Novo Nordisk s ability to extend by paying minimum royalties.

Exploratory Research Program

We conduct exploratory research, both independently and with collaborators, on therapeutic candidates, primarily proteins, using our enzymatic technologies. Successful therapeutic candidates may be advanced for development through our own drug development program, our partnering and licensing program, or a combination of the two.

Intellectual Property

Our success depends on our ability to protect and use our intellectual property rights in the continued development and application of our technologies, to operate without infringing the proprietary rights of others, and to prevent others from infringing on our proprietary rights. In connection with our proprietary protein drug program, we have devoted significant resources to investigating the patent protection for currently marketed proteins. We also devote significant resources to obtaining and maintaining patents, and we expect to aggressively enforce our rights if necessary, although we recognize that the scope and validity of patents is never certain.

Our patent strategy has two main components, the pursuit of a patent portfolio protecting our technologies and their anticipated applications, and the evaluation of patent protection for proteins we may target for development.

Patents and Proprietary Rights. We have continued to file patent applications covering new developments in our technologies, including compositions and methods for enzymatically introducing and modifying sugar chains on a multitude of proteins to form stable linkages between a sugar attached to a polypeptide and a water soluble polymer, therapeutic compound, targeting agent, or other biologically active molecule.

In addition to developing our own intellectual property, we have obtained and continue to seek complementary intellectual property from others. We have entered into license agreements with various institutions and individuals for certain patent rights, as well as sponsored research and option agreements for the creation and possible license to

us of additional intellectual property rights. We are obligated to pay royalties at varying rates based upon, among other things, levels of revenues from the sale of licensed products under our existing license agreements, and we expect to pay royalties

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under new license agreements for intellectual property. Generally, these agreements continue for a specified number of years or as long as any licensed patents remain in force, unless the agreements are terminated earlier.

We own 28 issued U.S. patents, and have licensed 78 issued U.S. patents from various institutions. In addition, we own or have licensed over 124 patent applications pending in the U.S. There are also 522 foreign patent applications pending or granted related to our owned and licensed patents. Additionally, we have assigned four issued U.S. patents and seven granted or pending foreign counterparts to Magnolia Nutritionals, our joint venture with McNeil Nutritionals (a subsidiary of Johnson & Johnson).

We recently received five U.S. patents and five Notices of Allowance from the U.S. Patent and Trademark Office from and for our patent applications related to our GlycoConjugation and GlycoPEGylation technologies. The granted U.S. claims broadly cover glycosyl-linked polyethylene glycol conjugates of therapeutic peptides, methods of GlycoConjugating a Factor VIII polypeptide, and GlycoConjugates comprising more than one peptide. These recently granted U.S. patents and U.S. allowances belong to a series of pending patent applications directed toward our broad GlycoConjugation technology platform and proprietary proteins.

Proprietary Protein Drugs. To pursue our strategy of developing proprietary protein drugs, we must ascertain the nature, scope and expiration of existing patent claims covering the proteins we may target for development, and our methods of improving them, such as adding PEG. The patent coverage on these proteins and methods of making them is complex. These patents must be analyzed on a claim-by-claim basis, and we must make decisions based on our analysis of these varied claims. The patents and their expiration dates often vary from the U.S. to Europe to Japan. It is possible that we are unaware of issued patents or pending patent applications that are relevant to our product candidates, either because our search did not find them or because they are not yet publicly available.

In order to market proprietary versions of currently marketed proteins, it is necessary to determine the expiration dates of existing patent claims that could cover a product candidate by analyzing numerous, complex patent claims and, in some cases, judicial opinions. The analysis of patents is subject to different interpretations. Our analysis of the patent coverage surrounding EPO in the U.S. has encouraged us that there may be opportunities to enter the U.S. market with NE-180 sooner than our competitors whose products would have different characteristics or manufacturing processes. If we pursue a strategy of early entry in the U.S., litigation could result, and would be costly regardless of whether we were successful. Litigation could also result in delays in the launch of a product, even if we ultimately were to prevail in the litigation.

Nature of Protection. The nature of patent protection in the pharmaceutical and biotechnology industry is complex, uncertain and unpredictable, and expensive. The patents we seek may not issue, or may issue with a narrower scope than originally sought, and may not be valid or effectively enforceable. Even if our patents are enforceable, enforcement of our patents could be time consuming and expensive. If the claims in our pending patent applications are narrowed prior to issuance, others will have greater opportunity to circumvent or design around our patent protection.

We also have proprietary trade secrets and know-how that are not patentable or that we have chosen to maintain as secret rather than filing for patent protection. We seek to protect our secret information by entering into confidentiality agreements with employees, consultants, licensees, and potential collaboration partners. These agreements generally provide that all confidential information developed by us, or made known by us to the other party, during the relationship shall be kept confidential and may not be disclosed to third parties, except in specific circumstances. Our agreements with employees also provide that inventions made by the employee during the period of employment will be solely owned by us if they are the result of tasks assigned by us or the use of property (including intellectual property) owned or used by us. Our agreements with consultants generally provide that inventions conceived by the consultant while rendering consulting services to us will be our exclusive property.

We are aware of numerous pending and issued U.S. and foreign patent rights and other proprietary rights owned by third parties in fields related to our technologies. We will continue to expend resources to protect our own technology and seek to avoid infringing the technology of others. Patent protection obtained by others may interfere with our ability to obtain patents, or our ability to effectively employ our technologies.

Others may claim that our technology infringes on their patents. Even if successful, the process of defending against such claims could result in substantial costs and delay our ability to commercialize our product candidates that

utilize the challenged technology.

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Government Regulation

Our research and development activities, the future manufacture of reagents and products incorporating our technologies, and the marketing of these products are subject to regulation for safety and efficacy by numerous governmental authorities in the U.S. and other countries.

Regulation of Pharmaceutical Product Candidates. The research and development, clinical testing, manufacture and marketing of products using our technologies are subject to regulation by the FDA and by comparable regulatory agencies in other countries. Product development and approval within this regulatory framework take a number of years and involve the expenditure of substantial resources. We anticipate that the development of our next-generation proprietary proteins will involve a traditional development program, including clinical trials.

After laboratory analysis and preclinical testing in animals, a regulatory filing is required to be submitted to the appropriate authorities before human testing may begin. In the U.S., an IND filing is made to the FDA. In Europe, a Clinical Trial Application, including an Investigational Medicinal Product Dossier (IMPD) in a country requiring adherence to guidance of the European Agency for the Evaluation of Medicinal Products (EMEA), or other country-specific filing, such as is the case in Switzerland, is submitted to the national health authority (Competent Authority) in each country in which a clinical trial is planned. Typically, a sequential three-phase human clinical testing program is then undertaken, but the phases may overlap or be combined. Certain phases may not be necessary for a particular product. Each clinical study is conducted according to an approved protocol after written approval is obtained from an independent Institutional Review Board (IRB) in the U.S, or Independent Ethics Committee (IEC) in Europe. During Phase I, small clinical trials are conducted to determine the safety of the product in healthy volunteers. During Phase II, clinical trials are expanded in size and are conducted to assess safety, establish an acceptable dose, and gain preliminary evidence of the efficacy of the product in a subset of the target population. During Phase III, clinical trials are further expanded in size and conducted to obtain sufficient data to establish statistically significant proof of safety and efficacy in the target population. The time and expense required to perform this clinical testing vary and can be substantial. The results of the non-clinical and clinical testing of a biological pharmaceutical product are then submitted to the appropriate authority in the form of a Biologics License Application (BLA), or New Drug Application (NDA) in the U.S., or a Marketing Authorization Application (MAA) or equivalent in Europe. If the application contains all pertinent information and data, the appropriate regulatory authority will formally accept the file for review. In responding to this filing, the regulatory authority may grant marketing approval, request additional information, or deny the application.

No action may be taken to market any new drug or biologic product in either the U.S. or Europe until an appropriate marketing application has been approved by the responsible regulatory authority. Even after initial regulatory approval is obtained, further clinical trials may be required to provide additional data on safety and effectiveness or to gain clearance for the use of a product as a treatment for indications other than those initially approved. Side effects or adverse events that are reported during clinical trials may delay, impede, or prevent marketing approval. Similarly, adverse events that are reported after obtaining marketing approval may result in additional limitations being placed on the use of a product and, potentially, withdrawal of the product from the market.

The regulatory requirements and approval processes of countries in Europe (including Switzerland, where we conducted the Phase I clinical trial for NE-180) are similar to, but not the same as, those in the U.S. The European clinical trials are being performed in a manner consistent with FDA requirements, which would potentially allow the data generated from the European trials to be used to support an IND or NDA in the United States.

In addition to regulating and auditing human clinical trials, the FDA regulates and inspects equipment, facilities, and processes used in the manufacture and control of products prior to providing approval to market a product. Among other conditions for marketing approval in the U.S., the prospective manufacturer s quality control and manufacturing procedures must conform on an ongoing basis with current Good Manufacturing Practices (cGMP). Before granting marketing approval, the FDA will perform a pre-licensing inspection of the facility to determine its compliance with cGMP and other rules and regulations. In complying with cGMP, manufacturers must continue to expend time, money and effort in the area of production, training and quality control to ensure full compliance. After approval of a BLA or NDA, manufacturers are subject to periodic inspections by the FDA. If, as a result of FDA inspections relating to our products or reagents, the FDA determines that equipment, facilities, or processes do not

comply with applicable FDA regulations or conditions of product approval, the FDA may seek civil, criminal, or administrative sanctions and remedies against us, such as the suspension of manufacturing operations, the seizure of products, and the suspension of sales of our products.

Products manufactured in the U.S. for distribution abroad are subject to FDA regulations regarding export, as well as to the requirements of the country to which they are shipped. Products distributed to European countries that are members

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of the EU are also subject to EU regulations. The requirements of the EU and foreign countries generally cover the conduct of clinical trials, the submission, review and approval of marketing applications, and all aspects of product manufacture and marketing. These requirements may vary significantly from country to country.

We expect to enter into agreements with third parties for the manufacture of enzymes, sugar nucleotides and other reagents that are used in the production of next-generation GlycoPEGylated protein therapeutics using our technology. Any third parties we contract with will be subject to substantially the same regulatory requirements as we are with regard to the items they manufacture for us.

Other Regulations Affecting our Business. We are subject to various other laws and regulations, such as those relating to safe working conditions, employee relations, employee benefits, the environment (including the use and disposal of hazardous or potentially hazardous substances), antitrust and international trade, securities law and taxation. We endeavor to comply with applicable laws and regulations. However, we recognize that this is a complex and expensive process, and that we cannot predict when changes will occur or whether they would have a material adverse effect on our operations.

We contract with third parties for supplies and services that are critical to our business. These third parties are also subject to government regulation. The failure of any of these third parties to comply with applicable laws and regulations could cause substantial delays to our drug development timelines and have a material adverse effect on our operations.

Third-Party Reimbursement. Our ability and the ability of each of our collaborators to successfully commercialize drug products may depend in part on the extent to which coverage and reimbursement for the cost of such products will be available from government health administration authorities, private health insurers, and other organizations. Uncertainty continues within the pharmaceutical and biotechnology industries as to the reimbursement status of new therapeutic products, and we cannot be sure that third-party reimbursement would be available for any therapeutic products that we or our collaborators may develop. Healthcare reform, especially as it relates to prescription drugs, is an area of increasing attention and a priority of many governmental officials.

Competition

The biotechnology and pharmaceutical industries are characterized by rapidly evolving technology and significant competition. Our competitors include pharmaceutical and biotechnology companies. In addition, many specialized biotechnology companies have formed collaborations with large, established companies to support research, development and commercialization of products that may be competitive with our current and future product candidates and technologies. Academic institutions, governmental agencies and other public and private research organizations are also conducting research activities and seeking patent protection and may commercialize competitive products or technologies on their own or through collaborations with pharmaceutical and biotechnology companies.

First-Generation EPO and G-CSF Products. In the U.S., first-generation EPO products are marketed by Amgen as Epogen®® for kidney disease and Ortho Biotech as Procrit® for cancer-related anemia. In Europe, Ortho Biotech s Eprex® and Roche s NeoRecormon® are marketed for both kidney and cancer indications. In Japan, Amgen s and Roche s products are sold respectively by Kirin Brewery (ESPO®) and Chugai (Epogin®) for kidney disease. 2005 worldwide sales of these first generation EPO products were approximately $8.0 billion. Shire s Dynepo was approved for marketing in the European Union, and has been launched in Germany.

First-generation G-CSF products are marketed in the U.S. and Europe by Amgen as Neupogen®, in Europe by Sanofi Aventis as Granocyte®, and in Japan by Kirin Brewery (GRAN®), Chugai (Neutrogin®) and Kyowa Hakko Kogyo (Neu-up®®). 2005 worldwide sales of these first generation G-CSF products were approximately $1.7 billion.

Competitive Next-Generation EPO and G-CSF Products. Other companies have programs focused on developing next-generation or improved versions of EPO and G-CSF, and some are already marketing improved versions of these products.

Amgen currently markets Aranesp®, its improved version of EPO, which has a longer circulating half-life than Amgen s first-generation EPO product, Epogen. Amgen launched Aranesp in the last quarter of 2001 and has reported that global sales of Aranesp were approximately $4.1 billion during 2006. Roche is developing an improved EPO known as Mircera. In April 2006, Roche filed a BLA with the FDA and EMEA for certain renal indications for

Mircera. Roche has indicated that it plans to seek regulatory approval for cancer-related anemia indications in 2009. In late 2005, Amgen filed a lawsuit against Roche alleging that Mircera infringes on Amgen s patents. Besides Amgen, Ortho Biotech and Roche, other companies are applying their technologies to develop improved EPO compounds. Syntonix (which announced in January

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2007 that it has signed a definitive agreement to be acquired by Biogen Idec) has tested its EPO-Fc fusion protein in a Phase I proof-of-principle study and has announced it is developing a different candidate. Fibrogen is developing FG-2216 and FG-4592, its small molecule promoter of endogenous EPO, which are in Phase II and Phase I respectively. Affymax is developing Hematide, its synthetic EPO-like peptide, which is currently in Phase II.

Amgen currently markets Neulasta®, which is a modified version of its original G-CSF product, Neupogen®. Neulasta is a chemically pegylated compound, with a longer circulating half-life than Neupogen. Amgen launched Neulasta in the first quarter of 2002 and has reported that global sales of Neulasta were approximately $2.3 billion during 2005. Other companies are also applying their technologies to develop long-acting competitors to G-CSF.

Next-Generation Protein Development. We are aware that other companies are working on the development of other next-generation protein therapeutics to which we are also applying our technology. Our product candidates will face competition from products already established in the marketplace and new therapies that may be developed by our competitors or may result from advances in biotechnology or other fields.

Follow-on Biologics (Biogenerics). Several companies are pursuing the opportunity to develop and commercialize follow-on versions of currently marketed biologic products, including EPO, G-CSF and others. These companies include Novartis (Sandoz), BioGeneriX, Stada (Bioceuticals), BioPartners, Teva Sicor USA and Pliva (which has been acquired by Barr Pharmaceuticals). In the U.S. and Japan, a clear development and regulatory path does not currently exist for biologic products that are, or soon will be, off-patent, although a bill was recently introduced in the U.S. Senate to authorize the FDA to approve generic versions of biologics. In Europe, the first guidelines regarding the quality, preclinical and clinical development of follow-on biologics was adopted in September 2005.

Research and Development Services. Although we are focused on the development of proprietary protein drugs, we also use our GlycoPEGylation technology to provide collaborative research services and product improvement opportunities to other pharmaceutical and biotechnology companies. These services may compete with efforts within these companies to improve therapeutic protein profiles and expression, and with services provided by other companies to improve proteins, such as chemical pegylation technology.

Manufacturing

We used our former Witmer Road pilot manufacturing facility (Witmer Road Facility), which we sold in September 2006, to develop manufacturing processes for NE-180, enzyme reagents and key sugar nucleotides (including our sugar-PEG nucleotides). We manufactured NE-180 in sufficient quantities to meet the needs of our expected preclinical development and early clinical trials. In 2006, we began to engage third-party contract manufacturing organizations (CMOs) to supply NE-180, enzyme reagents and sugar nucleotides for late Phase II and Phase III clinical development.

Our partners currently manufacture or otherwise provide the native proteins that are subsequently remodeled using GlycoPEGylation and will incorporate the remodeling processes at their facilities. Our supply chain obligations, outside of NE-180, are therefore confined to the supply of enzyme reagents and sugar nucleotides. We use CMOs for the supply of our enzyme reagents and sugar nucleotides, except those that are available commercially.

Marketing, Distribution, and Sales

We intend to capitalize on the significant experience and resources of our collaborative partners to commercialize proprietary products made using our technologies. These partners generally would be responsible for much of the development, regulatory approval, sales, marketing, and distribution activities for products incorporating our technologies. However, we intend to retain some commercial rights to some proteins in select territories, as we did in our collaboration with BioGeneriX. If we commercialize any products on our own, we will have to establish or contract for regulatory, sales, marketing, and distribution capabilities, and we may have to supplement our development capabilities. The marketing, advertising, and promotion of any product manufactured using our technology would be subject to regulation by the FDA or other governmental agencies.

Employees

As of December 31, 2006, we employed 78 individuals, consisting of 59 employees engaged in research and development activities, and 19 employees devoted to corporate and administrative activities. None of our employees is covered by collective bargaining agreements. We believe we have good relations with our employees.

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Restructurings and Employee Severance Costs

In March 2007, we initiated a restructuring of operations designed to allow for significantly higher clinical development costs for NE-180, while keeping anticipated 2007 net cash spending consistent with 2006 levels. The restructuring, which will be implemented over the next few months, will result in a workforce reduction of approximately 40%. We estimate that we will incur cash restructuring costs of approximately $1.0 million, most of which will be reflected in our operating results during the first half of 2007. We have not yet determined if we will incur any contract termination or non-cash impairment charges in connection with the restructuring.

In September 2006, we implemented a restructuring of operations in connection with the sale of the Witmer Road Facility. The employee severance costs incurred for this restructuring were payable pursuant to an employee severance plan established in August 2005. Therefore, these costs did not meet the definition for classification as a restructuring charge on our Statements of Operations. Our net loss for the year ended December 31, 2006 included $0.7 million of employee severance costs related to this restructuring, of which $0.6 million was included in research and development expenses and $0.1 million was included in general and administrative expenses.

In August 2005, we implemented a restructuring of operations to enable an enhanced focus on next-generation proteins, to allow for the transfer of production of proteins and reagents to our collaborative partners and CMOs, and to reduce cash burn. Our net loss for 2005 included $14.2 million of charges related to this restructuring, including $13.2 million of non-cash property and equipment impairment charges, most of which related to the Witmer Road Facility and related equipment, and $1.0 million of payments for employee severance and costs to close our leased facility in San Diego, California.

Internet Address and Securities Exchange Act Filings

Our internet address is www.neose.com. We make available free of charge through our website our annual report on Form 10-K, quarterly reports on Form 10-Q, current reports on Form 8-K, and amendments to those reports filed or furnished pursuant to Section 13(a) or 15(d) of the Securities Exchange Act of 1934, as amended. We make these reports and amendments available on our website as soon as practicable after filing them electronically with, or furnishing them to, the Securities and Exchange Commission (SEC).

ITEM 1A. RISK FACTORS.

Financial Risks

We require additional capital to fund our operations. Any additional financing could result in equity dilution.

To date, we have funded our operations primarily through proceeds from the public and private placements of equity securities. We have also funded our operations to a lesser extent from proceeds from the sale of the Witmer Road Facility, property and equipment financing, interest earned on investments, corporate collaborations, and the sale of investments. In March 2007, we sold 21.4 million shares of our common stock and warrants to purchase 9.6 million shares of common stock through a private placement at a price of $2.02 per unit, generating net proceeds of approximately $40.5 million. The warrants have a five-year term and an exercise price of $1.96 per share. We believe that our existing cash and cash equivalents (including the net proceeds from our March 2007 financing), expected proceeds from collaborations and license arrangements, and interest income should be sufficient to meet our operating and capital requirements at least through the second quarter of 2008, although changes in our collaborative relationships or our business, whether or not initiated by us, may affect the rate at which we deplete our cash and cash equivalents. Our present and future capital requirements depend on many factors, including:

- level of research and development investment required to develop our therapeutic proteins, and maintain and improve our technology position;
- the costs of process development and scale-up of proteins and reagents for research, development and at commercial scale;
- the results of non-clinical and clinical testing, which can be unpredictable in drug development;
- the time and costs involved in obtaining regulatory approvals;

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changes in product candidate development plans needed to address any difficulties that may arise in process development, scale-up, manufacturing, non-clinical activities, clinical studies or commercialization;

our ability to enter into new agreements with collaborators and to extend or maintain our existing collaborations, and the terms of these agreements;

the timing of milestone and royalty payments from our collaborators;

the costs of filing, prosecuting, defending, and enforcing patent claims and other intellectual property rights, and the costs of investigating patents that might block us from developing potential drug candidates;

the costs of recruiting and retaining qualified personnel;

the timing, willingness, and ability of our collaborators to commercialize products incorporating our technologies;

our need or decision to acquire or license complementary technologies or new drug targets; and

the evolution of the competitive landscape.

We will require significant amounts of additional capital in the future, and we do not have any assurance that funding will be available when we need it on terms that we find favorable, if at all. We may seek to raise these funds through public or private equity offerings, debt financings, credit facilities, or corporate collaborations and licensing arrangements. In addition, the investors in our March 2007 financing have the right to participate in future capital raising transactions by us until June 2008. The existence of this participation right may reduce or diminish our ability to establish terms with respect to, or enter into, any capital raising transaction with parties other than those investors until this participation right expires in June 2008.

If we raise additional capital by issuing equity securities, our existing stockholders percentage ownership will be reduced and they may experience substantial dilution. We may also issue equity securities that provide for rights, preference and privileges senior to those of our common stock. If we raise additional funds by issuing debt securities, these debt securities would have rights, preferences, and privileges senior to those of our common stock, and the terms of the debt securities issued could impose significant restrictions on our operations. If we raise additional funds through collaborations and licensing arrangements, we may be required to relinquish some rights to our technologies or drug candidates, or to grant licenses on terms that are not favorable to us. If adequate funds are not available or are not available on acceptable terms, our ability to fund our operations, take advantage of opportunities, develop products and technologies, and otherwise respond to competitive pressures could be significantly delayed or limited, and we may need to downsize or halt our operations.

We have a history of losses, and we may incur continued losses for some time.

We have incurred losses each year of our existence, including net losses of $27.1 million for the year ended December 31, 2006, $51.8 million for the year ended December 31, 2005, and $41.6 million for the year ended December 31, 2004. Given our planned level of operating expenses, we expect to continue incurring losses for some time. As of December 31, 2006, we had an accumulated deficit of $266.3 million. To date, we have derived substantially all of our revenue from corporate collaborations, license agreements, and investments. We expect that substantially all of our revenue for the foreseeable future will result from these sources and from the licensing of our technologies. We also expect to spend significant amounts to expand research and development on our proprietary drug candidates and technologies, maintain and expand our intellectual property position, and expand our business development and commercialization efforts. Our level of operating expenditures will vary depending upon the stage of development of our proprietary proteins and the number and nature of our collaborations. We may continue to incur substantial losses even if our revenues increase.

We have not yet commercialized any products or technologies, and we may never become profitable.

We have not yet commercialized any products or technologies, and we may never be able to do so. Since we began operations in 1990, we have not generated any revenues, except from corporate collaborations, license agreements, and investments. We do not know when or if we will complete any of our product development efforts, obtain regulatory approval for any product candidates incorporating our technologies, or successfully commercialize any approved products. Even if we are successful in developing products that are approved for marketing, we will not be successful unless these products gain market acceptance. The degree of market acceptance of these products will depend on a number of factors, including:

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the timing of regulatory approvals in the countries, and for the uses, we seek;

the competitive environment;

the establishment and demonstration in the medical community of the safety and clinical efficacy of our products and their potential advantages over existing therapeutic products;

the adequacy and success of distribution, sales and marketing efforts; and

the pricing and reimbursement policies of government and third-party payors, such as insurance companies, health maintenance organizations and other plan administrators.

Physicians, patients, payors or the medical community in general may be unwilling to accept, utilize or recommend any of our products or products incorporating our technologies. As a result, we are unable to predict the extent of future losses or the time required to achieve profitability, if at all. Even if we or our collaborators successfully develop one or more products that incorporate our technologies, we may not become profitable.

If the estimates we make and the assumptions on which we rely in preparing our financial statements prove inaccurate, our actual results may vary significantly.

Our financial statements have been prepared in accordance with accounting principles generally accepted in the United States. The preparation of these financial statements requires us to make estimates and judgments that affect the reported amounts of our assets, liabilities, revenues and expenses, the amounts of charges taken by us and related disclosure. Such estimates and judgments include the carrying value of our property, equipment and intangible assets, revenue recognition and the value of certain liabilities. We base our estimates and judgments on historical experience and on various other assumptions that we believe to be reasonable under the circumstances. However, these estimates and judgments, or the assumptions underlying them, may change over time, which could require us to restate some of our previously reported financial information. A restatement of previously reported financial information could cause our stock price to decline and could subject us to securities litigation. For a further discussion of the estimates and judgments that we make and the critical accounting policies that affect these estimates and judgments, see Management s Discussion and Analysis of Financial Condition and Results of Operations Critical Accounting Policies and Estimates elsewhere in this annual report on Form 10-K.

Risks Related to Development of Products and Technologies

We may be unable to develop next-generation therapeutic proteins.

We are seeking to use our enzymatic technologies to develop proprietary next-generation proteins, generally in collaboration with a partner. The development of protein drugs involves a range of special challenges at various stages of the process.

In the preclinical phase of product development, we and our partners will face several potential problems, including producing or obtaining supplies of the protein on commercially reasonable terms, successfully modifying the protein using our enzymatic technologies, and achieving adequate yields of the next-generation protein. Even if a protein development program appears to be proceeding well in the early phases, a product candidate may fail in clinical trials for several reasons, such as results indicating that the product candidate is less effective than desired (e.g., the trial failed to meet its primary objectives) or that it has harmful or problematic side effects. If clinical trials are successful, it is possible that problems may arise later during commercialization. For example, we are aware that certain marketed EPO products were associated with pure red cell aplasia that arose after marketing authorization. This highlights the fact that even after a product is approved for marketing, problems may arise that can negatively affect sales and increase costs.

Our failure to solve any of these problems could delay or prevent the commercialization of products incorporating our technologies and could negatively impact our business.

Non-clinical and clinical trial results for our products may not be favorable.

In order to obtain regulatory approval for the commercial sale of any of our product candidates, we must conduct both non-clinical studies and human clinical trials that demonstrate the product is safe and effective for the use for

which we are seeking approval. We may suffer significant setbacks in clinical trials, even after promising results in earlier trials. For

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example, Phase II activity may not replicate Phase I results or Phase III efficacy data may not replicate Phase II data. Adverse results from studies, including clinical trials, could have a negative effect on our ability to obtain the approval of the FDA or other regulatory agencies.

We and our collaboration partners also may not be permitted to undertake or continue clinical trials for any of our product candidates in the future or may otherwise be unable to do so because acceptable candidates to participate in such trials are unavailable. Even if we or our collaboration partners are able to conduct such trials, we or our collaboration partners may not be able to demonstrate satisfactorily that the products are safe and effective and thus qualify for the regulatory approvals necessary to commercialize them.

Safety and efficacy results from non-clinical studies involving animals and other models and from early clinical trials are often not accurate indicators of results of later-stage clinical trials that involve larger human populations, and, moreover, may not always be representative of results obtained while marketing an approved drug, particularly with regard to safety.

Unfavorable results of clinical trials conducted by our competitors or other biotechnology companies may also adversely affect our ability to gain regulatory approval of our product candidates by increasing government scrutiny of our clinical trials and reducing the number of treatments receiving approval from the FDA. Government and public concerns over safety issues associated with pharmaceutical and biological products could potentially result in termination of clinical trials on entire classes of drug candidates, lengthen the trial process and increase costs relating to certain drug categories, and/or expand the safety labeling for approved products. For example, we are aware that the FDA has scheduled a meeting of the Oncologic Drugs Advisory Committee (ODAC) for May 2007 to review the safety of erythropoiesis-stimulating agents (ESAs) based on the results of recent clinical studies. Invitees to the meeting include Amgen Inc. and Ortho Biotech Products, L.P., who market Aranesp® and Procrit®, respectively. On March 9, 2007, the FDA announced revised product labeling for ESAs, including updated warnings, a new boxed warning and modifications to dosing instructions. The changes in product labeling and the outcome of the ODAC meeting, which could include further revisions to labeling, could adversely affect the conduct of the clinical trials or commercialization opportunities for our drug candidates, although we cannot speculate at this time on the impact to us or the ESA drug category in general.

We depend on third parties to conduct our clinical trials.

We are highly dependent on third parties to conduct our clinical trials. We contract with these third parties, generally referred to as clinical research organizations or CROs, to oversee the operations of such clinical trials and to perform data collection and analysis, including finding investigators to conduct the clinical study; encouraging patient enrollment in the study; collecting the data and entering the data into computer systems; cleaning, outputting and analyzing the data from the study; and writing the Clinical Study Report(s). We are subject to the risk that these third parties could fail to perform their obligations properly, in a timely fashion, and/or in compliance with applicable FDA and other governmental regulations. The failure of any of these third parties to perform all of their obligations to us could substantially delay our development efforts, and delay or prevent regulatory approval of our product candidates.

Our clinical trials may be delayed.

One potential cause of a delay in product development is a delay in clinical trials. Many factors could delay clinical trials, including, without limitation:

the failure to obtain or maintain regulatory clearance to conduct clinical trials;

insufficient supplies of clinical trial materials;

slow rate of patient enrollment and early discontinuation of patient participation;

adverse events occurring during clinical trials;

adverse results from non-clinical studies; and

changes in regulatory requirements.

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Proteins are uniquely susceptible to neutralizing antibodies that could result in diminished efficacy of our products.

Proteins that are foreign to a living body often provoke an immune response. Protein drugs produced by recombinant technology, even though they have the same primary amino acid sequence as a native human protein, sometimes provoke formation of antibodies that bind to the protein drug. Some such antibodies bind so as to prevent the protein drug from engaging its receptor, and thus neutralize the drug activity of the protein. Furthermore, neutralizing antibodies provoked by administration of a protein drug may react with endogenous proteins whose natural activity the drug was intended to supplement, thereby inducing a total lack of both therapeutic and natural activities in the patient. Such a condition can prove fatal. We will not know if the proteins we develop as product candidates will provoke neutralizing antibody responses in humans until they are evaluated in clinical trials. It is possible that our product candidates may be rendered ineffective for the therapeutic purpose for which they are intended or could induce harm to patients because of the neutralizing effect of antibodies to endogenous proteins in humans in response to our proteins.

Additionally, all protein drugs expressed by recombinant technology retain some trace of contaminating proteins from the host cells used to express the protein drug. These host cell proteins may increase the chances of an immunogenic response that could diminish the therapeutic efficacy of the protein. Our GlycoAdvance technology enables the use of protein drugs produced in insect cells, an expression system which has certain technical advantages in enabling the application of our technology to this protein, but for which no product to date has received marketing authorization in the U.S. or Europe. It is possible that NE-180 may be rendered ineffective for the therapeutic purpose for which it is intended because of the neutralizing effects of antibodies provoked by the presence of trace amounts of insect cell proteins in our drug preparations.

We have no commercial manufacturing capability and rely on third parties to manufacture our product candidates and the materials used to make them.

Completion of our clinical trials and commercialization of our product candidates require access to, or the development of, facilities to manufacture a sufficient supply of our proteins, enzymes, sugar nucleotides and other reagents needed to produce and commercialize our technologies. Since we currently have no manufacturing capability of our own, we are highly dependent on contract manufacturers to produce these materials for us for non-clinical, clinical and/or commercial purposes. Our success depends on our ability to have these compounds manufactured on a commercial scale or to obtain commercial quantities, in either case, at reasonable cost. We may not be able to procure sufficient quantities of the products we develop to meet our needs for non-clinical or clinical development or commercialization. We may compete with other parties for access to manufacturing facilities and suitable alternatives may be unavailable to us. As a result, our products candidates may suffer delays in manufacture if our CMOs give other products greater priority than our product candidates. It is time-consuming and expensive to change contract manufacturers for pharmaceutical products, particularly when the products are under regulatory review in a New Drug Application (NDA) process. If we fail to maintain essential manufacturing and service relationships, we may not be able to replace an important CMO or to develop our own manufacturing capabilities, either of which could impede our ability to obtain regulatory approval for our products candidates and delay or prevent our product development and commercialization. If we do find replacement CMOs, we may not be able to enter into agreements with them on terms and conditions favorable to us and, there could be a considerable delay before a new facility could be qualified and registered with the appropriate authorities. If we encounter delays or difficulties in connection with manufacturing, commercialization of our products and technologies could be delayed, we could breach our obligations under our collaborative agreements and we could have difficulty obtaining necessary financing.

The manufacture of our product candidates is_a complex and highly-regulated process. If any of our CMOs encounters problems manufacturing materials for us, our business could suffer.

The FDA and foreign regulators require manufacturers to register manufacturing facilities. The FDA and foreign regulators also inspect these facilities to confirm compliance with current Good Manufacturing Practices (cGMP) or similar requirements that the FDA or foreign regulators establish. The manufacture of products and key reagents at any facility will be subject to strict quality control, testing, and record keeping requirements, and continuing obligations regarding the submission of safety reports and other post-market information. Ultimately, we, our CMOs, or other suppliers may not meet these requirements. Our CMOs may face manufacturing or quality control

problems causing product production and shipment delays or a situation where we or they may not be able to maintain compliance with the FDA s cGMP requirements, or those of foreign regulators, necessary to continue manufacturing our product candidates and materials. Any failure to comply with cGMP requirements or other FDA or foreign regulatory requirements could adversely affect our clinical research activities and our ability to market and develop our products candidates.

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We face challenges unique to proteins.

We and the third parties with whom we contract to manufacture our proteins face the significant, normal scale-up risks associated with protein manufacturing: proteins are difficult to produce; it is difficult to scale up protein manufacturing processes; and it is expensive to produce proteins. We also face special risks in connection with our first product, NE-180, an EPO protein. Our success with this program will depend on our ability to have this protein manufactured, at commercial scale, in the insect cell expression system (the production source of NE-180), by a collaborator or supplier. We do not know if we will be able to locate a CMO outside of the U.S. that will be able to manufacture this protein at commercial scale and on economically feasible terms. To our knowledge, no therapeutic protein produced in this expression system has yet received marketing authorization in the U.S. or Europe, which means that we may face previously unidentified problems resulting from the use of this expression system and related regulatory challenges.

Our long-term success depends upon our ability to develop, receive regulatory approval for and commercialize drug product candidates.

All of our product candidates are in the development stage and have not received regulatory approval, an important requirement to the commercialization of any product candidate. If we or our collaboration partners fail to complete the development, receive regulatory approvals for and/or commercialize our product candidates, we will not be able to generate revenues from the sale of products resulting from our product candidates. As we or our collaboration partners continue our product development, there is a high risk that testing will demonstrate that our product candidates are not suitable for commercialization, either because they are unsafe, inefficient, or too costly to manufacture, or because third party competitors market a more clinically effective, safer, or more cost-effective product

Moreover, even if we believe that the clinical data demonstrates the safety and efficacy of a product candidate, regulators may disagree with us, and we could be delayed, limited or prevented from obtaining the required regulatory approval of such product candidate. In addition, regulatory approval may take longer than we expected. Although we have received approval from Swissmedic for the initiation of a Phase II human trial for NE-180, the FDA or foreign regulators could at any point forbid us to initiate or continue testing of our product candidates in human clinical trials. There is also the risk that one of our product candidates is later discovered to cause adverse effects that prevent widespread use, require withdrawal from the market, or serve as the basis for product liability claims.

If we or our collaboration partners are unable to successfully develop and commercialize our product candidates, we will not have a sufficient source of revenue. Moreover, the failure of one or more of our product candidates in clinical development could harm our ability to raise additional capital.

Our ability to enter into new collaborations and to achieve success under existing collaborations is uncertain.

A material component of our business strategy is to establish and maintain collaborative arrangements with third parties to co-develop our products and to commercialize products made using our technologies. We also intend to establish collaborative relationships to obtain domestic or international sales, marketing and distribution capabilities for product candidates receiving regulatory approval. In fact, it is very likely that we will require a partner to develop our first product, NE-180, beyond the Phase II clinical trial stage given the scale and cost associated with late-stage clinical development. We currently have collaborative agreements with Novo Nordisk, BioGeneriX and MacroGenics, Inc. We anticipate that substantially all of our revenues during the next several years will continue to be generated from collaboration or license agreements.

The process of establishing collaborative relationships is difficult, time-consuming and involves significant uncertainty. Our partnering strategy entails many risks, including:

- we may be unsuccessful in entering into or maintaining collaborative agreements for the co-development of our products or the commercialization of products incorporating our technologies;
- we may not be successful in applying our technologies to the needs of our collaborative partners;
- our collaborators may not be successful in, or may not remain committed to, co-developing our products or commercializing products incorporating our technologies;

our collaborators may seek to develop other proprietary alternatives to our products or technologies;

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our collaborators may not commit sufficient resources to incorporating our technologies into their products;

our collaborators are not obligated to market or commercialize our products or products incorporating our technologies, and they are not required to achieve any specific commercialization schedule;

our collaborative agreements may be terminated by our partners on short notice; and

continued consolidation in our target markets may limit our ability to enter into collaboration agreements, or may result in terminations of existing collaborations.

Furthermore, even if we do establish collaborative relationships, it may be difficult for us to maintain or perform under such collaboration arrangements, as our funding resources may be limited or our collaborators may seek to renegotiate or terminate their relationships with us due to unsatisfactory clinical results, a change in business strategy, or other reasons. If we or any collaborator fails to fulfill any responsibilities in a timely manner, or at all, our research, clinical development or commercialization efforts related to that collaboration could be delayed or terminated. It may also become necessary for us to assume responsibility for activities that would otherwise have been the responsibility of our collaborator. Further, if we are unable to establish and maintain collaborative relationships on acceptable terms, we may have to delay or discontinue further development of one or more of our product candidates, undertake development and commercialization activities at our own expense or find alternative sources of funding.

We may be exposed to product liability and related risks.

The use in humans of compounds developed by us or incorporating our technologies may result in product liability claims. Product liability claims can be expensive to defend, and may result in large settlements of claims or judgments against us. Even if a product liability claim is not successful, the adverse publicity, time, and expense involved in defending such a claim may interfere with our business. We may not be able to obtain insurance coverage at a reasonable cost or in sufficient amounts to protect us against losses.

Risks Related to Intellectual Property

Blocking patents or claims of infringement may stop or delay the development of our proprietary products.

Our commercial success depends in part on avoiding claims of infringement of the patents or proprietary rights of third parties. We have devoted significant resources to investigating the patent protection surrounding the proteins that are the subject of our development programs. The numerous patents, each with multiple claims, may be difficult to uncover and interpret, leading to uncertainty about our freedom to operate. It is possible that we will not be aware of issued patents or pending patent applications that are relevant to our product candidates because our searches do not find them, or pending patent applications because they are not yet publicly available. Our interpretation of patents could be challenged, leading to litigation, and we could face claims of infringement of rights of which we are unaware.

There have been significant litigation and interference proceedings regarding patent rights, and the patent situation regarding particular products is often complex and uncertain. For example, with respect to EPO, the target of our first development program, the status of issued patents is currently being litigated by others and these patents could delay our ability to market a long-acting EPO in the U.S. As we proceed with this program and other targets, we may face uncertainty and litigation could result, which could lead to liability for damages, prevent our development and commercialization efforts, and divert resources from our business strategy.

The cost of any litigation challenging our right to pursue our target proteins or technologies could be substantial. Others seeking to develop next-generation versions of proteins, or the holders of patents on our target proteins, may have greater financial resources, making them better able to bear the cost of litigation. In particular, one company that produces products that will likely be in direct competition with our current product candidates has aggressively defended the patents related to its products and this could increase the likelihood of litigation or the cost of litigation. Uncertainties resulting from the initiation and continuation of patent litigation or other proceedings could have a material adverse effect on our ability to develop, manufacture, and market products, form strategic alliances, and compete in the marketplace.

Third parties from time to time may assert that we are infringing their patents, trade secrets or know-how. In addition, patents may issue in the future to third parties that our technology may infringe. We could incur substantial

costs in defending ourselves and our partners against any such claims. Furthermore, parties making such claims may be able to obtain injunctive or other equitable relief, which could effectively block our ability or our partners ability to further develop or commercialize some or all of our products or technologies in the U.S. and abroad, and could result in the award of substantial

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damages. If we are found to infringe, we may be required to obtain one or more licenses from third parties or be unable to proceed. There can be no assurance that we will be able to obtain such licenses at a reasonable cost, if at all. Defense of any lawsuit or failure to obtain any such required license could have a material adverse effect on us.

The failure to obtain, maintain or protect patents and other intellectual property could impact our ability to compete effectively.

To compete effectively, we need to develop and maintain a proprietary position with regard to our own technologies, products and business. We are seeking to develop patent protection for therapeutic proteins that include numerous claims for composition of matter, methods of use, and methods of making. Legal standards relating to the validity and scope of claims in our technology field are still evolving. Therefore, the degree of future protection in the U.S. and other countries for our proprietary rights in our core technologies and products made using these technologies is also uncertain. The risks and uncertainties that we face with respect to our patents and other proprietary rights include the following:

- the pending patent applications we have filed, or to which we have exclusive rights, may not result in issued patents, or may take longer than we expect to result in issued patents;
- we may be subject to interference proceedings;
- we may be subject to opposition proceedings in foreign countries;
- the claims of any patents that are issued may not provide meaningful protection;
- we may not be able to develop additional proprietary technologies that are patentable;
- the patents licensed or issued to us or our customers may not provide a competitive advantage;
- other companies may challenge patents licensed or issued to us or our customers;
- other companies may independently develop similar or alternative technologies, or duplicate our technologies;
- other companies may design around technologies we have licensed or developed; and
- enforcement of patents is complex, uncertain and expensive.

We cannot be certain that patents will be issued as a result of any of our pending applications, and we cannot be certain that any of our issued patents will give us adequate protection from competing products. For example, issued patents may be circumvented or challenged, declared invalid or unenforceable, or narrowed in scope. In addition, since publication of discoveries in the scientific or patent literature often lags behind actual discoveries, we cannot be certain that we were the first to make our inventions or to file patent applications covering those inventions. In the event that another party has also filed a patent application relating to an invention claimed by us, we may be required to participate in an interference proceeding declared by the U.S. Patent and Trademark Office to determine priority of invention, which could result in substantial uncertainties and costs for us, even if the eventual outcome were favorable to us. It is also possible that others may obtain issued patents that could prevent us from commercializing our products or require us to obtain licenses requiring the payment of significant fees or royalties in order to enable us to conduct our business. As to those patents that we have licensed, our rights depend on maintaining our obligations to the licensor under the applicable license agreement, and we may be unable to do so. Furthermore, patent protection available to us may vary in different jurisdictions. In particular, the laws in some countries provide little patent protection.

The cost to us of any patent litigation or other proceeding relating to our patents or applications, even if resolved in our favor, could be substantial. Our ability to enforce our patent protection could be limited by our

financial resources, and may be subject to lengthy delays. If we are unable to effectively enforce our proprietary rights, or if we are found to infringe the rights of others, we may be in breach of our license agreements with our partners.

In addition to patents and patent applications, we depend upon trade secrets and proprietary know-how to protect our proprietary technology. We require our employees, consultants, advisors, and collaborators to enter into confidentiality agreements that prohibit the disclosure of confidential information to any other parties. We require our employees and consultants to disclose and assign to us their ideas, developments, discoveries, and inventions. These agreements may not,

however, provide adequate protection for our trade secrets, know-how, or other proprietary information in the event of any unauthorized use or disclosure.

We may have to develop or license alternative technologies if we are unable to maintain or obtain key technology from third parties.

We have licensed patents and patent applications from a number of institutions. Some of our proprietary rights have been licensed to us under agreements that have performance requirements or other contingencies. The failure to comply with these provisions could lead to termination or modifications of our rights to these licenses. Additionally, we may need to obtain additional licenses to patents or other proprietary rights from other parties to facilitate development of our proprietary technology base. The ownership of patents exclusively licensed to us may be subject to challenge if inventorship was not adequately investigated and represented. If our existing licenses are terminated or if we are unable to obtain such additional licenses on acceptable terms, our ability to perform our own research and development and to comply with our obligations under our collaborative agreements may be delayed while we seek to develop or license alternative technologies.

Risks Related to Competition

Our competitors may develop better or more successful products.

Our business is characterized by extensive research efforts and rapid technological progress. New developments in molecular biology, medicinal chemistry and other fields of biology and chemistry are expected to continue at a rapid pace in both industry and academia. Our potential competitors include both public and private pharmaceutical and biotechnology companies, as well as academic institutions, governmental agencies and other public and private research organizations that are also conducting research activities and seeking patent protection.

A number of these competitors are working on the development of next-generation protein therapeutics. Some companies have programs focused on developing next-generation or improved versions of EPO and G-CSF, and some are already marketing improved versions of these products. These companies include Amgen, Ortho Biotech (Johnson & Johnson), Roche, Shire, Maxygen, Fibrogen, Affymax, CoGenesys and Syntonix. Other companies are active in this area, and we expect that competition will increase.

In addition, we may compete with companies commercializing first-generation protein therapeutics, as a result of pricing practices or reimbursement limitations. Even if we succeed in developing and marketing products that have significant advantages over first-generation products, if first-generation products are available at a lower out-of-pocket cost to the consumer, health-care providers and consumers may choose first-generation products instead of next-generation versions.

Compared to us, many of our likely and potential competitors have more:

financial, scientific and technical resources;

product development, manufacturing and marketing capabilities;

experience conducting non-clinical studies and clinical trials of new products; and

experience in obtaining regulatory approvals for products.

Competitors may succeed in developing products and technologies that are more effective or less costly than ours and that would render our products or technologies, or both, obsolete or noncompetitive. We know that other companies with substantial resources are working on the development of next-generation proteins, and they may achieve better results in enzymatically modifying our target proteins or the target proteins of our potential collaborators.

Competitors also may prove to be more successful in designing, manufacturing and marketing products. If we are successful in developing our own drug candidates or versions of drugs that are no longer patented, we will compete with other drug manufacturers for market share. If we are unable to compete successfully, our commercial opportunities will be diminished.

In addition, while there is no proven abbreviated regulatory pathway for follow-on biologics, this possibility is under discussion in the U.S. and other jurisdictions and has been adopted in part in Europe. A bill has recently been

introduced in the U.S. Senate to authorize the FDA to approve generic versions of biologics. If an abbreviated regulatory process is

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adopted for the approval of follow-on biologics in any major market, competition could increase in related segments of the therapeutic protein market.

We may be unable to retain key employees or recruit additional qualified personnel.

Because of the specialized scientific nature of our business, we are highly dependent upon qualified scientific, technical and managerial personnel, including our research and development team. The advancement of our business is dependent upon our management team s ability to evaluate collaboration opportunities and on their ability to focus our company s efforts. Our anticipated research and development efforts will require additional expertise and the addition of new qualified personnel.

There is intense competition for qualified management and research and development personnel in the pharmaceutical field. Therefore, we may not be able to attract and retain the qualified personnel necessary for our business. The loss of the services of existing personnel, as well as the failure to recruit additional key scientific, technical and managerial personnel in a timely manner, could harm our research and development programs and our ability to manage day-to-day operations, attract collaboration partners, attract and retain other employees, and generate revenues. We do not maintain key person life insurance on any of our employees.

Risks Related to Government Regulation

We are subject to extensive government regulation, and we or our collaborators may not obtain necessary regulatory approvals or may encounter long delays and large expenditures in obtaining such approvals.

The research, development, manufacture and control, marketing, and sale of our reagents and product candidates manufactured using our technologies are subject to significant, but varying, degrees of regulation by a number of government authorities in the U.S. and other countries.

Pharmaceutical product candidates manufactured using our technologies must undergo an extensive regulatory approval process before commercialization. This process is regulated by the FDA and by comparable agencies in Europe and in other countries. The U.S. and foreign regulatory agencies have substantial discretion to delay or withhold approval of the initiation of clinical trials, terminate clinical trials, require additional testing, delay or withhold registration and marketing approval, and mandate product withdrawals. In addition, the U.S. or other regulatory agencies could, at any time in the regulatory approval process, place the regulatory submission for a product candidate on hold pending the receipt, review and approval of additional information.

We and our collaborators intend to base our submissions for regulatory approval and the information contained in such submissions on our understanding of the requirements of the FDA and its foreign counterparts. If additional information is required in other jurisdictions, including EMEA countries, or if the submitted information is deemed insufficient, we may face delays and additional costs.

The specific risks of protein drugs may result in the application of more stringent regulatory requirements prior to approval of our product candidates. We face special challenges in connection with the development of proteins produced in the insect cell expression system. To our knowledge, no therapeutic protein for human use produced in this expression system has been submitted for marketing authorization in the U.S. or Europe, and we may encounter long delays and large expenditures or other regulatory hurdles in connection with the approval process for a product produced in this expression system.

Neither we nor our collaborators have submitted any product candidates incorporating our technologies for marketing approval to the FDA or any other regulatory authority. If any product candidate manufactured using our technology is submitted for regulatory approval, it may not receive the approvals necessary for commercialization, the desired labeling claims, or adequate levels of reimbursement. Any delay in receiving, or failure to receive, these approvals would adversely affect our ability to generate product revenues or royalties, and we will have already spent significant sums in pursuing approval.

We anticipate that the development of our next-generation proprietary proteins will involve a traditional development program, including clinical trials. Any new governmental regulations may delay or alter regulatory approval of any product candidate manufactured using our technology. If an abbreviated regulatory process is adopted for the approval of follow-on biologics in any major market, competition could increase in related segments of the therapeutic protein market. We cannot predict the impact of adverse governmental action that might arise from future legislative and administrative action.

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Even if we or our collaborators are successful in obtaining regulatory approvals for any of our products, our or their manufacturing processes will be subject to continued review by the FDA and other regulatory authorities. Any later discovery of unknown problems with our products, products incorporating our technologies, or manufacturing processes could result in restrictions on such products or manufacturing processes, including potential withdrawal of the products from the market. In addition, if regulatory authorities determine that we or our collaborators have not complied with regulations in the research and development of a product candidate or the manufacture and control of our reagents, then we or our collaborators may not obtain necessary approvals to market and sell the product candidate.

Third-party reimbursement for our collaborators or our future product candidates may not be adequate.

Even if regulatory approval is obtained to sell any product candidates incorporating our technologies, our future revenues, profitability, and access to capital will be determined in part by the price at which we or our collaborators can sell such products. There are continuing efforts by governmental and private third-party payors to contain or reduce the costs of health care through various means. We expect a number of federal, state, and foreign proposals to control the cost of drugs through governmental regulation. We are unsure of the form that any health care reform legislation may take or what actions federal, state, foreign, and private payors may take in response to the proposed reforms. Therefore, we cannot predict the effect of any implemented reform on our business.

Our and our collaborators ability to commercialize our products successfully will depend, in part, on the extent to which reimbursement for the cost of such products and related treatments will be available from government health administration authorities, such as Medicare and Medicaid in the U.S., private health insurers, and other organizations. Significant uncertainty exists as to the reimbursement status of newly approved healthcare products. Adequate third-party coverage may not be available to enable us to maintain price levels sufficient to realize an appropriate return on investment in product research and development. Inadequate coverage and reimbursement levels provided by government and third-party payors for use of our or our collaborators products may cause these products to fail to achieve market acceptance and would cause us to lose anticipated revenues and delay achievement of profitability. It is possible that reimbursement may be limited to that which is available for first-generation versions of one or more of our or our collaborator s products, making it harder for us and our collaborators to realize an appropriate return.

Risks Related to Facilities, Business Interruption, and the Environment

The use of hazardous materials in our operations may subject us to environmental claims or liability.

Our research and development processes involve the controlled use of hazardous materials, chemicals, and radioactive compounds. We conduct experiments that are quite common in the biotechnology industry, in which we use small quantities of corrosive, toxic and flammable chemicals, and trace amounts of radioactive materials. The risk of accidental injury or contamination from these materials cannot be entirely eliminated. We do not maintain a separate insurance policy for these types of risks. In the event of an accident or environmental discharge, we may be held liable for any resulting damages, and any liability could exceed our resources. We are subject to federal, state, and local laws and regulations governing the use, storage, handling, and disposal of these materials and specified waste products. The cost of compliance with these laws and regulations could be significant.

Destructive actions by activists or terrorists could damage our facilities, interfere with our research activities, and cause ecological harm.

Activists and terrorists have shown a willingness to injure people and damage physical facilities, equipment and biological materials to publicize or otherwise further their ideological causes. Our or our collaborators operations and research activities, and services conducted for us by third parties, could be adversely affected by such acts. Any such damage could delay our research projects and decrease our ability to conduct future research and development. Damage caused by activist or terrorist incidents could also cause the release of hazardous materials, including chemicals, radioactive and biological materials.

Any significant interruption to our ability to conduct our business operations, research and development activities, or manufacturing operations could reduce our revenue and increase our expenses.

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Risk Related to Stock Market and Foreign Exchange Rates

Our stock price may continue to experience fluctuations.

The market prices of securities of thinly-traded biotechnology companies such as ours generally are highly volatile. For example, since March 1, 2006, the price of our common stock reached a high of $4.34 per share in July 2006 and a low of $1.56 per share in March 2007.

In this market environment, the sale of a substantial number of shares of our common stock in the public market or the perception that such a sale might occur would likely have an adverse effect on the market price of our common stock, at least for the short term. We have a number of investors who hold relatively large positions in our securities. A decision by any of these investors to sell all or a block of their holdings of our common stock could cause our stock price to drop significantly.

The market also continues to experience significant price and volume fluctuations, some of which are unrelated to the operating performance of particular companies. In recent years, the price of our common stock has fluctuated significantly and may continue to do so in the future. Many factors could have a significant effect on the market price for our common stock, including:

non-clinical and clinical trial results;

product development delays;

regulatory delays;

an announcement or termination of a collaborative relationship by us or any of our partners or competitors;

developments relating to our patent position or other proprietary rights;

announcements of technological innovations or new therapeutic products;

government regulations;

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

general market conditions.

Any litigation brought against us as a result of this volatility could result in substantial costs and a diversion of our management s attention and resources, which could negatively impact our financial condition, revenues, results of operations, and the price of our common stock.

If we raise additional capital by issuing equity securities in a fluctuating market, many or all of our existing stockholders may experience substantial dilution, and if we need to raise capital by issuing equity securities at a time when our stock price is down, we may have difficulty raising sufficient capital to meet our requirements. If any of the risks described in these RISK FACTORS occurred, of if any unforeseen risk affected our performance, it could have a dramatic and adverse impact on the market price of our common stock.

Changes in foreign currency exchange rates could result in increased costs.

We have entered into some agreements denominated, wholly or partly, in Euros or other foreign currencies, and, in the future, we may enter into additional, significant agreements denominated in foreign currencies. If the values of these currencies increase against the dollar, our costs would increase. To date, we have not entered into any contracts to reduce the risk of fluctuations in currency exchange rates. In the future, depending upon the amounts payable under any such agreements, we may enter into forward foreign exchange contracts to reduce the risk of unpredictable changes in these costs. However, due to the variability of timing and amount of payments under any such agreements, foreign exchange contracts may not mitigate the potential adverse impact on our financial results.

ITEM 1B. UNRESOLVED STAFF COMMENTS.

None.

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ITEM 2. PROPERTIES.

In September 2006, we sold our Witmer Road Facility for approximately $21.0 million. In February 2007, we consolidated our operations into a 40,000 square foot facility that we currently lease in Horsham, Pennsylvania (Rock Road Facility). We entered into the lease agreement for the Rock Road Facility in February 2002. The initial term of the lease ends in July 2022, at which time we have an option to extend the lease for an additional five years, followed by another option to extend the lease for an additional four and one-half years. We also lease warehouse space nearby in Horsham.

ITEM 3. LEGAL PROCEEDINGS.

We are not a party to any material legal proceedings.

ITEM 4. SUBMISSION OF MATTERS TO A VOTE OF SECURITY HOLDERS.

We did not submit any matters to a vote of security holders during the fourth quarter of 2006.

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PART II

ITEM 5. MARKET FOR REGISTRANT S COMMON EQUITY AND RELATED STOCKHOLDER MATTERS.

Our common stock is listed on the Global Market of The NASDAQ Stock Market LLC under the symbol NTEC. We commenced trading on NASDAQ on February 15, 1996. The following table sets forth the high and low sale prices of our common stock for the periods indicated.

	Common Stock Price	
	High	Low
Year Ended December 31, 2005		
First Quarter	$7.25	$2.49
Second Quarter	3.23	1.95
Third Quarter	4.49	2.15
Fourth Quarter	2.85	1.70
Year Ended December 31, 2006		
First Quarter	3.95	1.85
Second Quarter	4.18	2.18
Third Quarter	4.34	1.90
Fourth Quarter	2.89	1.78

As of March 15, 2007, there were approximately 200 record holders and 3,400 beneficial holders of our common stock. We have not paid any cash dividends on our common stock and we do not anticipate paying any in the foreseeable future.

Common Stock Performance Graph

The following Common Stock Performance Graph shall not be deemed incorporated by reference into any of our filings under the Securities Act of 1933 or the Securities Exchange Act of 1934, except to the extent we specifically incorporate it by reference therein.

The following graph assumes that $100 was invested on December 31, 2001 in our common stock. The graph compares the cumulative return, which includes the reinvestment of dividends, of this investment with an equivalent investment on that date in the NASDAQ Stock Market U.S. Index (the NASDAQ Composite) and the NASDAQ Stock Market Biotech Index (the NASDAQ Biotech Index)

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ITEM 6. SELECTED FINANCIAL DATA.

The following Statements of Operations and Balance Sheet Data for each of the years in the five-year period ended December 31, 2006 are derived from our audited financial statements. The financial data set forth below should be read in conjunction with the sections of this Annual Report on Form 10-K entitled Management s Discussion and Analysis of Financial Condition and Results of Operations, and the financial statements and notes included elsewhere in this Annual Report on Form 10-K.

	Year Ended December 31,				
	2006	2005	2004	2003	2002
	(in thousands, except per share data)				
Statements of Operations Data:					
Revenue from collaborative agreements	$ 6,184	$ 6,137	$ 5,070	$ 1,435	$ 4,813
Operating expenses:					
Research and development	29,013	33,136	34,672	26,821	21,481
General and administrative	11,551	10,878	11,711	11,148	12,510
Restructuring charges		14,206			
Total operating expenses	40,564	58,220	46,383	37,969	33,991
Gain on sale of Witmer Road Facility	7,333				
Operating loss	(27,047)	(52,083)	(41,313)	(36,534)	(29,178)
Other income		22			1,653
Impairment of equity securities				(1,250)	
Interest income (expense), net	(60)	222	(329)	103	1,108
Net loss	$ (27,107)	$ (51,839)	$ (41,642)	$ (37,681)	$ (26,417)
Basic and diluted net loss per share	$ (0.82)	$ (1.64)	$ (1.82)	$ (2.14)	$ (1.85)
Weighted-average shares outstanding used in computing basic and diluted net loss per share	32,857	31,590	22,898	17,611	14,259
Balance Sheet Data:					

Cash, cash equivalents and marketable securities	$ 16,388	$ 37,738	$ 45,048	$ 53,060	$ 41,040
Total assets	31,243	65,363	90,731	94,845	83,092
Total debt and capital lease obligations	1,831	14,454	18,345	10,601	7,411
Accumulated deficit	(266,327)	(239,220)	(187,381)	(145,739)	(108,058)
Total stockholders equity	15,559	40,117	60,854	72,213	70,685

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SPECIAL NOTE REGARDING FORWARD-LOOKING STATEMENTS

This report includes forward-looking statements within the meaning of the Private Securities Litigation Reform Act of 1995. These forward-looking statements are not historical facts and include, but are not limited to, statements about our plans, objectives, representations and contentions that typically may be identified by use of terms such as anticipate, believe, estimate, plan, may, expect, intend, could, potential, and similar expressions, alth forward-looking statements are expressed differently. These forward-looking statements include, among others, the statements about our:

- estimate that our existing cash and cash equivalents (including the net proceeds from our March 2007 financing), expected proceeds from collaborations and license agreements, and interest income should be sufficient to meet our operating and capital requirements at least through the second quarter of 2008;
- expected losses;
- expectations for future capital requirements;
- expectations for increases in operating expenses;
- expectations for increases in research and development, and marketing, general and administrative expenses in order to develop products, procure commercial quantities of reagents and products, and commercialize our technology;
- expectations regarding the scope and expiration of patents;
- expectations regarding the timing of non-clinical activities, regulatory meetings and submissions, as well as the progression of clinical trials, for NE-180 and GlycoPEG-GCSF;
- expectations for the development of long-acting versions of EPO and G-CSF, and subsequent proprietary drug candidates;
- expectations regarding net cash utilization;
- expectations for generating revenue; and
- expectations regarding the timing and character of new or expanded collaborations and for the performance of our existing collaboration partners in connection with the development and commercialization of products incorporating our technologies.

You should be aware that the forward-looking statements included in this report represent management s current judgment and expectations, but our actual results, events and performance could differ materially from those in the forward-looking statements. Potential risks and uncertainties that could affect our actual results include the following:

- our ability to obtain the funds necessary for our operations;
- our ability to meet forecasted timelines due to internal or external causes;
- unfavorable non-clinical and clinical results for our products;
- our ability to develop commercial-scale manufacturing processes for our products and reagents, either independently or in collaboration with others;
- the performance of our CROs and CMOs;

our ability to enter into and maintain collaborative arrangements;

our ability to obtain adequate sources of proteins and reagents;

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our ability to develop and commercialize products without infringing the patent or intellectual property rights of others;

our ability to expand and protect our intellectual property and to operate without infringing the rights of others;

our ability and our collaborators ability to develop and commercialize therapeutic proteins and our ability to commercialize our technologies;

our ability to attract and retain key personnel;

our ability to compete successfully in an intensely competitive field; and

general economic conditions.

These and other risks and uncertainties that could affect our actual results are discussed in this report, particularly in Item 1A of Part I of this Annual Report on Form 10-K in the section entitled Risk Factors.

Although we believe that the expectations reflected in the forward-looking statements are reasonable, we cannot guarantee future results, events, levels of activity, performance, or achievements. We do not assume responsibility for the accuracy and completeness of the forward-looking statements other than as required by applicable law. We do not undertake any duty to update any of the forward-looking statements after the date of this report to conform them to actual results, except as required by the federal securities laws.

ITEM 7. MANAGEMENT S DISCUSSION AND ANALYSIS OF FINANCIAL CONDITION AND RESULTS OF OPERATIONS.

The following discussion should be read in conjunction with our financial statements and related notes included in this Annual Report on Form 10-K.

Overview

We are a clinical-stage biopharmaceutical company focused on the development of next-generation therapeutic proteins that we believe will be competitive with best-in-class protein drugs currently on the market. Our lead therapeutic protein candidates are NE-180 and GlycoPEG-GCSF. In 2005, the EPO and G-CSF drug categories had aggregate worldwide sales of approximately $11.2 billion and $4.0 billion, respectively.

NE-180 is a long-acting version of EPO produced in insect cells. EPO is prescribed to stimulate production of red blood cells, and is approved for sale in major markets around the world for treatment of chemotherapy-induced anemia and anemia associated with chronic renal failure. NE-180 is being developed for the treatment of anemia in adult cancer patients with non-myeloid malignancies receiving chemotherapy and for the treatment of anemia associated with chronic kidney disease, including patients on dialysis and patients not on dialysis. During 2006, we completed a Phase I clinical trial for NE-180 in Switzerland. In January 2007, we received approval from Swissmedic, the Swiss Agency for Therapeutic Products, for the initiation of a Phase II human trial to evaluate the safety, tolerability and dose response of NE-180 in cancer patients receiving platinum-based chemotherapy. In March 2007, we received clearance from the U.S. Food and Drug Administration (FDA) to initiate clinical trials in the U.S. in response to our amended Investigational New Drug application (IND).

Our second proprietary protein, GlycoPEG-GCSF, is a long-acting version of G-CSF that we are co-developing with BioGeneriX AG, a company of the ratiopharm Group. G-CSF is prescribed to stimulate production of neutrophils (a type of white blood cell) and is approved for sale in major markets around the world for treatment of neutropenia associated with myelosuppressive chemotherapy. In November 2006, BioGeneriX initiated the first of two planned Phase I clinical trials for GlycoPEG-GCSF. We expect BioGeneriX to initiate and complete the second Phase I trial during 2007.

We believe that our enzymatic pegylation technology, GlycoPEGylation , can improve the drug properties of therapeutic proteins by building out, and attaching PEG to, carbohydrate structures on the proteins. We are using our technology to develop proprietary versions of protein drugs with proven safety and efficacy and to improve the therapeutic profiles of proteins being developed by our partners. We expect these modified proteins to offer significant

advantages,

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including less frequent dosing and possibly improved efficacy, over the original versions of the drugs now on the market, as well as to meet or exceed the pharmacokinetic profile of next-generation versions of the drugs now on the market. We believe this strategy of targeting drugs with proven safety and efficacy allows us to lower the risk profile of our proprietary development portfolio as compared to *de novo* protein drug development. We intend to continue to focus our research and development resources on therapeutic proteins that we believe have the highest probability of clinically meaningful therapeutic profile improvements from our technology and are in commercially attractive categories.

In March 2007, we sold 21.4 million shares of common stock and warrants to purchase 9.6 million shares of common stock through a private placement, including 5.0 million shares of common stock and warrants to purchase 2.2 million shares of common stock to investment funds affiliated with certain members of our board of directors, at a price of $2.02 per unit, generating net proceeds of approximately $40.5 million. The warrants have a five-year term and an exercise price of $1.96 per share.

In March 2007, we initiated a restructuring of operations designed to allow for significantly higher clinical development costs for NE-180, while keeping anticipated 2007 net cash spending consistent with 2006 levels. The restructuring, which will be implemented over the next few months, will result in a workforce reduction of approximately 40%. We estimate that we will incur cash restructuring costs of approximately $1.0 million, most of which will be reflected in our operating results during the first half of 2007. We have not yet determined if we will incur any contract termination or non-cash impairment charges in connection with the restructuring.

In September 2006, we sold our Witmer Road Facility for approximately $21.0 million. We owned the Witmer Road Facility subject to mortgages supporting our term loan and industrial development authority bond.. After payment of selling fees and expenses, we received net proceeds of approximately $19.3 million. Concurrent with the closing, we repaid outstanding debt associated with the facility and related equipment of approximately $9.6 million, which included accrued interest and prepayment penalties. The remaining net proceeds from the sale of the Witmer Road Facility of approximately $9.7 million will be used to further our research, preclinical development, and clinical development objectives and to fund the capital expenditures described below to the extent such expenditures are not financed through the issuance of new debt. In conjunction with the sale of the Witmer Road Facility, we reduced the size of our workforce by approximately 25 employees. We anticipate cash severance and retention costs of approximately $1.0 million, of which $0.6 million had been paid as of December 31, 2006.

In February 2007, we consolidated our operations into our Rock Road Facility, a 40,000 square foot facility that we currently lease in Horsham, Pennsylvania. We anticipate total costs for construction of additional laboratory and office space in the Rock Road Facility of approximately $3.7 million, of which $2.1 million was included in construction-in-progress as of December 31, 2006.

We have incurred operating losses each year since our inception. As of December 31, 2006, we had an accumulated deficit of $266.3 million. We expect additional losses over the next several years as we continue product research and development efforts and expand our intellectual property portfolio. We have financed our operations through private and public offerings of equity securities, proceeds from debt financings, and revenues from our collaborative agreements.

We believe that our existing cash and cash equivalents (including the net proceeds from our March 2007 financing), expected proceeds from collaborations and license arrangements, and interest income should be sufficient to meet our operating and capital requirements at least through the second quarter of 2008, although changes in our collaborative relationships or our business, whether or not initiated by us, may cause us to deplete our cash and cash equivalents sooner than the above estimate.

Liquidity and Capital Resources

Overview

We had $16.4 million in cash and cash equivalents as of December 31, 2006, compared to $37.7 million as of December 31, 2005. The decrease for 2006 was primarily attributable to the use of cash to fund our operating activities, capital expenditures, and debt repayments, which were partly offset by net proceeds received from the sale of the Witmer Road Facility. In March 2007, we sold 21.4 million shares of our common stock and warrants to purchase 9.6 million shares of our common stock at $2.02 per unit, generating net proceeds of approximately

$40.5 million. The warrants have a five-year term and an exercise price of $1.96 per share.

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The development of next-generation proprietary protein therapeutics, which we are pursuing both independently and in collaboration with selected partners, will require substantial expenditures by us and our collaborators. We plan to continue financing our operations through private and public offerings of equity securities, proceeds from debt financings, and proceeds from existing and future collaborative agreements. Because our 2007 revenues could be substantially affected by entering into new collaborations and on the financial terms of any new collaborations, we cannot estimate our 2007 revenues. Other than proceeds from our collaborations with Novo Nordisk and BioGeneriX, and any future collaborations with others, we do not expect to generate significant revenues until such time as products using our technologies are commercialized, which is not expected during the next several years. We expect an additional several years to elapse before we can expect to generate sufficient cash flow from operations to fund our operating and investing requirements. We believe that our existing cash and cash equivalents (including the net proceeds from our March 2007 financing), expected revenue from collaborations and license arrangements, and interest income should be sufficient to meet our operating and capital requirements at least through the second quarter of 2008. Accordingly, we will need to raise substantial additional funds to continue our business activities and fund our operations until we are generating sufficient cash flow from operations. If we are unable to raise additional capital when required, we may need to delay, scale back, or eliminate some or all of our research and development programs.

Operating Activities

Net cash used in operating activities during 2006 and 2005 was $26.8 million and $33.1 million, respectively. The decrease of $6.3 million in net cash used in operating activities during 2006 was substantially the result of a $4.1 million reduction in research and development costs from 2005 to 2006. In addition, during 2006, $2.0 million of cash was provided by changes in operating assets and liabilities compared to $0.6 million for 2005. Fluctuations in operating items vary period-to-period due to, among other factors, the timing of research and development activities, such as the initiation and progress of clinical trials and non-clinical studies.

Investing Activities

Net cash provided by investing activities during 2006 was $18.5 million, compared to net cash used in investing activities during 2005 of $0.5 million. In September 2006, we sold our Witmer Road Facility for approximately $21.0 million. After payment of selling fees and expenses, we received net proceeds of approximately $19.3 million. Concurrent with the closing, we repaid outstanding debt associated with the facility and related equipment of approximately $9.6 million, which included accrued interest and prepayment penalties. The remaining net proceeds from the sale of the Witmer Road Facility of approximately $9.7 million will be used to further our research, preclinical development, and clinical development objectives and to fund the capital expenditures described below to the extent such expenditures are not financed through the issuance of new debt. In February 2007, we consolidated our operations into our Rock Road Facility. We anticipate total costs for construction of additional laboratory and office space in our Rock Road Facility of approximately $3.7 million, of which $2.1 million was included in construction-in-progress as of December 31, 2006.

During 2006 and 2005, cash expenditures for property and equipment were $0.9 million and $0.8 million, respectively. The improvements to our Rock Road Facility contributed significantly to our capital expenditures during 2006. In 2007, we expect our investment in capital expenditures to be approximately $3.5 million to $4.0 million, which includes approximately $3.2 million to complete the construction at our Rock Road Facility. We may finance some or all of these capital expenditures through capital leases or the issuance of new debt or equity. The terms of any new debt could require us to maintain a minimum cash and investments balance, or to transfer cash into an escrow account to collateralize some portion of the debt, or both.

Financing Activities

Equity Financing Activities

In March 2007, we sold 21.4 million shares of common stock and warrants to purchase 9.6 million shares of common stock through a private placement, including 5.0 million shares of common stock and warrants to purchase 2.2 million shares of common stock to investment funds affiliated with certain members of our board of directors, at a price of $2.02 per unit, generating net proceeds of approximately $40.5 million. The warrants have a five-year term and an exercise price of $1.96 per share.

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In February 2005, we offered and sold 8.1 million shares of our common stock at a public offering price of $4.00 per share, generating net proceeds of $30.0 million. In May 2004, we sold 4.7 million shares of common stock in a registered direct offering to a number of institutional and individual investors, including 0.8 million shares sold to officers and an investment fund affiliated with a director, at a price of $6.77 per share, generating net proceeds of $29.9 million.

Debt Financing Activities

Our total debt decreased by $12.6 million to $1.8 million at December 31, 2006, compared to $14.4 million at December 31, 2005. This decrease primarily resulted from $9.3 million of early repayments of principal in connection with the sale of our Witmer Road Facility in September 2006. During 2006, we also made planned debt principal repayments of $3.8 million, which were partially offset by $0.5 million in proceeds from the issuance of debt to finance insurance policy premiums.

Note Payable Secured by Insurance Policies

In March 2006, we borrowed $0.5 million to finance insurance policy premiums due on certain insurance policies. We made the last payment in November 2006, and, therefore, there was no outstanding principal balance under this agreement as of December 31, 2006. The interest was calculated based on an annual percentage rate of 5.4%. To secure payment of the amounts financed, we granted the lender a security interest in all of our right, title and interest to the insurance policies.

Term Loan from Bank and Industrial Development Authority Bond

In September 2006, we repaid the outstanding balance of the term loan from a bank and the Industrial Development Authority bond in connection with the sale of the Witmer Road Facility. In connection with these repayments, we incurred $0.1 million of prepayment penalties and included this amount in interest expense during 2006.

Term Loan from Landlord

In May 2004, we borrowed $1.5 million from the landlord of our Rock Road Facility in Horsham, Pennsylvania. As of December 31, 2006, we owed the landlord $0.6 million. The terms of the financing require us to pay monthly principal and interest payments over 48 months at an interest rate of 13%. During 2007, we expect to make principal and interest payments totaling $0.5 million under this agreement.

Notes Payable to Equipment Lender

As of December 31, 2006, we owed $1.1 million to an equipment lender that financed the purchase of certain equipment and facility improvements, which collateralize the amounts borrowed. We made $1.6 million of early principal repayments in September 2006 upon the closing of the sale of the Witmer Road Facility. In connection with these early principal payments, we incurred $0.1 million of prepayment penalties and included this amount in interest expense during 2006. In October 2006, we amended six promissory notes with our equipment lender in connection with the early repayment of a portion of the outstanding debt as a result of the sale of the Witmer Road Facility. Under the amended promissory notes, our last payment is scheduled for September 2008, and interest rates applicable to the equipment loan range from 8.1% to 9.5%. During 2007, we expect to make principal and interest payments totaling $0.8 million under these agreements.

Capital Lease Obligations

We did not enter into any agreements with capital lease obligations during 2006 and 2005. We entered into agreements with capital lease obligations during 2004 for equipment with a value of $0.2 million. The terms of existing leases require us to make monthly payments through August 2009. As of December 31, 2006, the present value of aggregate minimum lease payments under these agreements was $0.1 million. During 2007, we expect to make lease payments totaling $50,000 under these agreements.

Operating Leases

We lease laboratory, office, warehouse facilities, and equipment under operating lease agreements. In 2002, we entered into a lease agreement for our Rock Road Facility. The initial term of this lease ends 2022, at which time we have an option to extend the lease for an additional five years, followed by another option to extend the lease for an additional four and one-half years. This lease contains escalation clauses, under which the base rent increases annually by 2%. We lease

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approximately 5,000 square feet of office and warehouse space in Horsham, Pennsylvania under a lease agreement that expires April 2007. In January 2007, we entered into a five-year lease agreement for approximately 6,800 square feet of office and warehouse space in Horsham, Pennsylvania to replace similar space subject to the expiration described above. Our rental expense was $1.0 million for each of the years ended December 31, 2006, 2005, and 2004.

Summary of Contractual Obligations

The following table summarizes our obligations to make future payments under current contracts as of December 31, 2006:

	Payments due by period				
	Total	Less than 1 Year	1 - 3 Years	4 - 5 Years	After 5 Years
Long-term debt obligations[1]					
Debt maturities	$ 1,723,000	$1,201,000	$ 522,000	$	$
Contractual interest	139,000	122,000	17,000		
Capital lease obligations[2]					
Debt maturities	108,000	50,000	58,000		
Contractual interest	11,000	8,000	3,000		
Operating leases[3]	8,121,000	519,000	917,000	955,000	5,730,000
Purchase obligations[4]	800,000	796,000	4,000		
Total contractual obligations	$10,902,000	$2,696,000	$1,521,000	$955,000	$5,730,000

1. See Financing Activities Debt Financing Activities in this Liquidity and Capital Resources section and Note 7 of the Notes to Financial Statements included in Item 8 of this Annual Report on Form 10-K for a description of the material features of our long-term debt. Contractual interest is the

interest we contracted to pay on the long-term debt obligations.

2. See Financing Activities Capital Lease Obligations in this Liquidity and Capital Resources section and Note 13 of the Notes to Financial Statements included in Item 8 of this Annual Report on Form 10-K for a description of the material features of our capital lease obligations. At December 31, 2006, the present value of our capital lease obligations was $108,000 and the amount of imputed interest, calculated using an assumed incremental borrowing rate at the time we entered into the capital lease obligations, was $11,000.

3. See Note 13 of the Notes to Financial Statements included in

Item 8 of this Annual Report on Form 10-K for a description of our significant operating leases.

4. See Note 13 of the Notes to Financial Statements included in Item 8 of this Annual Report on Form 10-K for a description of our commitments as of December 31, 2006 to purchase goods and services from various suppliers.

Off-Balance Sheet Arrangements

We are not involved in any off-balance sheet arrangements that have or are reasonably likely to have a material current or future effect on our financial condition, changes in financial condition, revenues or expenses, results of operations, liquidity, capital expenditures, or capital resources.

Critical Accounting Policies and Estimates

Our Management s Discussion and Analysis of Financial Condition and Results of Operations (MD&A) focuses on our liquidity, capital resources, and financial statements. The financial statements have been prepared in accordance with U.S. generally accepted accounting principles. The preparation of financial statements requires management to make estimates and assumptions that affect the carrying amounts of assets and liabilities, and the reported amounts of revenues and expenses during the reporting period. These estimates and assumptions are developed and adjusted periodically by management based on historical experience and on various other factors that are believed to be reasonable under the circumstances. Actual results may differ from these estimates.

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Our summary of significant accounting policies is described in Note 2 of the Notes to Financial Statements included in Item 8 of this Annual Report on Form 10-K. Management considers the following policies and estimates to be the most critical in understanding the more complex judgments that are involved in preparing our financial statements and the uncertainties that could impact our results of operations, financial position, and cash flows. Management has discussed the development and selection of these critical accounting policies and estimates with the audit committee of our board of directors, and the audit committee has reviewed our disclosure relating to it in this MD&A.

Revenue Recognition

We have entered into collaborative agreements with other companies for the development and commercialization of our product candidates. The terms of the agreements typically include non-refundable up-front license fees, funding of research and development, payments based upon achievement of development milestones, and royalties on product sales.

License Fees and Multiple Element Arrangements

Non-refundable license fees are recognized as revenue when we have a contractual right to receive such payment, the contract price is fixed or determinable, the collection of the resulting receivable is reasonably assured, and we have no further performance obligations under the license agreement.

Multiple element arrangements, such as license and development arrangements are analyzed to determine whether the deliverables, which often include a license and performance obligations, such as research and development services, can be separated or whether they must be accounted for as a single unit of accounting in accordance with Emerging Issues Task Force (EITF) Issue No. 00-21*, Accounting for Revenue Arrangements with Multiple Deliverables*. If the fair value of the undelivered performance obligations can be determined, such obligations would then be accounted for separately as performed. However, if the license is considered to either (i) not have stand-alone value or (ii) have stand-alone value but the fair value of any of the undelivered performance obligations cannot be determined, the arrangement would then be accounted for as a single unit of accounting and the license payments and payments for performance obligations are recognized as revenue over the estimated period of when the performance obligations are performed. In our collaborative arrangements with Novo Nordisk and BioGeneriX, we have determined the license to each does not have stand-alone value.

Whenever we determine that an arrangement should be accounted for as a single unit of accounting, we must determine the period over which the performance obligations will be performed and revenue will be recognized. Significant management judgment is required in determining the period over which we are expected to complete our performance obligations under an arrangement.

Substantive Milestone Payments

Our collaboration agreements may also contain substantive milestone payments. Substantive milestone payments are considered to be performance bonuses that are recognized upon achievement of the milestone only if all of the following conditions are met:

- the milestone payments are non-refundable;
- achievement of the milestone involves a degree of risk and was not reasonably assured at the inception of the arrangement;
- substantive effort is involved in achieving the milestone;
- a reasonable amount of time passes between the up-front license payment and the first milestone payment as well as between each subsequent milestone payment; and
- the amount of the milestone payment is reasonable in relation to the effort expended or the risk associated with achievement of the milestone.

Determination as to whether a payment meets the aforementioned conditions involves management s judgment. If any of these conditions are not met, the resulting payment would not be considered a substantive milestone, and

therefore the resulting payment would be considered part of the consideration for the single unit of accounting and be recognized as revenue as such performance obligations are performed.

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Reimbursement of Research and Development Costs

Reimbursement of research and development costs is recognized as revenue provided the provisions of EITF Issue No. 99-19, *Reporting Revenue Gross as a Principal Versus Net as an Agent*, are met, the amounts are fixed and determinable, and collection of the related receivable is reasonably assured. In our collaborative arrangements with Novo Nordisk and BioGeneriX, we recognize revenue as such costs are incurred because we have evidence of fair value for these delivered items.

Deferred Revenue

Amounts received prior to satisfying the above revenue recognition criteria are r