NEOSE TECHNOLOGIES INC
Form 10-K
February 17, 2004
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SECURITIES AND EXCHANGE COMMISSION

Washington, D.C. 20549

FORM 10-K

(Mark One)

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

For the fiscal year ended December 31, 2003

or

¨ 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 Witmer 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:

None	**None**
(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)

Common Stock, par value $0.01 per share

(Title of class)

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

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

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

As of June 30, 2003, the aggregate market value of the Common Stock held by non-affiliates of the registrant was approximately $88,792,350 based on the last sale price of the Common Stock on such date as reported by The Nasdaq Stock Market. This calculation excludes 8,362,360 shares held on June 30, 2003 by directors, executive officers, and two holders of more than 10% of the registrant s Common Stock.

As of February 15, 2004, there were 19,944,671 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 6, 2004, 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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This report includes forward-looking statements within the meaning of the Private Securities Litigation Reform Act of 1995. These forward-looking statements include, but are not limited to, statements about our plans, objectives, representations and contentions and are not historical facts, which typically may be identified by use of terms such as anticipate, believe, estimate, plan, may, expect, intend, cou potential, and similar expressions, although some forward-looking statements are expressed differently. 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. The forward looking statements are subject to a number of risks and uncertainties which are discussed in the section of Part II entitled Factors Affecting the Company s Prospects. We do not intend to update any of these factors or to publicly announce the results of any revisions to these forward-looking statements.

PART I

ITEM 1. BUSINESS.

Overview

We are a biopharmaceutical company focused on improving protein therapeutics using our proprietary technologies. Most protein therapeutics currently on the market or in development today are glycoproteins that is, they consist of a protein backbone (comprised of amino acids) to which carbohydrate structures (chains of simple sugars) are attached. While the protein backbone determines what the protein will do, the attached carbohydrate structures known as glycosylation - are often essential to ensure its proper functioning. Inadequate glycosylation is also frequently a significant limitation to the efficiency of the manufacturing process for existing glycoprotein therapeutics.

Our core technologies, GlycoAdvance and GlycoPEGylation, enable us to manipulate, enzymatically, the carbohydrate structures of glycoproteins, and thereby pursue the objective of improving the therapeutic profiles of proteins that have already been marketed or substantially developed by other companies. We use GlycoAdvance, either to complete the carbohydrate structures on proteins that are inadequately glycosylated, or to initiate and extend the carbohydrate structures on proteins that are not glycosylated at all. As a technology, GlycoAdvance is sufficiently versatile that it enables us to work with many proteins secreted from a variety of expression systems (the basic platform for manufacturing proteins), and with proteins having various glycosylation patterns. We may also use GlycoPEGylation to attach a sugar molecule linked to polyethylene glycol (PEG) to selected carbohydrate structures. PEG is an inert polymer, which, when added to a protein, increases its size, and in most cases improves its pharmaceutical profile, such as enabling the protein to be administered less frequently.

In sum, our core business is to use our novel technologies to improve proteins for which there is already a substantial body of data demonstrating safety and efficacy. The development of next-generation products (i.e. products with improvements over the original product) has been a key strategy used by pharmaceutical and biopharmaceutical companies for decades. We intend to apply this strategy to products we are developing on our own and to products we co-develop and co-own with others, and we expect to make our technologies available, through strategic partnerships, to improve the products of other parties.

Opportunities in the Protein Market

Worldwide sales of protein drugs (which include monoclonal antibodies and fusion proteins) were over $39 billion in 2003, and by some estimates are expected to grow to over $70 billion by 2008. 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 GlycoAdvance and GlycoPEGylation technologies can be applied to many of these marketed drugs to create next-generation products with improved clinical profiles. We are pursuing opportunities in this field through our own proprietary drug development program, our partnering and licensing program, and our exploratory research program.

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Neose Proprietary Drug Program. The initial targets of our own proprietary drug program are an improved erythropoietin (EPO) and an improved granulocyte colony stimulating factor (G-CSF). The EPO and G-CSF drug categories had combined worldwide sales of approximately $10.6 billion in 2002.

Partnering and Licensing Program. During 2003, we entered into two new agreements with Novo Nordisk A/S (Novo Nordisk) that allow us to partner the development and commercialization of next-generation versions of three marketed proteins, one of which is currently marketed by Novo Nordisk. These three marketed proteins had combined worldwide sales of approximately $2.0 billion in 2002.

Exploratory Research Program. Our exploratory research program is currently focused on the development of two undisclosed marketed proteins, one in collaboration with Rentschler Biotechnologie GmbH (Rentschler) and another with Sandoz GmbH (Sandoz). The marketed versions of these proteins had combined worldwide sales of approximately $5.5 billion in 2002.

Core Technology

Our GlycoAdvance and GlycoPEGylation technologies evolve from the same core the use of enzymes to modify or initiate carbohydrate structures on glycoproteins. We have developed a special expertise and strong intellectual property position in this area. Our technologies may permit the development of therapeutic proteins with improved clinical profiles. In some cases, these improvements to therapeutic proteins may also give rise to new intellectual property. 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 technology has broad application to protein drug development and can be extended to provide an opportunity for sustainable growth.

GlycoAdvance. We use GlycoAdvance, either to complete the carbohydrate structures on proteins that are inadequately glycosylated, or to initiate and extend the carbohydrate structures on proteins that are not glycosylated at all. Currently, recombinant glycoprotein drugs are most often produced in mammalian cell culture expression systems, primarily Chinese hamster ovary (CHO) cells. The carbohydrates are added to these 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, may break down too rapidly, and may stimulate unwanted antibody responses. Conventional approaches to improving the glycosylation of recombinant protein drugs, such as changing expression cell types, re-engineering the protein, and modifying cell culture conditions or media, are time consuming and frequently provide only partial solutions. When a protein is inconsistently glycosylated, additional purification may be required to remove the incompletely glycosylated drug molecules from the desired drug product, resulting in lower manufacturing yields and increased expense.

Some proteins (e.g., human growth hormone), in their natural state, lack attached carbohydrates. Others (e.g., G-CSF) may be expressed in bacteria, an expression system that fails to add sugars at natural glycosylation sites. Using our GlycoAdvance technology, we employ enzymes to initiate glycosylation at engineered or natural acceptor sites on such proteins and to further elaborate these carbohydrate structures with natural or modified sugar units. By attaching and modifying carbohydrate structures, we have been able to demonstrate with several drug candidates a prolonged drug effect in animals. We are using GlycoAdvance in our own proprietary drug program, in our partnering and licensing program, and in our exploratory research program. We are also exploring the use of GlycoAdvance to enable alternative protein production systems, such as plants and insect cells that naturally produce only partial versions of the carbohydrate structures found in human glycoproteins.

GlycoPEGylation. Common protein drug delivery problems include poor solubility and stability, proteolysis (rapid degradation by proteases), 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, polyethylene glycol (PEG), directly to the amino acid backbone of the protein. Pegylation increases the effective size of the drug and in some cases improves its solubility, stability, half-life and immunogenicity profile.

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.

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Our GlycoPEGylation technology enables us to attach a sugar molecule linked to PEG to the ends of carbohydrate structures, rather than attaching PEG directly on the protein backbone. Using enzymes, we are able to do this efficiently and selectively. By specifically 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. During the research stage, we attach PEGs of various molecular weights to create a family of different molecular sizes of the GlycoPEGylated protein, which we screen for optimal receptor binding and pharmacokinetic properties. We believe that significant clinical benefits may be achieved through the application of our GlycoPEGylation technology to proteins.

Business Strategy

Our primary business strategy is to develop next-generation protein drugs through three focused programs: our own proprietary drug program, our partnering and licensing program, and our exploratory research program.

Neose Proprietary Drug Program. During 2003, we focused our own proprietary drug program on the identification and development of two next-generation proprietary protein therapeutics: an improved EPO and an improved G-CSF. During 2004 and 2005, we intend to limit the number of proteins in our own proprietary drug program to two proteins, which we are prepared to develop independently into Phase II clinical studies before we require a corporate partner for further development. We may decide to substitute a different protein for our improved EPO or improved G-CSF, or both. Substitutions could occur for several reasons, including various problems that may arise in the drug development process and the timing of desirable opportunities for partnering the continuing development of these next-generation proteins. We will continue to evaluate the progress of our own proprietary drug program and appropriate partnering opportunities.

Improved EPO. In January 2003, we announced the selection of an improved EPO as the first target for our proprietary drug development program. 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 anemia associated with oncology chemotherapy, end-stage renal disease, and chronic renal insufficiency. EPO accounts for more sales worldwide than any other glycoprotein drug. Worldwide sales of the EPO category in 2002 were over $8 billion. Of this amount, approximately $5.7 billion in sales were in the U.S., approximately $1.9 billion in sales were in Europe and other countries outside Asia, and $0.8 billion in sales were in Japan and other Asian markets.

Based on preclinical studies conducted during 2002 and 2003, we believe it is feasible to develop a long-acting EPO through GlycoPEGylation. These studies suggest that the pharmacokinetic profile of EPO can be adjusted by manipulating the number of GlycoPEGylation sites and the molecular weight of the PEG that we attach to the compound. In these early studies, the biological activity of constructs of GlycoPEGylated EPO was comparable to the activity of unmodified EPO and Aranesp®, Amgen s longer acting EPO analog. Based on our preliminary market research, we believe that clinicians, particularly oncologists, would favor a long-acting EPO. This is supported by quantitative data for Aranesp, indicating that, six quarters after launch, annualized sales were greater than $1 billion.

We believe that the expiration of key patents covering EPO will provide commercial opportunities in a time frame consistent with our development timeline. We expect that regulatory approval for our improved EPO will be sought both in and outside the U.S. In Europe and Japan, the key patents will expire in the middle of this decade. In the U.S., the patent situation surrounding EPO is more complex, making the time frame less predictable. There are existing patent claims that may cover our improved EPO, and we continue to evaluate whether these patent claims will prevent our entry into the U.S. market prior to their expiration. Some of the issues relevant to our analysis are the subject of ongoing litigation between other parties. While our objective is to pursue early entry opportunities in the U.S., we expect that the first regulatory and marketing applications will be made in Europe, where the risk of patent conflict appears to be lower. We expect to complete various preclinical activities during the first half of 2004, and, if the results are successful, our goal is to initiate clinical trials by the end of 2004. We expect that data from these trials will be submitted to the appropriate government agencies for regulatory approval.

Improved G-CSF. In October 2003, we selected an improved G-CSF as our second proprietary drug development target. G-CSF is prescribed to stimulate production of neutrophils (a type of white blood

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cell), and is approved for sale in major markets around the world for treatment of neutropenia associated with oncology chemotherapy. Based on proof-of-concept data, we believe it is feasible to develop a long acting G-CSF through GlycoPEGylation. We are planning to continue various preclinical development activities during 2004, with the goal of initiating clinical trials in the second half of 2005. In Europe, the key patents covering G-CSF will expire in 2005. In the U.S., key patents will expire in late 2013. Nevertheless, we are evaluating early entry strategies for the U.S. market. Although it is too early to predict the likely success of these strategies, we expect that applications for regulatory and marketing approvals will be submitted first in Europe.

Partnering and Licensing Program. We also work in collaboration with partners to incorporate our technology in next-generation proteins. In our partnering and licensing program, we generally seek collaborations where:

- our partner supplies protein,
- we use our technologies to modify the protein and to develop manufacturing-scale reagents and protocols for production,
- our partner licenses our technologies for the development and commercialization of the modified protein,
- our partner pays for our research and development activities, and
- our partner pays development milestones and royalties on the resulting next-generation protein sales.

Novo Nordisk. In November 2003, we announced two new agreements with Novo Nordisk to use our technologies to develop and commercialize three next-generation versions of currently marketed proteins, one of which is marketed by Novo Nordisk. These agreements are the result of exploratory research we previously conducted with Novo Nordisk and the successful application of our GlycoPEGylation technology to three complex proteins. Under our new agreements, we received a $4.3 million upfront fee, and Novo Nordisk is funding our research and development activities for these three proteins. We may also receive up to $51.3 million in development milestones, as well as royalties on sales of the licensed products. Under these agreements, Novo Nordisk s license with respect to each protein will continue 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, after giving us 90 days notice. We have the right to terminate the agreement with respect to two of the proteins if there are no commercial sales of licensed products within a specified period of years.

Exploratory Research Program. We conduct exploratory research, both independently and with collaborators, to identify proteins that are likely candidates for development using our technologies. Successful candidates may be advanced for development through our own proprietary drug program or through our partnering and licensing program. In 2003, we announced two collaborative exploratory research agreements, one with Rentschler and one with Sandoz.

- Under our collaboration agreement with Rentschler, we are working on the development of a next-generation protein, using an undisclosed protein supplied by Rentschler. If Neose decides to proceed with the commercialization of this next-generation protein, Rentschler may continue to collaborate with Neose as a co-developer or as a supplier of the protein.
- Under our collaboration with Sandoz, we are working on the development of a next-generation protein, using an undisclosed protein that is supplied by Sandoz. If Neose and Sandoz decide to proceed with the commercialization of this next-generation protein, we would have co-exclusive worldwide rights.

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Other Programs. Since we are now focused on developing next-generation proprietary protein therapeutics through our own drug development program, our partnering and licensing program, and our exploratory research program, we are evaluating the most effective means of continuing some of the other projects we have pursued in the past. We are considering whether to continue allocating some of our resources to two of these projects during 2004:

- the development of glycolipids for treating Parkinson s disease and other neurological diseases, on which we previously collaborated with Neuronyx, Inc., and
- the development of our GlycoConjugation technology, in which we would use an enzymatic approach, similar to GlycoPEGylation, to attach therapeutic or functional compounds (rather than PEG) to the carbohydrate structures on proteins.

We are looking for opportunities to out-license the technologies we have developed in two other projects:

- our joint venture with McNeil Nutritionals (a subsidiary of Johnson & Johnson) to explore inexpensive, enzymatic production of complex carbohydrates for use as bulking agents, and
- our work with Wyeth Nutrition to develop a manufacturing process for a bioactive carbohydrate to be used as an ingredient in infant and pediatric nutritional products.

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. As we pursue our strategy of developing next-generation proteins, we have increased our focus on 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 application, 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 adding 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 seek to obtain rights to 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 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 29 issued U.S. patents, and have licensed 63 issued U.S. patents from 12 institutions. In addition, we own or have licensed over 90 patent applications pending in the U.S. There are also 418 foreign patent applications pending or granted related to our owned and licensed patents. In addition, we have assigned four issued U.S. patents and 34 granted or pending foreign counterparts to Magnolia Nutritionals, our joint venture with McNeil Nutritionals (a subsidiary of Johnson & Johnson).

Next-Generation Proteins. To pursue our strategy of developing next-generation proteins, we must ascertain the nature, scope and expiration of existing patent claims covering proteins we may target for development. 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 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.

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In order to market next-generation versions of currently marketed proteins, we will have to determine the expiration dates of existing patent claims that could cover our 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 both EPO and G-CSF in the U.S. has encouraged us that there may be opportunities to enter the market sooner than our competitors whose products would have different characteristics or manufacturing processes. If we pursue a strategy of early entry, 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 prevailed in the litigation.

Nature of Protection. The nature of patent protection in the pharmaceutical and biotechnology industry is complex, uncertain and unpredictable. 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 which 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, or made known, by Neose 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 Neose if they are the result of tasks assigned by Neose or the use of property (including intellectual property) owned or used by Neose. Our agreements with consultants generally provide that inventions conceived by the consultant while rendering consulting services to Neose 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.

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 U.S. Food and Drug Administration (FDA) and by comparable regulatory agencies in other countries. These national agencies and other federal, state and local entities regulate, among other things, research and development activities, and the manufacturing and control, safety, effectiveness, labeling, storage, record keeping, approval, advertising and promotion of therapeutic products. 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.

In the U.S., after laboratory analysis and preclinical testing in animals, an investigational new drug application (or IND) is required to be filed with the FDA before human testing may begin. 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, or IRB. In Phase I, small clinical trials are conducted to determine the safety of the product. In Phase II, clinical trials are conducted to assess safety, establish an acceptable dose, and gain preliminary evidence of the efficacy of the product. In Phase III, clinical trials are conducted to obtain sufficient data to establish statistically significant proof of safety and efficacy.

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The time and expense required to perform this clinical testing vary and can be substantial. The results of the preclinical and clinical testing of a biological pharmaceutical product are then submitted to the FDA in the form of a Biologics License Applications (or BLA), or for a chemical pharmaceutical product in the form of a New Drug Application (or NDA), for approval to commence commercial sales. If the application contains all pertinent information and data, the FDA will formally accept the file for review. In responding to a BLA or NDA, the FDA 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 the U.S. until an appropriate marketing application has been approved by the FDA. Even after initial FDA approval is obtained, further clinical trials may be required to provide additional data on safety and effectiveness, and will be required 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 the European Union (EU) are similar to those in the U.S. In the EU, depending on the type of drug for which approval is sought, there are currently two potential tracks for marketing approval in member countries: mutual recognition and the centralized procedure. Typically, recombinant products are reviewed through the centralized procedure. The EU review mechanisms may ultimately lead to approval in all EU countries, but each method grants all participating countries some decision-making authority in product approval.

Sales of pharmaceutical and biopharmaceutical products in other areas of the world vary from country to country. Whether or not FDA licensure has been obtained, licensure of a product by comparable regulatory authorities in other countries must be obtained prior to marketing the product in those countries. The time required to obtain such licensure may be longer or shorter than that required for FDA approval, and regulatory authorities in other areas of the world, like the FDA, may approve or deny applications for licensure and marketing.

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 prelicensing 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 our 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, including the suspension of our manufacturing operations.

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 countries within 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 manufacture enzymes, sugar nucleotides and other reagents for use by our collaborators, as well as for our own manufacturing use in the development of next-generation proprietary protein therapeutics. Our partners may be responsible for clinical and regulatory approval procedures, but we would expect to participate in this process by submitting to the FDA a drug master file developed and maintained by us that contains data concerning the manufacturing and control processes for our reagents.

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, public securities 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.

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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 each of our collaborator s ability 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 might 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.

Next-Generation Protein Development. We are aware that other companies are working on the development of next-generation protein therapeutics in anticipation of the expiration of certain patent claims covering marketed proteins. Companies such as Maxygen and Applied Molecular Evolution are designing and manipulating protein structures to improve the properties of therapeutic proteins, including safety, efficacy and patient convenience. Nektar, Enzon and other companies utilize chemical pegylation technologies to increase the circulating half-life of certain proteins. Some of these companies are combining protein structure manipulation and pegylation. In addition, established large pharmaceutical and biotechnology companies are utilizing chemical pegylation technologies on their own proteins. Human Genome Sciences and BioRexis are applying in-vivo fusion technologies using albumin and other carrier proteins to increase circulating half-life and potentially improve other therapeutic properties on specific proteins. In addition, drug delivery companies such as Alkermes continue to exploit formulation technologies to improve administration and dosing of therapeutic proteins. Some of these companies have greater financial, technical, manufacturing, marketing and other resources than ours, and may be better equipped than we are to develop, market and manufacture next-generation proteins. 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.

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 EPO. Amgen launched Aranesp in the last quarter of 2001 and has reported that global sales of Aranesp were approximately $1.5 billion in 2003. Roche is developing an improved EPO known as CERA (Continuous Erythropoiesis Receptor Activator). In addition, non-originator companies are applying their technologies to develop improved EPO compounds, such as: Gryphon, with its precision length polymer and chemical ligation technology; Transkaryotic Therapeutics, utilizing its gene activation technology; Human Genome Sciences, with its albumin fusion technology; ARIAD, with its gene therapy and small molecule promoter technology; and Affymax, with its synthetic EPO-like peptides.

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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 $1.3 billion in 2003. Other companies, such as Human Genome Sciences and Affymax, are also applying their technologies to develop next-generation versions of G-CSF.

Follow-on Biologics (Biogenerics). Although a clear development and regulatory path does not currently exist for biologic products that are, or soon will be, off-patent in the U.S., Europe and Japan, we are aware that companies are pursuing the opportunity to develop and commercialize follow-on versions of currently marketed products, including EPO, G-CSF and others. Companies that are expected to work in this area include Sandoz, BioGeneriX, STADA, SICOR (now a wholly owned subsidiary of Teva Pharmaceutical Industries Ltd.) and others.

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

There are several companies that are engaged in glycobiology research. Their work includes efforts to develop better-glycosylating cell lines, optimize cell culture conditions to improve glycosylation, and generate carbohydrate therapeutics. Companies working in this area include Crucell, GLYCART, GlycoFi and Momenta. Crucell has developed human cell lines for glycoprotein production. GLYCART is pursuing the glycosylation of antibodies, and GlycoFi is focused on expressing glycoproteins in yeast systems. Momenta is utilizing sophisticated analysis and design for carbohydrate-based therapeutics.

Manufacturing

We have invested in the construction and validation of a manufacturing pilot plant in Horsham, PA to support our business objectives. Our goals in manufacturing are:

- to operate facilities that provide economies of scale to produce enzymes, sugar nucleotides and other reagents to support our GlycoAdvance and GlycoPEGylation technologies,
- to enable production of EPO, and our next-generation GlycoPEGylated EPO, from insect cells for preclinical and Phase I and Phase II clinical studies,
- to produce our next-generation GlycoPEGylated G-CSF for preclinical immunotoxicology studies, and
- to permit our collaborators to bring potentially improved therapeutic protein products to market faster.

Additional work may be necessary to optimize manufacturing processes for regulatory approval, including the modification of fermentation conditions, downstream protein purification, and enhancements of operational reliability.

In 2003, we completed the qualification and validation of our pilot manufacturing facility in Horsham for the production of enzymes, sugar nucleotides and other reagents in accordance with applicable U.S. Food and Drug Administration s current Good Manufacturing Practices regulations (cGMP). The facility consists of approximately 24,000 square feet of processing area and utility space. Separate areas are dedicated to sugar nucleotide processing, enzymes expressed in bacterial organisms, and enzymes expressed in fungal organisms. A fourth area was remodeled to provide cell culture growth and protein isolation in support of our manufacture of EPO in insect cells. This space is segregated into two areas to provide separate space for growth of the insect cells and amplification of baculovirus genomic constructs. Additional work may be necessary to scale the processes to provide sufficient quantities of the EPO active pharmaceutical ingredient to meet our needs for preclinical immunotoxicology studies and other work in preparation for our IND filing. We plan to supply our improved, GlycoPEGylated EPO for Phase I and Phase II clinical studies and to transfer the manufacturing process to a third-party contract manufacturer or partner for Phase III and commercial supplies.

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We continue to discover and develop improved reagents and technologies, and we plan to use our pilot plant to manufacture these reagents. In addition, our facility is expected to support the manufacture of reagents to glycosylate proteins produced from bacterial origin to potentially improve their therapeutic profile. We also plan to develop processes to GlycoPEGylate G-CSF for research and development. We will be working to secure supplies of protein on acceptable terms and to develop fermentation and purification processes for the reagents necessary to produce GlycoPEGylated G-CSF.

Marketing, Distribution, and Sales of Proprietary Protein Products

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. 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, 2003, we employed 142 individuals, consisting of 104 employees engaged in research, development and manufacturing activities, 7 employees devoted to business development and licensing activities, and 31 employees devoted to corporate and administrative activities. Our scientific staff includes carbohydrate biochemists as well as scientists with expertise in organic chemistry, analytic chemistry, molecular biology, microbiology, cell biology, scale-up manufacture, and regulatory affairs. During the last year, our most substantial investments in human resources have been made in the protein development and manufacturing groups, and we expect this to continue. A significant number of our employees have prior experience with pharmaceutical or biotechnology companies, and many have specialized training in carbohydrate technology. None of our employees is covered by collective bargaining agreements. We believe we have good relations with our employees.

Internet Address and Securities Exchange Act Filings

Our internet address is www.neose.com. We make available 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.

ITEM 2. PROPERTIES.

We own, subject to our mortgages, approximately 50,000 square feet of cGMP manufacturing, laboratory, and corporate office space in Horsham, Pennsylvania, and we lease approximately 5,000 square feet of additional office and warehouse space in a building nearby. We lease approximately 10,000 square feet of laboratory and office space in San Diego, California. The initial term of the San Diego lease ends in March 2006, at which time we have an option to extend the lease for an additional five years.

In 2001 and 2002, we made capital expenditures of $17.4 million to provide additional cGMP manufacturing capacity in our Horsham, Pennsylvania facility. We entered into a lease agreement in 2002 for a 40,000 square foot building, which we intended to convert into laboratory and office space. Later in 2002, we suspended plans to complete these renovations. In November 2003, we resumed renovation activities on approximately 25,000 square feet of the facility, leaving approximately 15,000 square feet available for future expansion. We estimate these activities will cost approximately $6.3 million, of which approximately $1.0 million had been expended as of December 31, 2003.

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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 2003.

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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 NASDAQ Stock Market under the symbol NTEC. We commenced trading on The Nasdaq Stock Market 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, 2002		
First Quarter	$ 37.30	$ 29.80
Second Quarter	32.58	9.07
Third Quarter	11.06	6.41
Fourth Quarter	14.00	5.90
Year Ended December 31, 2003		
First Quarter	9.31	6.03
Second Quarter	12.64	6.88
Third Quarter	11.06	8.50
Fourth Quarter	9.83	7.20
Year Ended December 31, 2004		
First Quarter (through February 15, 2004)	13.80	9.14

As of February 15, 2004, there were approximately 200 record holders and 3,700 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.

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ITEM 6. SELECTED FINANCIAL DATA.

The following Statements of Operations and Balance Sheet Data for the years ended December 31, 1999, 2000, 2001, 2002, and 2003, and for the period from inception (January 17, 1989) through December 31, 2003, 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 Form 10-K.

	Year ended December 31,					Period from inception (January 17, 1989) to December 31,
	1999	2000	2001	2002	2003	2003
	(in thousands, except per share data)					
Statements of Operations Data:						
Revenue from collaborative agreements	$ 422	$ 4,600	$ 1,266	$ 4,813	$ 1,435	$ 18,881
Operating expenses:						
Research and development	10,649	12,094	14,857	21,481	26,821	126,499
Marketing, general and administrative	4,520	5,648	9,374	12,510	11,148	60,220
Total operating expenses	15,169	17,742	24,231	33,991	37,969	186,719
Other income			6,120	1,653		7,773
Impairment of equity securities						