VERTEX PHARMACEUTICALS INC / MA
Form 424B5
September 11, 2006

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Filed Pursuant to Rule 424(b)(5)
Registration No. 333-137232

The information in this prospectus supplement and the accompanying prospectus is not complete and may be changed. This prospectus supplement and the accompanying prospectus are not an offer to sell these securities and are not soliciting an offer to buy these securities in any state where the offer or sale is not permitted.

Subject to Completion
Preliminary Prospectus Supplement dated September 11, 2006

PROSPECTUS SUPPLEMENT
(To prospectus dated September 11, 2006)

8,000,000 Shares

VERTEX PHARMACEUTICALS INCORPORATED

Common Stock

We are offering 8,000,000 shares of our common stock.

Our common stock is listed on the Nasdaq Global Select Market under the symbol "VRTX." The last reported sale price of our common stock on the Nasdaq Global Select Market on September 8, 2006 was $35.34 per share.

Investing in our common stock involves risks. See "Risk Factors" on page S-10 of this prospectus supplement.

	Per Share	Total
Public offering price	$	$
Underwriting discount	$	$
Proceeds, before expenses, to Vertex	$	$

The underwriters may also purchase up to an additional 1,200,000 shares from us at the public offering price, less the underwriting discount, within 30 days from the date of this prospectus supplement to cover any overallotments. If the overallotment option is exercised in full, we will receive additional proceeds, before expenses, of $.

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

The shares will be ready for delivery on or about , 2006.

Merrill Lynch & Co. **Morgan Stanley**

UBS Investment Bank

The date of this prospectus supplement is , 2006.

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You should rely only on the information contained in this prospectus supplement or contained in or incorporated by reference in the accompanying prospectus to which we have referred you. We have not authorized anyone to provide you with information that is different. The information contained in this prospectus supplement and contained, or incorporated by reference, in the accompanying prospectus is accurate only as of the respective dates thereof, regardless of the time of delivery of this prospectus supplement and the accompanying prospectus or of any sale of common stock. It is important for you to read and consider all information contained in this prospectus supplement and the accompanying prospectus, including the documents incorporated by reference therein, in making your investment decision. You should also read and consider the information in the documents to which we have referred you under the caption "Available Information" and "Incorporation of Certain Information by Reference" in the prospectus.

We are offering to sell, and are seeking offers to buy, the common stock only in jurisdictions where offers and sales are permitted. The distribution of this prospectus supplement and the accompanying prospectus and the offering of the common stock in certain jurisdictions may be restricted by law. Persons outside the United States who come into possession of this prospectus supplement and the accompanying prospectus must inform themselves about and observe any restrictions relating to the offering of the common stock and the distribution of this prospectus supplement and the accompanying prospectus outside the United States. This prospectus supplement and the accompanying prospectus do not constitute, and may not be used in connection with, an offer to sell, or a solicitation of an offer to buy, any securities offered by this prospectus supplement and the accompanying prospectus by any person in any jurisdiction in which it is unlawful for such person to make such an offer or solicitation.

ABOUT THIS PROSPECTUS SUPPLEMENT

This document is in two parts. The first part is this prospectus supplement, which describes the specific terms of this common stock offering and also adds to and updates information contained in the accompanying prospectus and the documents incorporated by reference into the prospectus. The second part, the accompanying prospectus, gives more general information, some of which does not apply to this offering.

If the description of the offering varies between this prospectus supplement and the accompanying prospectus, you should rely on the information contained in this prospectus supplement. However, if any statement in one of these documents is inconsistent with a statement in another document having a later date for example, a document incorporated by reference in the accompanying prospectus the statement in the document having the later date modifies or supersedes the earlier statement.

We further note that the representations, warranties and covenants made by us in any agreement that is filed as exhibit to any document that is incorporated by reference in the accompanying prospectus were made solely for the benefit of the parties to such agreement, including, in some cases, for the purpose of allocating risk among the parties to such agreements, and should not be deemed to be a representation, warranty or covenant to you. Moreover, such representations, warranties or covenants were accurate only as of the date when made. Accordingly, such representations, warranties and covenants should not be relied on as accurately representing the current state of our affairs.

Unless we have indicated otherwise, or the context otherwise requires, references in this prospectus supplement and the accompanying prospectus to "Vertex," "Company," "we," "us" and "our" or similar terms are to Vertex Pharmaceuticals Incorporated and its subsidiaries.

PROSPECTUS SUPPLEMENT SUMMARY

This summary highlights information contained elsewhere in this prospectus supplement and the accompanying prospectus or incorporated by reference in the accompanying prospectus. This summary does not contain all of the information that you should consider before deciding to invest in our common stock. You should read this entire prospectus supplement and the accompanying prospectus carefully, including the "Risk Factors" section contained in this prospectus supplement and our consolidated financial statements and the related notes and the other documents incorporated by reference in the accompanying prospectus.

Business Overview

We are a biotechnology company in the business of discovering, developing and commercializing small molecule drugs for the treatment of serious diseases. We have built a drug discovery capability that integrates biology, chemistry, biophysics, automation and information technologies, with a goal of making the drug discovery process more efficient and productive. Currently, a Vertex-discovered compound for the treatment of HIV infection, fosamprenavir calcium (marketed as Lexiva in the United States and Telzir in Europe), is being marketed by our collaborator GlaxoSmithKline plc. We have a number of drug candidates in development and a broad-based discovery effort.

We are concentrating most of our drug development resources at the present time on three compounds in specific markets: telaprevir (VX-950) for the treatment of hepatitis C virus, or HCV, infection in North America, VX-702 for the treatment of rheumatoid arthritis, or RA, in North America and Europe and VX-770 for the treatment of cystic fibrosis, or CF, worldwide. We rely on collaborators (i) for financial support for certain drug development programs and (ii) to conduct all or a portion of the development, manufacturing and commercialization activities for certain of our other drug candidates, either worldwide or in the markets in which we are not currently concentrating our resources. We expect to continue to invest in our research and development capabilities as we advance our product candidates to market.

Commercial Product and Clinical Development Programs

Our product pipeline is focused on viral diseases, inflammatory and autoimmune diseases, cancer, pain and bacterial infection.

Product Candidate	Clinical Indication(s)	Development Phase	Company with Marketing Rights (Region)
Principal Vertex-Led Programs			
telaprevir (VX-950)	Chronic HCV infection	Phase 2b	Vertex (North America); Mitsubishi (Far East); Janssen (Rest of World)
VX-702	Rheumatoid arthritis and other inflammatory diseases	Phase 2	Kissei (Far East); Vertex (Rest of World; Co-exclusive in certain Far East countries)
VX-770	Cystic fibrosis	Phase 1	Vertex (Worldwide)
VX-883	Bacterial infection	Preclinical	Vertex (Worldwide)
Collaborator-Led Programs			
Lexiva/Telzir (fosamprenavir calcium)*	HIV infection and AIDS	Marketed	GlaxoSmithKline (Worldwide)
brecanavir (VX-385)	HIV infection and AIDS	Phase 2	Vertex (Far East); GlaxoSmithKline (Rest of World)
VX-680	Oncology	Phase 2	Merck (Worldwide)
VX-667	Oncology	Preclinical	Merck (Worldwide)
VX-409	Pain	Preclinical	GlaxoSmithKline (Worldwide)
VX-944	Oncology	Phase 1	Avalon Pharmaceuticals (Worldwide)
VX-467	Transplant	Preclinical	Novartis (Worldwide)
Other Vertex-Led Programs			
VX-692	Bacterial infection	Preclinical	Vertex (Worldwide)
VX-398	Oncology	Preclinical	Vertex (Worldwide)
VX-166	Sepsis/Acute liver disease	Preclinical	Vertex (Worldwide)
VX-765	Psoriasis	Phase 2	Vertex (Worldwide)
pralnacasan (VX-740)	Rheumatoid arthritis and other inflammatory diseases	Phase 2	Vertex (Worldwide)
merimepodib (VX-497)	Chronic HCV infection	Phase 2	Vertex (Worldwide)

* Fosamprenavir calcium is marketed under the trade names "Lexiva" in North America and "Telzir" in the European Union. Lexiva/Telzir is a prodrug of amprenavir (marketed as Agenerase), our first drug for the treatment of HIV infection and AIDS. Lexiva/Telzir has replaced Agenerase in worldwide markets.

Recent Developments

Telaprevir (VX-950)

Telaprevir (VX-950) is our lead oral hepatitis C protease inhibitor, and one of the most advanced of a new class of antiviral treatments in development targeting HCV infection. Telaprevir (VX-950) is designed to inhibit NS3-4A serine protease, an enzyme believed to be necessary for HCV replication. The U.S. Food and Drug Administration, or FDA, has granted "Fast-Track" designation to telaprevir (VX-950).

We currently are conducting two major Phase 2b clinical trials of telaprevir (VX-950), PROVE 1 in the United States and PROVE 2 in Europe, as part of a global Phase 2b development program for that compound. The expected total number of patients, and description of each of the clinical trial arms, is set forth in the following table:

PROVE 1 and PROVE 2 Clinical Trials
telaprevir (VX-950)

Treatment Regimen	Number of Patients in PROVE 1	Number of Patients in PROVE 2	TOTAL
12-week regimens of telaprevir (VX-950) in combination with peg-IFN and RBV	20	80	100
12-week regimens of telaprevir (VX-950) in combination with only peg-IFN	0	80	80
12-week regimens of telaprevir (VX-950) in combination with peg-IFN and RBV, followed by 12 weeks of therapy with peg-IFN and RBV	80	80	160
12-week regimens of telaprevir (VX-950) in combination with peg-IFN and RBV, followed by 36 weeks of therapy with peg-IFN and RBV	80	0	80
Standard of Care HCV Treatment	80	80	160
Total	**260**	**320**	**580**

In both clinical trials, patients in the 12 and 24-week treatment arms who achieve a rapid viral response, or RVR, defined as undetectable (less than 10 IU/mL) viral levels by the end of week 4, and who maintain this status through to either week 10 or 20 respectively, will stop all treatment at the 12 or 24-week time point, respectively, and will be followed post-treatment to evaluate whether they achieve sustained viral response, or SVR. Patients in these treatment arms who do not meet the RVR criterion will continue on pegylated interferon, or peg-IFN, and ribavirin, or RBV, for a total duration of 48 weeks. The 24-week treatment arm will evaluate whether 12 weeks of additional treatment with peg-IFN and RBV adds substantially to the SVR rate compared to 12 weeks of telaprevir (VX-950) in combination with peg-IFN and RBV.

We expect that together, the two clinical trials will evaluate SVR rates in 580 treatment-naïve patients infected with genotype 1 HCV, the most prevalent form of HCV. Our global Phase 2b development program in treatment-naïve patients has three objectives: (i) to evaluate the optimal SVR rate that can be achieved with telaprevir (VX-950) therapy in combination with the current standard of care; (ii) to evaluate the optimal treatment duration for telaprevir (VX-950) combination therapy; and (iii) to evaluate the role of RBV in telaprevir (VX-950)-based therapy.

PROVE 1 is fully enrolled and we expect that PROVE 2 enrollment will be complete in the fourth quarter of 2006. In addition to PROVE 1 and PROVE 2, we expect to begin additional clinical trials of telaprevir (VX-950) in the second half of 2006, including a Phase 2b clinical trial, or the "PROVE 3" trial, in patients who have failed prior standard of care treatment. We anticipate that PROVE 3 will enroll approximately 400 patients. By the end of the first quarter of 2007, we expect to have enrolled an aggregate of approximately 1,000 patients in clinical trials of telaprevir (VX-950).

In data presented at two different scientific meetings in April and May 2006, researchers reported that 19 out of 20 patients who received 2 or 4 weeks of telaprevir (VX-950) in our earlier clinical trials, and who then received peg-IFN and RBV as follow-on therapy, demonstrated plasma HCV RNA levels that were undetectable (less than 10 IU/mL) after 12 weeks of follow-on therapy. While we believe this provides some information regarding the likelihood of continued viral suppression during 12 weeks of follow-on therapy, on-treatment results such as these are not necessarily predictive of whether or not a patient will achieve SVR. Researchers have subsequently continued to follow some of these patients during continued therapy with peg-IFN and RBV and we expect that they will update the initial data in October 2006. However, we expect that the data from the PROVE clinical trials, in which all patients in treatment arms of the trials will receive at least 12 weeks of telaprevir (VX-950) dosing, will comprise more complete and meaningful information about viral breakthrough rates, and ultimately SVR rates, in patients treated with 12 weeks or more of telaprevir (VX-950) in combination therapy. We do not expect that the follow up research conducted with the patients who received 28 or fewer days of telaprevir (VX-950) dosing to be predictive of viral breakthrough or SVR rates for telaprevir (VX-950) in combination therapy for 12 weeks or longer.

On June 30, 2006, we entered into a License, Development, Manufacturing and Commercialization Agreement with Janssen Pharmaceutica, N.V., an affiliate of the Johnson & Johnson company, for the development, manufacture and commercialization of telaprevir (VX-950). Under our agreement with Janssen, we will collaborate with Janssen to develop telaprevir (VX-950) worldwide except for the Far East, and Janssen will be responsible for commercializing the compound worldwide except for North America and the Far East. Tibotec Pharmaceuticals, Ltd., another Johnson & Johnson company, will lead the development and commercialization of telaprevir (VX-950) for Janssen. We believe that our collaboration with Janssen will accelerate our pathway to market in Europe and other markets while enabling us to invest fully in the development and commercialization of telaprevir (VX-950) in North America. We collaborate in the Far East clinical development of telaprevir (VX-950) with Mitsubishi Pharma Corporation, which began the first Phase 1 clinical trial of telaprevir (VX-950) in the Far East in the third quarter of 2006.

Under our agreement with Janssen, we have retained exclusive commercial rights to telaprevir (VX-950) in North America and will lead the global clinical development program. We received an upfront payment of $165 million in July 2006. In addition, the agreement provides for up to $380 million in milestone payments, contingent upon the successful development and commercialization of telaprevir (VX-950). Janssen will fund 50% of costs for the telaprevir (VX-950) development program for North America and the Janssen territories beginning on the date of the agreement. Janssen is responsible for commercialization of telaprevir (VX-950) in Janssen's territories and will pay us tiered royalties on any product sales, averaging in the mid-20% range, contingent upon successful development and commercialization, and will be responsible for paying certain third-party royalties related to sales in the Janssen territories. We and Janssen are each responsible for drug supply in our respective territories. In addition, in connection with the development and commercialization of telaprevir (VX-950), we will work with Tibotec to establish a global health initiative to increase the prevention, diagnosis, treatment and cure of HCV infection, to be principally directed toward developing countries.

We have successfully completed the technical development work for the Phase 3 and commercial formulation of telaprevir (VX-950). With this formulation, the dosing of telaprevir (VX-950) will be comprised of two 375 mg tablets to be taken every eight hours. We have begun to manufacture telaprevir (VX-950) drug product, in advance of obtaining regulatory marketing approval, in sufficient quantities to support a timely commercial product launch if we are successful in obtaining such approval. We expect that the level of our investment in commercial supply of telaprevir (VX-950) will increase significantly in 2007, and that we will incur significant costs to manufacture and store this inventory between now and the projected product launch.

VX-702

VX-702 is our lead oral p38 mitogen-activated protein, or MAP, kinase inhibitor, which we currently are developing for the treatment of RA. We plan to initiate a 12-week, 120 patient Phase 2a clinical trial in patients with RA in the fourth quarter of 2006 to evaluate the safety of and clinical and biomarker responses to, treatment with VX-702 on a background of methotrexate. We expect to submit an investigational new drug application with the FDA to support a Thorough QTc study of VX-702, which we expect to initiate in the fourth quarter of 2006. Pending successful outcomes of the 12-week trial and the Thorough QTc study, we plan to conduct a 6-month Phase 2b trial in approximately 400 RA patients, starting in the second half of 2007. We believe that an all oral therapeutic regimen in RA would be positioned well for those patients not ready for, or unwilling to undergo, injectable anti-cytokine therapy.

VX-770

VX-770 is an oral small molecule compound designed to potentiate the gating activity of the cystic fibrosis transmembrane regulator, or CFTR, protein, a chloride ion transporter on the cell surface that is functionally defective in patients with CF. We recently completed the dosing portion of our Phase 1 clinical trial of VX-770 in healthy volunteers and patients with CF. We currently are evaluating the full pharmacokinetic results of that trial, in which we achieved targeted blood levels of the drug candidate. We are currently evaluating the full safety results of the trial. In the multidose arms of the trial, rash was identified in some subjects. Data from the Phase 1 clinical trial will be used to select the appropriate dose of VX-770 for a Phase 2 proof of concept clinical trial of VX-770, which we expect to initiate in early 2007.

VX-883

We have elected to further invest in the preclinical and clinical development of our novel, Vertex-discovered antibiotic, VX-883, and expect to initiate a Phase 1 clinical trial of this molecule in 2008. VX-883 targets both DNA gyrase and topoisomerase IV, which are enzymes that are essential to bacteria during the replication process. VX-883 is active against Gram-positive and Gram-negative bacterial pathogens prevalent in both community and hospital settings, including certain pathogens that are less susceptible to other classes of antibiotics. VX-883 may be useful in treating infections caused by drug resistant bacteria, including methicillin resistant Staphylococcus aureus, commonly referred to as MRSA, a major and growing problem with marketed antibiotics. We hold worldwide development and commercial rights to VX-883.

VX-680

In the clinical development program being conducted by our collaborator Merck & Co., Inc. for VX-680, an investigational drug candidate targeting Aurora kinase, Merck is conducting a Phase 2 clinical trial of VX-680 in patients with advanced lung cancer. Merck is also conducting a Phase 2 clinical trial of VX-680 in patients with advanced colorectal cancer and an extended Phase 1 clinical trial of patients with hematologic cancers. Clinical results for VX-680 are emerging in blood cancers and we expect data will be communicated when it is available. We believe that there is a potential for advancement of VX-680 into late stage clinical development.

Our Strategy

Our goal is to mature into a fully integrated pharmaceutical company with industry-leading capabilities in research, development and commercialization. As we continue building these capabilities, we have elected to diversify our research and development activities across a relatively broad array of

investment opportunities in order to increase the likelihood that one or more of our product candidates will succeed.

The key elements of our strategy are:

Maximize the value of telaprevir (VX-950). Our plan is to invest early and fully in the clinical development and preparation for launch of telaprevir (VX-950), in order to maximize the value of this compound. We have designed a comprehensive clinical development program for telaprevir (VX-950) consisting of multiple concurrent trials that will study the use of telaprevir (VX-950) in over 1,000 patients through the end of Phase 2b trials, which we believe will accelerate the time to market for this compound, if approved. In addition, we have begun to manufacture telaprevir (VX-950) drug product to ensure that we have sufficient quantities to support a timely commercial product launch if we are successful in obtaining marketing approval. We expect that the level of our investment in commercial supply of telaprevir (VX-950) will increase significantly in 2007, and that we will incur significant costs to manufacture and store this inventory between now and the projected product launch. We also have retained rights to telaprevir (VX-950) in North America and will benefit from Janssen and Mitsubishi's resources and development efforts in the rest of the world as we advance the development of this compound in our territory. The goal of this early and comprehensive investment strategy in telaprevir (VX-950) is to capture the full commercial potential of the compound if it is approved for sale.

Continue to increase research and development investment to retain a greater proportion of rights to proprietary products. We intend to continue to invest significant amounts in our research and development programs. We expect that, in the future, we will fund a greater proportion of our research programs using internal funds, rather than collaborator funds. We believe that this strategy will ultimately allow us to retain greater development control of, and commercial rights to, a higher proportion of our proprietary compounds as we mature.

Invest in a broad-based portfolio of product candidates. We have elected to diversify our research and development activities across a relatively broad array of investment opportunities, due in part to the high risks associated with the biotechnology and pharmaceutical business. We plan to expend significant resources on development and commercialization of some of our drug product candidates in certain markets, and rely on collaborators to develop and commercialize certain of our other drug candidates either worldwide or in markets in which we are not currently concentrating our resources. We continually assess our portfolio of drug candidates in order to make judgments about the role of pharmaceutical company collaborators in the commercial path forward for each compound.

Continue existing and new collaborations to research, develop and commercialize products. Collaborations with pharmaceutical companies have played an important role in helping us advance our drug discovery as well as to grow and advance our product pipeline. Collaborations provide us with financial support and other valuable resources for our research programs, development resources for our clinical drug candidates and marketing and sales support for our products and product candidates. We will continue to pursue strategic transactions with collaborators to accelerate research, development and commercialization of our novel drug candidates where we believe collaborators have the development and commercial infrastructure to access therapeutic areas that would be more difficult for us to pursue. We expect that for the near term the revenue and funding from collaborations that support our development-stage compounds will provide a proportionately higher level of financial support for our research and development activities than the revenue from research collaboration agreements.

We currently are collaborating with Janssen, Merck, GlaxoSmithKline, Cystic Fibrosis Foundation Therapeutics Incorporated, Mitsubishi, Kissei and other companies.

Continue to introduce multiple product candidates into development each year. We plan to continue to add promising potential products to our development pipeline through our continuing commitment

to discovery research. In addition to our efforts to research and develop kinase inhibitors, we currently are conducting research programs in other areas, including the areas of ion channel modulation and second generation HCV protease inhibitors.

License and acquire technologies, resources and products. In addition to forging new collaborations, we also seek to opportunistically license and acquire technologies, resources and products that have the potential to strengthen our drug discovery platform, product pipeline and commercial capabilities.

Corporate Information

We were incorporated in Massachusetts in 1989. Our principal executive offices are located at 130 Waverly Street, Cambridge, Massachusetts 02139, and our telephone number is (617) 444-6100. Our internet address is *www.vrtx.com*. The information found on our website and on websites linked from it are not incorporated into or a part of this prospectus supplement or the prospectus.

The Offering

Unless otherwise indicated, all information in this prospectus supplement assumes that the underwriters do not exercise their overallotment option.

Common stock offered by Vertex	8,000,000 shares
Common stock to be outstanding after the offering	118,600,314 shares
Overallotment option	1,200,000 shares
Use of proceeds	For general corporate purposes, which may include research and development expenditures, clinical trial expenditures, manufacture and supply of drug substance and drug products, acquisitions of new technologies, capital expenditures, investments and working capital. See "Use of Proceeds" on page S-28.
Risk factors	See "Risk Factors" beginning on page S-10 and other information included in this prospectus supplement for a discussion of factors you should carefully consider before deciding to invest in shares of the common stock.
Nasdaq Global Select Market symbol	VRTX

The information above is based on 110,600,314 shares of common stock outstanding as of June 30, 2006. It does not include:

- 14,616,774 shares of common stock issuable upon the exercise of stock options outstanding as of June 30, 2006 at a weighted average exercise price of $25.30 per share;
- 1,020,900 shares of common stock issuable upon the exercise of stock options granted to employees after June 30, 2006 at a weighted exercise price of $35.27 per share;
- 148,020 restricted shares of common stock issued to employees after June 30, 2006, at a purchase price of $0.01 per share; and
- 456,340 shares of common stock reserved for issuance upon conversion of our outstanding of 5% Convertible Subordinated Notes due in September 2007 and 7,897,791 shares of common stock reserved for issuance upon conversion of our outstanding 5.75% Convertible Senior Subordinated Notes due in February 2011. In August 2006, we exchanged $58,345,000 in aggregate principal amount of 5.75% Convertible Senior Subordinated Notes due 2011 for approximately 4,064,500 shares of common stock, reducing the number of shares of common stock reserved for issuance upon conversion of the 2011 notes to 3,992,503. The 4,064,500 shares is approximately 159,000 shares more than the number of shares into which the notes were convertible under their original terms. The additional shares largely relate to unpaid interest through February 2007, when we could have called the notes.

RISK FACTORS

Investing in our common stock involves a high degree of risk. You should carefully consider the following risk factors and all other information contained in this prospectus supplement and the accompanying prospectus and incorporated by reference into the accompanying prospectus before purchasing our common stock. The risks and uncertainties described below are not the only ones facing us. Additional risks and uncertainties that we are unaware of, or that we currently deem immaterial, also may become important factors that affect us. If any of such risks or the risks described below occur, our business, financial condition or results of operations could be materially and adversely affected. In that case, the trading price of our common stock could decline, and you may lose some or all of your investment.

Risks Related to Our Business

We expect to incur future losses and we may never become profitable.

We have incurred significant operating losses each year since our inception and expect to incur a significant operating loss in 2006. We believe that operating losses will continue beyond 2006, even if we receive significant future payments under our existing and future collaborative agreements, because we are planning to make significant investments in research and development, and because we will incur significant selling, general and administrative expenses in the course of researching, developing and commercializing our product candidates. We expect that losses will fluctuate from quarter to quarter and year to year, and that such fluctuations may be substantial. We cannot predict when we will become profitable, if at all.

Many of our drug candidates are still in the early stages of development and all of our drug candidates remain subject to clinical testing and regulatory approval. If we are unable to successfully develop and test our drug candidates, we will not be successful.

The success of our business depends primarily upon our ability to develop and commercialize our drug candidates successfully. Our drug candidates are in various stages of development. Our drug candidates must satisfy rigorous standards of safety and efficacy before they can be approved by the FDA and other regulatory authorities for sale. To satisfy these standards, we must engage in expensive and lengthy testing of our drug candidates. Despite our efforts, our drug candidates may not:

offer therapeutic or other improvement over existing comparable drugs;

be proven safe and effective in clinical trials;

meet applicable regulatory standards;

be capable of being produced in commercial quantities at acceptable costs; or

if approved for commercial sale, be successfully commercialized.

Positive results in preclinical studies of a drug candidate may not be predictive of similar results in humans during clinical trials, and promising results from early clinical trials of a drug candidate may not be replicated in later clinical trials. Findings in nonclinical studies conducted concurrently with clinical trials could result in abrupt changes in our development activities, including the possible cessation of development activities associated with a drug candidate. Furthermore, results from our clinical trials may not meet the level of statistical significance required by the FDA or other regulatory authorities for approval of a drug candidate.

A number of companies in the pharmaceutical and biotechnology industries have suffered significant setbacks in late stage clinical trials even after achieving promising results in early stage development. Accordingly, the results from the completed preclinical studies and clinical trials and ongoing clinical trials for our drug candidates may not be predictive of the results we may obtain in

later stage trials, and are not predictive of the likelihood of approval of a drug candidate for commercial sale.

If we are unable to obtain U.S. and/or foreign regulatory approval, we will be unable to commercialize our drug candidates.

Our drug candidates are subject to extensive governmental regulations relating to their development, clinical trials, manufacturing and commercialization. Rigorous preclinical testing and clinical trials and an extensive regulatory approval process are required in the United States and in most other countries prior to the commercial sale of our drug candidates. Satisfaction of these and other regulatory requirements is costly, time consuming, uncertain and subject to unanticipated delays. It is possible that none of the drug candidates we are developing will be approved for marketing.

We have limited experience in conducting and managing the clinical trials necessary to obtain regulatory approvals, including approval by the FDA. The time required to complete clinical trials and for the FDA and other countries' regulatory review processes is uncertain and typically takes many years. Our analysis of data obtained from preclinical and clinical activities is subject to confirmation and interpretation by regulatory authorities, which could delay, limit or prevent regulatory approval. We may also encounter unanticipated delays or increased costs due to government regulation from future legislation or administrative action or changes in FDA policy during the period of product candidate development, clinical trials and FDA regulatory review.

Any delay in obtaining or failure to obtain required approvals could materially adversely affect our ability to successfully commercialize any drug candidate. Furthermore, any regulatory approval to market a drug product may be subject to unexpected limitations on the indicated uses for which we may market the drug product. These limitations may limit the size of the market for the drug product.

We are also subject to numerous foreign regulatory requirements governing the conduct of clinical trials, manufacturing and marketing authorization, pricing and third-party reimbursement. The foreign regulatory approval process includes all of the risks associated with the FDA approval process described above, as well as risks attributable to the satisfaction of foreign requirements. Approval by the FDA does not ensure approval by regulatory authorities outside the United States. Foreign jurisdictions may have different approval procedures than those required by the FDA and may impose additional testing requirements for our drug candidates.

If clinical trials for our drug candidates are prolonged or delayed, we may be unable to commercialize our drug candidates on a timely basis, which would require us to incur additional costs and would delay our receipt of any product revenue.

We cannot predict whether or not we will encounter problems with any of our completed, ongoing or planned clinical trials that will cause us or regulatory authorities to delay or suspend clinical trials, or delay the analysis of data from our completed or ongoing clinical trials. Any of the following could delay the clinical development of our drug candidates:

- ongoing discussions with the FDA or comparable foreign authorities regarding the scope or design of our clinical trials;
- delays in receiving or the inability to obtain required approvals from the independent institutional review board at the institution at which a clinical trial is conducted or other reviewing entities at clinical sites selected for participation in our clinical trials;
- delays in enrolling volunteers and patients into clinical trials;
- a lower than anticipated retention rate of volunteers and patients in clinical trials;

the need to repeat clinical trials as a result of inconclusive results or unforeseen complications in testing;

inadequate supply or deficient quality of drug candidate materials or other materials necessary for the conduct of our clinical trials;

unfavorable FDA inspection and review of a clinical trial site or records of any clinical or preclinical investigation;

serious and unexpected drug-related side effects experienced by participants in our clinical trials; or

the placement by the FDA of a clinical hold on a trial.

Our ability to enroll patients in our clinical trials in sufficient numbers and on a timely basis will be subject to a number of factors, including the size of the patient population, the nature of the protocol, the proximity of patients to clinical sites, the availability of effective treatments for the relevant disease and the eligibility criteria for the clinical trial. In addition, subjects may drop out of our clinical trials, and thereby possibly impair the validity or statistical significance of the trials. Delays in patient enrollment or unforeseen drop out rates may result in increased costs and longer development times. While all or a portion of these additional costs may be covered by payments under our collaborative agreements, we bear all of the costs for our development candidates for which we have no financial support from a collaborator.

We, the FDA or other applicable regulatory authorities may suspend clinical trials of a drug candidate at any time if we or they believe the subjects or patients participating in such clinical trials are being exposed to unacceptable health risks or for other reasons.

We cannot predict whether any of our drug candidates will encounter problems during clinical trials which will cause us or regulatory authorities to delay or suspend these trials, or which will delay the analysis of data from these trials. In addition, it is impossible to predict whether legislative changes will be enacted, or whether FDA regulations, guidance or interpretations will be changed, or what the impact of such changes, if any, may be. If we experience any such problems, we may not have the financial resources to continue development of the drug candidate that is affected or the development of any of our other drug candidates.

If our processes and systems are not compliant with regulatory requirements, we could be subject to delays in filing new drug applications or restrictions on marketing of products after they have been approved.

We currently are developing drug product candidates for regulatory approval for the first time since our inception, and are in the process of implementing regulated processes and systems required to obtain and maintain regulatory approval for our product candidates. Certain of these processes and systems for conducting clinical trials and manufacturing material must be compliant with regulatory requirements before we can apply for regulatory approval for our drug product candidates. These processes and systems will be subject to continual review and periodic inspection by the FDA and other regulatory bodies. If we are unable to achieve compliance in a timely fashion, we may experience delays in filing for regulatory approval for our drug product candidates. In addition, any later discovery of previously unknown problems or safety issues with approved products or manufacturing processes, or failure to comply with regulatory requirements, may result in restrictions on such products or manufacturing processes, withdrawal of products from the market, the imposition of civil or criminal penalties or a refusal by the FDA and/or other regulatory bodies to approve pending applications for marketing approval of new drugs or supplements to approved applications, any of which could have a material adverse effect on our business. In addition, we are a party to collaboration agreements that transfer responsibility for complying with specified regulatory requirements, such as filing and

maintenance of marketing authorizations and safety reporting, to our collaborator. If our collaborators do not fulfill these regulatory obligations, any products for which we or they obtain approval may be withdrawn from the market, which would have a material adverse effect on our business.

Even if we obtain regulatory approvals, our drug candidates will be subject to ongoing regulatory review. If we fail to comply with continuing U.S. and applicable foreign regulations, we could lose those approvals, and our business would be seriously harmed.

Even if we receive regulatory approval of any drug candidates that we are developing, we will be subject to continuing regulatory review, including the review of clinical results that are reported after our drug candidates become commercially available, approved drugs. Since drugs are more widely used by patients once approval has been obtained, side effects and other problems may be observed after approval that were not seen or anticipated during pre-approval clinical trials. In addition, the manufacturers and the manufacturing facilities we engage to make any of our drug candidates will also be subject to periodic review and inspection by the FDA. The subsequent discovery of previously unknown problems with the drug, manufacturers or manufacturing facilities may result in restrictions on the drug, manufacturers or facilities, including withdrawal of the drug from the market or our inability to use the facilities to make our drug. If we fail to comply with applicable continuing regulatory requirements, we may be subject to fines, suspension or withdrawal of regulatory approval, product recalls and seizures, operating restrictions and criminal prosecutions.

Our drug development efforts are data-driven and therefore potentially subject to abrupt changes in expected outcomes.

Small molecule drug discovery and development involve, initially, the identification of chemical compounds which may have promise as treatments for specific diseases. Once identified as drug candidates, compounds are subjected to years of testing in a laboratory setting, in animals and in people. Our ultimate objective is to determine whether the compounds have physical characteristics, both intrinsically and in animal and human systems and including a toxicological profile, that are compatible with clinical and commercial success in treatment of the disease being targeted. Throughout this process, experiments are conducted and data are gathered that could reinforce a decision to move to the next step in the evaluation process for a particular drug candidate, could result in uncertainty over the proper course to pursue, or could result in the termination of further drug development efforts with respect to the compound being evaluated. We monitor the results of our discovery research and our nonclinical studies and clinical trials and regularly evaluate and re-evaluate our portfolio investments with the objective of balancing risk and potential return in view of new data and scientific, business and commercial insights. This process can result in relatively abrupt changes in focus and priority as new information comes to light and we gain additional insights into ongoing programs and potential new programs.

If we are unable to attract and retain collaborators for research support and the development and commercialization of our products, we may not be able to fund our research, development and commercialization activities.

Our research, development and commercialization collaborators have agreed to fund portions of our research and development programs and/or to conduct the development and commercialization of specified product candidates and, if they are approved, products. In exchange, we have given them technology, product and marketing rights relating to those products. Some of our corporate collaborators have rights to control the planning and execution of product development and clinical programs. Our collaborators may exercise their control rights in ways that may negatively affect the timing and success of those programs. Our collaborations are subject to termination rights by the collaborators. If any of our collaborators were to terminate its relationship with us, or fail to meet its

contractual obligations, that action could have a material adverse effect on our ability to undertake research, to fund related and other programs and to develop, manufacture and market any products that may have resulted from the collaboration. We expect to seek additional collaborative arrangements, which may not be available to us, to provide research support and to develop and commercialize our products in the future. Even if we are able to establish acceptable collaborative arrangements in the future, they may not be successful.

We depend on our collaborators to work with us to develop, manufacture and commercialize many of our drug candidates.

We are currently focusing our development activities on three drug candidates, telaprevir (VX-950), VX-702, and VX-770. We have granted development and commercialization rights to telaprevir (VX-950) to Mitsubishi (Far East) and to Janssen (rest of world other than North America and Far East). We also have granted Far East rights to VX-702 to our collaborator Kissei. We expect to receive significant financial support under our Janssen collaboration agreement, as well as meaningful technical and manufacturing contributions to the telaprevir (VX-950) program. The success of our key in-house programs, such as for telaprevir (VX-950) and VX-702, is dependent upon the continued financial and other support that our collaborators have agreed to provide.

For some compounds on which we are not currently focusing our development efforts, we have granted worldwide rights to a collaborator, such as our VX-680 collaboration with Merck, our Lexiva/Telzir, brecanavir (VX-385) and VX-409 collaborations with GlaxoSmithKline and our VX-944 collaboration with Avalon Pharmaceuticals, Inc.

The success of our collaborations depends on the efforts and activities of our collaborators. Each of our collaborators has significant discretion in determining the efforts and resources that it will apply to the collaboration. Our existing collaborations may not be scientifically or commercially successful.

The risks that we face in connection with these existing and any future collaborations include the following:

- Our collaboration agreements are subject to termination under various circumstances, including, as in the case of our agreement with Janssen, termination without cause. Any such termination could delay the development and commercial sale of our drug candidates, including telaprevir (VX-950).

- Our collaborators may change the focus of their development and commercialization efforts. Pharmaceutical and biotechnology companies historically have re-evaluated their development and commercialization priorities following mergers and consolidations, which have been common in recent years in these industries. The ability of some of our product candidates to reach their potential could be limited if our collaborators decrease or fail to increase development or commercialization efforts related to those products.

- Our collaboration agreements may have the effect of limiting the areas of research and development that we may pursue, either alone or in collaboration with third parties.

- Our collaborators may develop and commercialize, either alone or with others, products that are similar to or competitive with the products that are the subject of the collaboration with us.

Our investment in the clinical development and manufacture of commercial supply of telaprevir (VX-950) may not result in any benefit to us if the product candidate is not approved for commercial sale.

We are investing significant resources in the clinical development of telaprevir (VX-950). In 2006, we increased our investment in this compound to support its global Phase 2b clinical development program. We also currently are incurring significant costs to manufacture commercial supply of telaprevir (VX-950) drug product, in advance of obtaining regulatory marketing approval, in sufficient quantities to support a timely commercial product launch if we are successful in obtaining such approval and we expect that the level of our investment in commercial supply will increase significantly in 2007. Investment in these activities at the current stage of clinical development of this compound is subject to considerable risk that telaprevir (VX-950) will not advance to product registration. If telaprevir (VX-950) is not approved for commercial sale or if its development is delayed for any reason, our full investment in this compound may be at risk and our business and financial condition could be materially adversely affected.

We depend on third-party manufacturers and suppliers, and as a result we may be subject to manufacturing and supply disruptions outside of our control.

We currently are significantly augmenting our manufacturing, supply chain and quality assurance resources for our later-stage drug product candidates. We have no experience in manufacturing pharmaceutical products and in conducting manufacturing testing programs required to obtain FDA and other regulatory approvals, and there can be no assurance that we will develop those capabilities successfully. If we are unable to establish these capabilities, we may be unable to achieve our development and commercialization goals. We are currently relying on networks of third-party manufacturers and suppliers worldwide to synthesize, tablet, and package our drug candidates for clinical trials and we expect that we will continue to do so to meet our commercial supply needs for these products, if they are approved for sale. As a result of our reliance on these third-party manufacturers and suppliers, including sole source suppliers of certain components of our product candidates and drug product, we may be subject to significant supply disruptions outside of our control. These supply disruptions may result from a number of factors including shortages in product raw materials, labor or technical difficulties, regulatory inspections or restrictions, and shipping and customs delays. We plan to identify and enter into commercial relationships with multiple suppliers of the materials and manufacturing services necessary for the synthesis, tableting and packaging of our drug candidates and, if approved for sale, our drugs. We expect that this approach will reduce our risk of supply chain disruptions by reducing our reliance on any one manufacturer or supplier, but we will remain vulnerable to disruptions arising from performance failure by a vendor in our manufacturing supply chain, particularly if we are unable to secure second sources for necessary products and services. Any supply disruptions could impact the timing of our clinical trials and the commercial launch of any approved pharmaceutical products. Furthermore, we may be required to modify our production methods to permit us to economically manufacture our products for commercial launch and sale. Upon approval of a pharmaceutical product for sale, if any, we similarly may be at risk of supply chain disruption for our commercial drug supply. These modifications may require us to reevaluate our resources and the resources of our third-party manufacturers and suppliers, which could result in abrupt changes in our production methods and supplies. The production of our drug candidates is based in part on technology that we believe to be proprietary. We have licensed this technology to enable our third-party manufacturers and suppliers to manufacture drug candidates for us. However, in the course of their services, a contract manufacturer may develop process technology related to the manufacture of our drug candidates that the manufacturer owns, either independently or jointly with us. This would increase our reliance on that manufacturer or require us to obtain a license from that manufacturer in order to have our products manufactured by other suppliers utilizing the same process.

We rely on third parties to conduct our clinical trials, and those third parties may not perform satisfactorily, including failing to meet established deadlines for the completion of such trials.

We do not have the ability to independently conduct clinical trials for our drug candidates, and we rely on third parties such as contract research organizations, medical institutions and clinical investigators to enroll qualified patients and conduct our clinical trials. Our reliance on these third parties for clinical development activities reduces our control over these activities. Accordingly, these third-party contractors may not complete activities on schedule, or may not conduct our clinical trials in accordance with regulatory requirements or our trial design. If these third parties do not successfully carry out their contractual duties or meet expected deadlines, we may be required to replace them. Although we believe that there are a number of other third-party contractors we could engage to continue these activities, it may result in a delay of the affected trial. Accordingly, our efforts to obtain regulatory approvals for and commercialize our drug candidates may be delayed.

Our sales and marketing experience is limited.

We have limited experience in marketing and selling pharmaceutical products. We must either develop a marketing and sales force or enter into arrangements with third parties to market and sell any of our product candidates that are approved by regulatory authorities. We do not know whether we will be able to enter into marketing and sales agreements with others on acceptable terms, if at all. We may not be able to successfully develop our own sales and marketing force for drug candidates for which we have retained marketing or co-promotion rights. As we develop our own marketing and sales capability, we may be competing with other companies that currently have experienced and well-funded marketing and sales operations. We have granted exclusive marketing rights for Lexiva/Telzir, brecanavir (VX-385) and VX-409 to GlaxoSmithKline worldwide (except for brecanavir (VX-385) in the Far East where we have retained rights), and for VX-680 and VX-667 to Merck. Avalon Pharmaceuticals has exclusive, worldwide marketing rights to VX-944. Mitsubishi has exclusive marketing rights to telaprevir (VX-950) in Japan and certain Far East countries and Janssen has commercialization rights to telaprevir (VX-950) worldwide except North America and the Far East. In addition, we have granted marketing rights to VX-702 to Kissei in the Far East. Even though we retain some co-promotion rights in some collaborations, to the extent that our collaborators have commercial rights to our products, any revenues we receive from those products will depend primarily on the sales and marketing efforts of others.

We may need to raise additional capital that may not be available.

We expect to incur substantial research and development and related supporting expenses as we design and develop existing and future compounds, undertake clinical trials of drug candidates resulting from such compounds, and build our manufacturing, regulatory, development and commercial capabilities. We also expect to incur substantial administrative and commercialization expenditures in the future and substantial expenses related to the filing, prosecution, defense and enforcement of patent and other intellectual property claims. We may need to make significant capital investment in building our manufacturing capacity and creating pre-launch inventory for one or more of our potential products. We anticipate that we will finance these substantial cash needs with:

- the proceeds of this offering;
- cash received from our existing collaborative agreements;
- cash received from new collaborative agreements;
- Lexiva/Telzir royalty revenue;
- existing cash reserves, together with interest earned on those reserves; and
- future product sales to the extent that we market products directly.

We expect that funds from these sources will be sufficient to fund our planned activities for at least the next eighteen months from the date of this filing. If not, it will be necessary to raise additional funds through public offerings or private placements of equity or debt securities or other methods of financing. Even if our financial resources are sufficient to meet our short or intermediate term needs, we may still decide, as we have in the past, to raise additional funds when we believe financial market conditions are favorable. Any equity financings could result in dilution to our then-existing security holders. Any debt financing, if available at all, may be on terms that, among other things, restrict our ability to pay dividends and interest (although we do not intend to pay dividends for the foreseeable future). The required interest payments associated with any significant additional debt financing could materially adversely affect our ability to service our convertible subordinated notes and convertible senior subordinated notes. The terms of any additional debt financing may also, under certain circumstances, restrict or prohibit us from making interest payments on our convertible subordinated notes and convertible senior subordinated notes. If adequate funds are not available, we may be required to curtail significantly or discontinue one or more of our research, drug discovery or development programs (including clinical trials), or attempt to obtain funds through arrangements with collaborators or others that may require us to relinquish rights to certain of our technologies or products in research or development. Additional financing may not be available on acceptable terms, if at all.

If our competitors bring superior products to market or bring their products to market before we do, we may be unable to find a market for our products.

Our products in development may not be able to compete effectively with products that are currently on the market or new products that may be developed by others. There are many other companies developing products for the same indications that we are pursuing in development. In order to compete successfully in these areas, we must demonstrate improved safety, efficacy and ease of manufacturing and gain market acceptance over competing products that may receive regulatory approval before or after our products, and over those that currently are marketed. Many of our competitors, including major pharmaceutical companies such as GlaxoSmithKline, Merck, Roche, Amgen, Boerhinger Ingelheim, Novartis, Johnson & Johnson and Schering-Plough possess substantially greater financial, technical and human resources than we possess. In addition, many of our competitors have significantly greater experience than we have in conducting preclinical and nonclinical testing and human clinical trials of new pharmaceutical products, scaling up manufacturing operations and obtaining regulatory approvals of products and manufacturing facilities. Accordingly, our competitors may succeed in obtaining regulatory approval for products more rapidly than we do. If we obtain regulatory approval and launch commercial sales of our products, we also will compete with respect to manufacturing efficiency and sales and marketing capabilities, areas in which we currently have limited experience.

If we fail to expand our human resources and manage our growth effectively, our business may suffer.

We expect that if our clinical candidates continue to progress in development, we continue to build our commercial organization and our drug discovery efforts continue to generate drug candidates, we will require significant additional investment in personnel, management systems and resources. Our ability to commercialize our products, achieve our research and development objectives, and satisfy our commitments under our collaboration agreements depends on our ability to respond effectively to these demands and expand our internal organization to accommodate additional anticipated growth. If we are unable to manage our growth effectively, there could be a material adverse effect on our business.

If we lose our technological advantages, we may not be able to compete in the marketplace.

We believe that our integrated drug discovery capability gives us a technological advantage over our competitors. However, the pharmaceutical research field is characterized by rapid technological progress and intense competition. As a result, we may not realize the expected benefits from these technologies. For example, a large pharmaceutical company, with significantly more resources than we have, could pursue a systematic approach to the discovery of drugs based on gene families, using proprietary drug targets, compound libraries, novel chemical approaches, structural protein analysis and information technologies. Such a company might identify broadly applicable compound classes faster and more effectively than we do. Further, we believe that interest in the application of structure-based drug design, parallel drug design and related approaches has accelerated as the strategies have become more widely understood. Businesses, academic institutions, governmental agencies and other public and private research organizations are conducting research to develop technologies that may compete with those we use. It is possible that our competitors could acquire or develop technologies that would render our technology obsolete or noncompetitive. For example, a competitor could develop information technologies that accelerate the atomic-level analysis of potential compounds that bind to the active site of a drug target, and predict the absorption, toxicity, and relative ease-of-synthesis of candidate compounds. If we were unable to access the same technologies at an acceptable price, our business could be adversely affected.

The loss of the services of key employees or the failure to hire qualified employees would negatively impact our business and future growth.

Because our product discovery and development activities are highly technical in nature, we require the services of highly qualified and trained scientists who have the skills necessary to conduct these activities. Our future success will depend in large part on the continued services of our key scientific and management personnel. We have entered into employment agreements with some individuals and provide compensation-related benefits to all of our key employees that vest over time and therefore induce them to remain with us. However, the employment agreements can be terminated by the employee on relatively short notice. The value to employees of stock-related benefits that vest over time such as options and restricted stock will be significantly affected by movements in our stock price that we cannot control, and may at any point in time be insufficient to counteract more lucrative offers from other companies.

We face intense competition for our scientific personnel from our competitors, our collaborators and other companies throughout our industry. Moreover, the growth of local biotechnology companies and the expansion of major pharmaceutical companies into the Boston area have increased competition for the available pool of skilled employees, especially in technical fields, and the high cost of living in the Boston and San Diego areas makes it difficult to attract employees from other parts of the country. A failure to retain, as well as hire, train and effectively integrate into our organization a sufficient number of qualified scientists and professionals would negatively impact our business and our ability to grow our business. In addition, the level of funding under certain of our collaborative agreements depends on the number of our scientists performing research under those agreements. If we cannot hire and retain the required personnel, funding received under the agreements may be reduced.

If our patents do not protect our products, or our products infringe third-party patents, we could be subject to litigation and substantial liabilities.

We have numerous patent applications pending in the United States, as well as foreign counterparts in other countries. Our success will depend, in significant part, on our ability to obtain and maintain U.S. and foreign patent protection for our products, their uses and our processes, to preserve our trade secrets and to operate without infringing the proprietary rights of third parties. We do not know whether any patents will issue from any of our patent applications or, even if patents issue

or have issued, that the issued claims will provide us with any significant protection against competitive products or otherwise be valuable commercially. Legal standards relating to the validity of patents and the proper scope of their claims in the pharmaceutical field are still evolving, and there is no consistent law or policy regarding the valid breadth of claims in biopharmaceutical patents or the effect of prior art on them. If we are not able to obtain adequate patent protection, our ability to prevent competitors from making, using and selling similar products will be limited. Furthermore, our activities may infringe the claims of patents held by third parties. Defense and prosecution of infringement or other intellectual property claims, as well as participation in other inter-party proceedings, can be expensive and time-consuming, regardless of whether or not the outcome is favorable to us. If the outcome of any such litigation or proceeding were adverse, we could be subject to significant liabilities to third parties, could be required to obtain licenses from third parties or could be required to cease sales of affected products, any of which outcomes could have a material adverse effect on our business.

We do not know whether Lexiva/Telzir will continue to be competitive in the market for HIV protease inhibitors or if brecanavir (VX-385), if approved, will be successful in the market.

We currently receive royalties from sales of Lexiva/Telzir under our collaboration with GlaxoSmithKline and will receive product royalty payments on sales of brecanavir (VX-385), if any, if brecanavir (VX-385) is approved for sale. Lexiva/Telzir's share of the worldwide protease inhibitor market may decrease due to competitive forces and market dynamics. Other HIV protease inhibitors, or HIV PIs, and a number of other products, including Viread (tenofovir dispoproxil fumerate), Sustiva (efavirenz) and Ziagen (abacavir) are on the market for the treatment of HIV infection and AIDS. Other drugs are still in development by our competitors, including Bristol-Myers Squibb, Boehringer Ingelheim and Johnson & Johnson, which may have better efficacy, fewer side effects, easier administration and/or lower costs than Lexiva/Telzir or brecanavir (VX-385). Moreover, the growth in the worldwide market for HIV PIs has, to a certain extent, occurred as a result of early and aggressive treatment of HIV infection with a protease inhibitor-based regimen. Changes in treatment strategy, in which treatment is initiated later in the course of infection, or in which treatment is more often initiated with a regimen that does not include a protease inhibitor, may result in reduced use of HIV PIs. As a result, the total market for HIV PIs may decline, decreasing the sales potential of Lexiva/Telzir and/or brecanavir (VX-385). Further, although we provide education efforts related to the promotion of Lexiva/Telzir in the United States and key markets in Europe, GlaxoSmithKline directs the majority of the marketing and sales efforts and the positioning of Lexiva/Telzir in the overall market, and we have little control over the direction or success of those efforts. GlaxoSmithKline has the right to terminate its agreement with us without cause upon twelve months' notice, and would have no obligation to pay further royalties to us upon any such termination.

If physicians, patients and third-party payors do not accept our future drugs, we may be unable to generate significant revenue, if any.

Even if our drug candidates obtain regulatory approval, they may not gain market acceptance among physicians, patients and health care payors. Physicians may elect not to recommend our drugs for a variety of reasons including:

- the timing of the market introduction of competitive drugs;
- lower demonstrated clinical safety and efficacy compared to other drugs;
- lack of cost-effectiveness;
- lack of availability of reimbursement from third-party payors;
- convenience and ease of administration;
- prevalence and severity of adverse side effects;

other potential advantages of alternative treatment methods; and

ineffective marketing and distribution support.

If our approved drugs fail to achieve market acceptance, we would not be able to generate significant revenue.

If the government and other third-party payors fail to provide coverage and adequate payment rates for our future drugs, our revenue and prospects for profitability will be harmed.

In both domestic and foreign markets, our sales of any future drugs will depend in part upon the availability of reimbursement from third-party payors. Such third-party payors include government health programs such as Medicare, managed care providers, private health insurers and other organizations. These third-party payors are increasingly attempting to contain healthcare costs by demanding price discounts or rebates and limiting both the types and variety of drugs that they will cover and the amounts that they will pay for these drugs. As a result, they may not cover or provide adequate payment for our future drugs. We might need to conduct post-marketing studies in order to demonstrate the cost-effectiveness of any future drugs to such payors' satisfaction. Such studies might require us to commit a significant amount of management time and financial and other resources. Our future drugs might not ultimately be considered cost-effective. Adequate third-party reimbursement might not be available to enable us to maintain price levels sufficient to realize an appropriate return on investment in product development.

Reimbursement rates may vary according to the use of the drug and the clinical setting in which it is used, may be based on payments allowed for lower-cost products that are already reimbursed, may be incorporated into existing payments for other products or services, and may reflect budgetary constraints and/or imperfections in Medicare or Medicaid data used to calculate these rates. Net prices for drugs may be reduced by mandatory discounts or rebates required by government health care programs. In addition, legislation has been introduced in Congress that, if enacted, would permit more widespread importation of drugs from foreign countries into the United States, which may include importation from countries where the drugs are sold at lower prices than in the United States. Such legislation, or similar regulatory changes or relaxation of laws that restrict imports of drugs from other countries, could reduce the net price we receive for our marketed drugs.

Recent federal legislation will increase the pressure to reduce prices of pharmaceutical products paid for by Medicare, which could adversely affect our revenues, if any.

The Medicare Prescription Drug Improvement and Modernization Act of 2003, or MMA, changed the way Medicare will cover and pay for pharmaceutical products. The legislation expanded Medicare coverage for drug purchases by the elderly and eventually will introduce a new reimbursement methodology based on average sales prices for drugs. In addition, this legislation provides authority for limiting the number of drugs that will be covered in any therapeutic class. As a result of this legislation and the expansion of federal coverage of drug products, we expect that there will be additional pressure to contain and reduce costs. These cost reduction initiatives and other provisions of this legislation could decrease the coverage and price that we receive for any approved products and could seriously harm our business. While the MMA applies only to drug benefits for Medicare beneficiaries, private payors often follow Medicare coverage policy and payment limitations in setting their own reimbursement rates, and any reduction in reimbursement that results from the MMA may result in a similar reduction in payments from private payors.

Our business has a substantial risk of product liability claims. If we are unable to obtain appropriate levels of insurance, a product liability claim could adversely affect our business.

Our business exposes us to significant potential product liability risks that are inherent in the development, manufacturing and sales and marketing of human therapeutic products. We currently have clinical trial insurance and will seek to obtain product liability insurance prior to the sales and marketing of any of our drug candidates. However, our insurance may not provide adequate coverage against potential liabilities. Furthermore, clinical trial and product liability insurance is becoming increasingly expensive. As a result, we may be unable to maintain current amounts of insurance coverage or obtain additional or sufficient insurance at a reasonable cost to protect against losses that could have a material adverse effect on us. If a claim is brought against us, we might be required to pay legal and other expenses to defend the claim, as well as uncovered damages awards resulting from a claim brought successfully against us. Furthermore, whether or not we are ultimately successful in defending any such claims, we might be required to direct significant financial and managerial resources to such defense, and adverse publicity is likely to result.

If we do not comply with laws regulating the protection of the environment and health and human safety, our business could be adversely affected.

Our research and development efforts involve the controlled use of hazardous materials, chemicals and various radioactive compounds. Although we believe that our safety procedures for handling and disposing of these materials comply with the standards prescribed by state and federal regulations, the risk of accidental contamination or injury from these materials cannot be eliminated. If an accident occurs, we could be held liable for resulting damages, which could be substantial. We are also subject to numerous environmental, health and workplace safety laws and regulations, including those governing laboratory procedures, exposure to blood-borne pathogens and the handling of biohazardous materials. Although we maintain workers' compensation insurance to cover us for costs we may incur due to injuries to our employees resulting from the use of these materials, this insurance may not provide adequate coverage against potential liabilities. Due to the small amount of hazardous materials that we generate, we have determined that the cost to secure insurance coverage for environmental liability and toxic tort claims far exceeds the benefits. Accordingly, we do not maintain any insurance to cover pollution conditions or other extraordinary or unanticipated events relating to our use and disposal of hazardous materials. Additional federal, state and local laws and regulations affecting our operations may be adopted in the future. We may incur substantial costs to comply with, and substantial fines or penalties if we violate any of these laws or regulations.

Our outstanding indebtedness may make it more difficult to obtain additional financing or reduce our flexibility to act in our best interests.

As of August 31, 2006, we had approximately $42.1 million in aggregate principal amount of 5% Convertible Subordinated Notes due in September 2007 and approximately $59.6 million in aggregate principal amount of 5.75% Convertible Senior Subordinated Notes due in February 2011 outstanding. The high level of our indebtedness will affect us by:

- exposing us to fixed rates of interest, which may be in excess of prevailing market rates;
- making it more difficult to obtain additional financing for working capital, capital expenditures, debt service requirements or other purposes;
- constraining our ability to react quickly in an unfavorable economic climate or to changes in our business or the pharmaceutical industry; and
- requiring the dedication of a substantial portion of our expected cash flow to service of our indebtedness, thereby reducing the amount of expected cash flow available for other purposes.

Our estimates of our liability under our Kendall Square lease may be inaccurate.

We leased a 290,000 square foot facility in Kendall Square, Cambridge, Massachusetts in January 2003 for a 15-year term. Under the lease, we are required to complete certain build-outs and improvements of the facility. We currently occupy approximately 120,000 square feet of the facility. We have sublease arrangements in place for the remaining rentable square footage of the facility. In determining our obligations under the lease for the portion of the facility that we do not expect to occupy, we have made certain assumptions relating to the costs that will be incurred to satisfy our build-out commitments under the lease, operating costs, the time necessary to sublease the space after the expiration of the initial subleases, projected future sublease rental rates and the anticipated durations of future subleases. Our estimates have changed in the past, and may change in the future, resulting in additional adjustments to the estimate of liability, and the effect of any such adjustments could be material.

Government investigations or litigation against our collaborators could impact our business.

The federal government, certain state governments and private payors are investigating and have begun to file actions against numerous pharmaceutical and biotechnology companies alleging that the reporting of prices for pharmaceutical products has resulted in a false and overstated Average Wholesale Price, or AWP, which in turn is alleged to have improperly inflated the reimbursement paid by Medicare beneficiaries, insurers, state Medicaid programs, medical plans and others to health care providers who prescribed and administered those products. Some payors are also alleging that pharmaceutical and biotechnology companies are not reporting their "best price" to the states under the Medicaid program. In addition, recent government litigation against pharmaceutical companies has focused on allegations of off-label promotion in connection with the filing of false claims for government reimbursement. In any AWP cases or other cases brought by the government where our collaborators or licensees are named as defendants with respect to any products licensed from us, the outcome of the case could have a material adverse effect on our financial results.

Risks Related to Our Common Stock and This Offering

Our stock price may fluctuate based on factors beyond our control.

Market prices for securities of companies such as Vertex are highly volatile. Within the twelve months ended August 31, 2006, our common stock traded between $17.42 and $44.71. The market for our stock, like that of other companies in the biotechnology field, has from time to time experienced significant price and volume fluctuations that are unrelated to our operating performance. The future market price of our securities could be significantly and adversely affected by factors such as:

- announcements of results of nonclinical studies or clinical trials;
- announcements of financial results and other operating performance measures, or capital structuring activities;
- technological innovations or the introduction of new products by our competitors;
- developments relating specifically to other companies and market conditions for pharmaceutical and biotechnology stocks in general;
- government regulatory action;
- public concern as to the safety of products developed by others;
- developments in patent or other intellectual property rights or announcements relating to these matters;

developments in domestic and international governmental policy or regulation, for example relating to intellectual property rights; and

developments relating specifically to other companies and market conditions for pharmaceutical and biotechnology stocks in general.

Management will have broad discretion as to the use of the proceeds from this offering, and we may not use the proceeds effectively.

We have not designated the amount of net proceeds we will use for any particular purpose. Accordingly, our management will have broad discretion as to the application of the net proceeds and could use them for purposes other than those contemplated at the time of this offering. Our stockholders may not agree with the manner in which our management chooses to allocate and spend the net proceeds. Moreover, our management may use the net proceeds for corporate purposes that may not yield profitable results or increase our market value.

Sales of additional shares of our common stock could cause the price of our common stock to decline.

Sales of substantial amounts of our common stock in the open market, or the availability of such shares for sale, could adversely affect the price of our common stock. In addition, the issuance of common stock upon exercise of any outstanding option or the conversion of any of our outstanding convertible debt could be dilutive, and may cause the market price for a share of our common stock to decline. As of August 31, 2006, we had approximately 115.1 million shares of common stock issued and outstanding, together with outstanding options to purchase approximately 15.2 million shares of common stock with a weighted average exercise price of $26.13 per share, and notes convertible into approximately 4.4 million shares of common stock with conversion prices of $14.94 and $92.26 per share and a weighted average conversion price of $22.87 per share. Outstanding options and convertible notes may be exercised or converted, as the case may be, if the market price of our common stock exceeds the applicable exercise or conversion price.

You will experience immediate dilution in the book value per share of the common stock you purchase.

Because the price per share of our common stock being offered is substantially higher than the net tangible book value per share of our common stock, you will suffer substantial dilution in the net tangible book value of the common stock you purchase in this offering. Based on an assumed public offering price of $35.34 per share, if you purchase shares of common stock in this offering, you will suffer immediate and substantial dilution of $31.62 per share in the net tangible book value of the common stock. If the underwriters exercise their overallotment option, you will experience additional dilution. See "Dilution" on page S-28 for a more detailed discussion of the dilution you will incur in this offering.

Anti-takeover provisions of Massachusetts law, provisions in our charter and bylaws and our stockholders' rights plan, or poison pill, could make a third-party acquisition of us difficult and may frustrate any attempt to remove or replace our current management.

Because we are a Massachusetts corporation, the anti-takeover provisions of Massachusetts law could make it more difficult for a third party to acquire control of us, even if the change in control would be beneficial to stockholders. We are subject to the provisions of Chapter 110F of the Massachusetts General Laws, which prohibits us from engaging in certain business combinations, unless the business combination is approved or consummated in a prescribed manner. We are subject to the provisions of Chapter 110D of the Massachusetts General Laws which prohibits voting by any stockholder who acquires 20% or more of our voting stock without stockholder approval.

Our corporate charter and by-law provisions and stockholder rights plan may discourage certain types of transactions involving an actual or potential change of control of Vertex that might be beneficial to the Company or its security holders. Our charter provides for staggered terms for the members of the Board of Directors. Our by-laws grant the directors a right to adjourn annual meetings of stockholders, and certain provisions of the by-laws may be amended only with an 80% stockholder vote. Pursuant to our stockholder rights plan, each share of common stock has an associated preferred share purchase right. The rights will not trade separately from the common stock until, and are exercisable only upon, the acquisition or the potential acquisition through tender offer by a person or group of 15% or more of the outstanding common stock. We may issue shares of any class or series of preferred stock in the future without stockholder approval and upon such terms as our Board of Directors may determine. The rights of the holders of common stock will be subject to, and may be adversely affected by, the rights of the holders of any class or series of preferred stock that may be issued in the future. As a result, stockholders or other parties may find it more difficult to remove or replace our current management.

These provisions may discourage certain types of transactions in which our stockholders might otherwise receive a premium for their shares over then current market price, and may limit the ability of our stockholders to approve transactions that they think may be in their best interests.

SPECIAL NOTE REGARDING FORWARD-LOOKING STATEMENTS

This prospectus supplement, the accompanying prospectus and the documents incorporated by reference in the accompanying prospectus contain forward-looking statements within the meaning of Section 27A of the Securities Act of 1933, as amended and Section 21E of the Securities Exchange Act of 1934, as amended. These statements relate to future events and our future financial performance. These statements include but are not limited to statements:

that we expect to continue to invest in our research and development capabilities as we advance our product candidates to market;

that set forth the expected total number of patients, and descriptions of each of the clinical trial arms in our two major Phase 2b clinical trials of telaprevir (VX-950);

that we expect together, PROVE 1 and PROVE 2 trials will evaluate SVR rates in 580 treatment-naïve patients infected with genotype 1 HCV;

that we expect PROVE 2 enrollment will be complete in the fourth quarter of 2006;

that we expect to begin additional clinical trials of telaprevir (VX-950) in the second half of 2006, including PROVE 3 in patients who have failed prior standard of care treatment;

that we anticipate PROVE 3 will enroll approximately 400 patients;

that by the end of the first quarter of 2007, we expect to have enrolled an aggregate of approximately 1,000 patients in clinical trials of telaprevir (VX-950);

that we expect that in October 2006, researchers will update data on patients undergoing follow-on therapy after participating in earlier, short-duration (2 to 4 week) clinical trials of telaprevir (VX-950);

that we believe our collaboration with Janssen will accelerate our pathway to market in Europe and other markets while enabling us to invest fully in the development and commercialization of telaprevir (VX-950) in North America;

that the dosing of telaprevir (VX-950) will be comprised of two 375 mg tablets to be taken every eight hours;

that we expect the level of our investment in commercial supply of telaprevir (VX-950) will increase significantly in 2007, and that we will incur significant costs to manufacture and store this inventory between now and the projected product launch;

that we plan to initiate a 12-week, 120 patient Phase 2a clinical trial in patients with RA in the fourth quarter of 2006 to evaluate the safety of, and clinical and biomarker responses to, treatment with VX-702 on a background of methotrexate;

that we expect to submit an investigational new drug application with the FDA to support a Thorough QTc study of VX-702, which we expect to initiate in the fourth quarter of 2006;

that pending successful outcomes of the 12-week trial and the Thorough QTc study, we plan to conduct a 6-month Phase 2b trial in approximately 400 RA patients, starting in the second half of 2007;

that we believe an all oral therapeutic regimen in RA would be positioned well for those patients not ready for, or unwilling to undergo, injectable anti-cytokine therapy;

that we expect to initiate a Phase 2 proof of concept clinical trial of VX-770 in early 2007;

that we have elected to further invest in the preclinical and clinical development of our novel, Vertex-discovered antibiotic, VX-883, and expect to initial a Phase 1 clinical trial of this molecule in 2008;

that VX-883 may be useful in treating infections caused by drug resistant bacteria, including methicillin resistant Staphylococcus aureus, commonly referred to as MRSA, a major and growing problem with marketed antibiotics;

that clinical results are emerging for VX-680 in blood cancers and we expect data will be communicated when it is available;

that we believe there is a potential for advancement of VX-680 into late stage clinical development;

that our plan is to invest early and fully in the clinical development and preparation for launch of telaprevir (VX-950), in order to maximize the value of this compound;

that we have designed a comprehensive clinical development program for telaprevir (VX-950) consisting of multiple concurrent trials that will study the use of telaprevir (VX-950) in over 1,000 patients through the end of Phase 2b trials, which we believe will accelerate the time to market for this compound, if approved;

that we intend to continue to invest significant amounts in our research and development programs;

that we expect that, in the future, we will fund a greater proportion of our research programs using internal funds, rather than collaborator funds;

that we believe that this strategy will ultimately allow us to retain greater development control of, and commercial rights to, a higher proportion of our proprietary compounds as we mature;

that we plan to expend significant resources on development and commercialization of some of our drug product candidates in certain markets, and rely on collaborators to develop and commercialize certain of our other drug candidates either worldwide or in markets in which we are not currently concentrating our resources;

that we will continue to pursue strategic transactions with collaborators to accelerate research, development and commercialization of our novel drug candidates where we believe collaborators have the development and commercial infrastructure to access therapeutic areas that would be more difficult for us to pursue;

that we expect for the near term the revenue and funding from collaborations that support our development-stage compounds will provide a proportionately higher level of financial support for our research and development activities than the revenue from research collaboration agreements;

that we plan to continue to add promising potential products to our development pipeline through our continuing commitment to discovery research;

that we will also seek to opportunistically license and acquire technologies, resources and products that have the potential to strengthen our drug discovery platform, product pipeline and commercial capabilities;

that our losses on a quarterly and annual basis will continue;

that we expect to receive significant financial support under our Janssen collaboration agreement, as well as meaningful technical and manufacturing contributions to the telaprevir (VX-950) program;

that we expect the level of our investment in commercial supply of telaprevir (VX-950) drug product will increase significantly in 2007;

that we are currently relying on networks of third-party manufacturers and suppliers worldwide to synthesize, tablet, and package our drug candidates for clinical trials and we expect that we will continue to do so to meet our commercial supply needs for these products, if they are approved for sale;

that we plan to identify and enter into commercial relationships with multiple suppliers of the materials and manufacturing services necessary for the synthesis, tableting and packaging of our drug candidates and, if approved for sale, our drugs;

that we expect this approach will reduce our risk of supply chain disruptions by reducing our reliance on any one manufacturer or supplier;

that we expect funds from our anticipated sources will be sufficient to fund our planned activities for at least the next eighteen months from the date of this filing; and

that we expect if our clinical candidates continue to progress in development, we continue to build our commercial organization and our drug discovery efforts continue to generate drug candidates, we will require significant additional investment in personnel, management systems and resources.

In some cases, you can identify forward-looking statements by terminology such as "may," "will," "should," "expects," "anticipates," "believes," "estimates," "predicts," "potential," or "continue" or the negative of such terms or other comparable terminology. These statements are only predictions and involve known and unknown risks, uncertainties and other factors, including the risks outlined above under "Risk Factors," that may cause our or our industry's actual results to differ materially from the results, levels of activity, performance or achievements expressed or implied by such forward-looking statements. Before deciding to purchase our securities you should carefully consider the risks described in the "Risk Factors" section, in addition to the information set forth in this prospectus supplement and in the prospectus and the documents incorporated by reference therein. Although we believe that the expectations reflected in the forward-looking statements are reasonable, we cannot guarantee future results, levels of activity, performance or achievements.

USE OF PROCEEDS

We estimate that the net proceeds we will receive from this offering, assuming a public offering price of $35.34 per share, will be approximately $268.3 million, after deducting the underwriting discounts and our estimated offering expenses. If the underwriters exercise their overallotment option, we estimate that our net proceeds will be approximately $308.7 million. We intend to use the net proceeds from this offering for general corporate purposes, which may include research and development expenditures, clinical trial expenditures, manufacture and supply of drug substance and drug products, acquisitions of new technologies, capital expenditures, investments and working capital.

We have not determined the amounts we plan to spend on any of the areas listed above or the timing of these expenditures. As a result, our management will have broad discretion to allocate the net proceeds from this offering. We have no current plans, commitments or agreements with respect to any acquisitions and may not make any acquisitions. Pending application of the net proceeds as described above, we intend to invest the net proceeds of the offering in short-term, investment-grade, interest-bearing securities.

DILUTION

If you purchase our common stock in this offering, your interest will be diluted to the extent of the difference between the public offering price per share and the net tangible book value per share of our common stock after this offering. We calculate net tangible book value per share by subtracting our total liabilities from our total tangible assets and dividing the difference by the number of outstanding shares of our common stock. Total tangible assets excludes deferred debt costs included in other assets on our condensed consolidated balance sheets at June 30, 2006.

Our net tangible book value at June 30, 2006 was $173.0 million, or $1.56 per share, based on 110.6 million shares of our common stock outstanding. After giving effect to the sale of 8,000,000 shares of common stock by us at an assumed public offering price of $35.34 per share, less the underwriting discounts and commissions and our estimated offering expenses, our net tangible book value at June 30, 2006 would be $441.3 million, or $3.72 per share. This represents an immediate increase in net tangible book value of $2.16 per share to existing stockholders and an immediate dilution of $31.62 per share to investors in this offering. The following table illustrates this per share dilution:

Assumed public offering price per share		$ 35.34
Net tangible book value per share as of June 30, 2006	$ 1.56	
Increase per share attributable to new investors purchasing shares in this offering	$ 2.16	
Net tangible book value per share after this offering		3.72
Dilution per share to new investors		$ 31.62

This does not reflect our issuance of 4,064,500 shares of common stock in August 2006 in connection with the exchange of $58,345,000 in principal amount of the 5.75% Convertible Senior Subordinated Notes due in February 2011, plus unpaid interest thereon.

PRICE RANGE OF COMMON STOCK

Our common stock is listed on the Nasdaq Global Select Market under the symbol "VRTX." The last reported sale price for our common stock on September 8, 2006 was $35.34 per share. The table below sets forth closing information on the range of high and low closing prices for our common stock during the periods indicated.

	Price Range of Common Stock	
	High	**Low**
Fiscal Year ended December 31, 2004:		
Quarter Ended:		
March 31, 2004	$ 11.37	$ 8.90
June 30, 2004	10.84	8.17
September 30, 2004	10.88	8.17
December 31, 2004	11.91	10.01
Fiscal Year ended December 31, 2005:		
Quarter Ended:		
March 31, 2005	$ 11.99	$ 9.23
June 30, 2005	17.06	8.61
September 30, 2005	22.68	15.33
December 31, 2005	29.24	20.31
Fiscal Year ended December 31, 2006:		
Quarter Ended:		
March 31, 2006	$ 27.90	$ 44.20
June 30, 2006	29.26	39.50
September 30, 2006 (through September 8, 2006)	30.12	36.57

DIVIDEND POLICY

We have never declared or paid any cash dividends on our common stock, and we currently expect that future earnings, if any, will be retained for use in our business. Accordingly, we do not expect to pay cash dividends on our common stock in the foreseeable future.

CAPITALIZATION

The following table sets forth our capitalization as of June 30, 2006:

- on an actual basis;
- on a pro forma basis to give effect to the issuance of 4,064,500 shares of common stock in August 2006 in connection with the exchange of $58,345,000 in principal amount of the 5.75% Convertible Senior Subordinated Notes due in February 2011, plus unpaid interest thereon; and
- on a pro forma as adjusted basis to give effect to the issuance and sale of the common stock (assuming no exercise of the underwriters' overallotment option) in this offering, assuming a public offering price of $35.34 per share, and after deducting the underwriting discounts and commissions and estimated offering expenses payable by us.

The table excludes the following shares:

- 14,616,774 shares of common stock issuable upon the exercise of stock options outstanding as of June 30, 2006 at a weighted average exercise price of $25.30 per share;
- 1,020,900 shares of common stock issuable upon the exercise of stock options granted to employees after June 30, 2006 at a weighted exercise price of $35.27 per share;
- 148,020 restricted shares of common stock issued to employees after June 30, 2006 at a purchase price of $0.01 per share; and
- 8,354,131 shares of common stock on an actual basis and 4,448,843 shares of common stock on a pro forma basis and a pro forma as adjusted basis reserved for issuance upon conversion of our outstanding 5% Convertible Subordinated Notes due in September 2007 and 5.75% Convertible Senior Subordinated Notes due in February 2011.

You should read this table with the financial statements and the notes thereto incorporated by reference into the accompanying prospectus.

	June 30, 2006 (Unaudited) (In thousands, except share data)		
	Actual	Pro Forma(1)	Pro Forma As Adjusted(1)
Collaborator development loan	$ 19,997	$ 19,997	$ 19,997
Convertible subordinated notes (due September 2007)	42,102	42,102	42,102
Convertible senior subordinated notes (due February 2011)	117,993	59,648	59,648
Stockholders' equity (deficit):			
Preferred stock, $0.01 par value; 1,000,000 shares authorized; none issued and outstanding at June 30, 2006			
Common stock, $0.01 par value; 200,000,000 shares authorized; 110,600,314 shares actual, 114,664,814 shares pro forma, 122,664,814 shares pro forma as adjusted, issued and outstanding at June 30, 2006	$ 1,089	$ 1,130	$ 1,210
Additional paid-in capital	1,282,984	1,347,176	1,615,387
Accumulated other comprehensive income	8,252	8,252	8,252
Accumulated deficit	(1,117,329)	(1,122,480)	(1,122,480)
Total stockholders' equity	174,996	234,078	502,369
Total capitalization	$ 355,088	$ 355,825	$ 624,116

(1) In August 2006, we exchanged approximately 4.1 million shares of newly issued common stock for $58.3 million in aggregate principal amount of outstanding 5.75% Convertible Subordinated Notes due in February 2011, plus unpaid interest thereon. As a result of this exchange, we incurred a non-cash charge of approximately $5.2 million. This charge is related to the incremental shares issued in the transaction over the number that would have been issued upon the conversion of these notes under their original conversion terms. The following items related to this exchange were recorded as an offset to additional paid in capital: accrued interest of approximately $1.6 million; and remaining unamortized issuance costs and estimated expenses of the exchanged notes of approximately $0.8 million.

UNDERWRITING

We intend to offer the shares of common stock through the underwriters named below. Merrill Lynch, Pierce, Fenner & Smith Incorporated is acting as representative of the underwriters named below. Subject to the terms and conditions described in a purchase agreement among us and the underwriters, we have agreed to sell to the underwriters, and the underwriters severally have agreed to purchase from us, the number of shares listed opposite their names below.

Underwriter	Number of Shares
Merrill Lynch, Pierce, Fenner & Smith Incorporated	
Morgan Stanley & Co. Incorporated	
UBS Securities LLC	
Total	8,000,000

The underwriters have agreed to purchase all of the shares sold under the purchase agreement if any of these shares are purchased. If an underwriter defaults, the purchase agreement provides that the purchase commitments of the non-defaulting underwriters may be increased or the purchase agreement may be terminated.

We have agreed to indemnify the underwriters against certain liabilities, including liabilities under the Securities Act of 1933, as amended, or to contribute to payments the underwriters may be required to make in respect of those liabilities.

The underwriters are offering the shares, subject to prior sale, when, as and if issued to and accepted by them, subject to approval of legal matters by their counsel, including the validity of the shares, and other conditions contained in the purchase agreement, such as the receipt by the underwriters of officers' certificates and legal opinions. The underwriters reserve the right to withdraw, cancel or modify offers to the public and to reject orders in whole or in part.

Commissions and Discounts

The representative has advised us that the underwriters propose initially to offer the shares to the public at the public offering price on the cover page of this prospectus supplement and to dealers at that price less a concession not in excess of $ per share. The underwriters may allow, and the dealers may reallow, a discount not in excess of $ per share to other dealers. After the offering, the public offering price, concession and discount may be changed.

The following table shows the public offering price, underwriting discount and proceeds before expenses to us. The information assumes either no exercise or full exercise by the underwriters of their overallotment option.

	Per Share	Without Option	With Option
Public offering price	$	$	$
Underwriting discount	$	$	$
Proceeds, before expenses, to Vertex	$	$	$

The expenses of the offering, not including the underwriting discount (and assuming no exercise of the overallotment option), are estimated at $1,000,000 and are payable by us.

Overallotment Option

We have granted an option to the underwriters to purchase up to 1,200,000 additional shares at the public offering price less the underwriting discount. The underwriters may exercise this option for 30 days from the date of this prospectus supplement solely to cover any overallotments. If the underwriters exercise this option, each will be obligated, subject to conditions contained in the purchase agreement, to purchase a number of additional shares proportionate to that underwriter's initial amount reflected in the above table.

No Sale of Similar Securities

We, our directors and our executive officers have agreed, with certain exceptions, not to sell or transfer any common stock for 90 days after the date of this prospectus supplement without first obtaining the consent of Merrill Lynch. Specifically, we and these directors and officers have agreed, subject to such exceptions, not to directly or indirectly:

- offer, pledge, sell or contract to sell any common stock;
- sell any option or contract to purchase any common stock;
- purchase any option or contract to sell any common stock;
- grant any option, right or warrant for the sale of any common stock;
- otherwise dispose of or transfer any common stock;
- file, or cause to be filed, any registration statement under the Securities Act of 1933, as amended, with respect to any common stock; or
- enter into any swap or any other agreement or any transaction that transfers, in whole or in part, directly or indirectly, the economic consequence of ownership of any common stock, whether any such swap or transaction is to be settled by delivery of common stock or other securities, in cash or otherwise.

This lockup provision applies both to our common stock and to any securities convertible into or exchangeable or exercisable for our common stock. This lockup provision applies to common stock owned now and, subject to certain exceptions, to common stock acquired later by the person executing the agreement or for which the person executing the agreement later acquires the power of disposition.

Quotation on the Nasdaq Global Select Market

Our shares of common stock are traded on the Nasdaq Global Select Market under the symbol "VRTX."

Price Stabilization, Short Positions and Penalty Bids

Until the distribution of our shares is completed, SEC rules may limit underwriters from bidding for and purchasing our common stock. However, the representative may engage in transactions that stabilize the price of the common stock, such as bids or purchases to peg, fix or maintain that price.

If the underwriters create a short position in the common stock in connection with the offering, i.e., if they sell more shares than are listed on the cover of this prospectus supplement, the representative may reduce that short position by purchasing shares in the open market. The representative may also elect to reduce any short position by exercising all or part of the overallotment option described above. Purchases of the common stock to stabilize its price or to reduce a short position may cause the price of the common stock to be higher than it might be in the absence of such purchases.

"Covered" short sales are sales made in an amount not greater than the underwriters' option to purchase additional shares from us in the offering. The underwriters may close out any covered short position by either exercising their option to purchase additional shares or purchasing shares in the open market. In determining the source of shares to close out the covered short position, the underwriters will consider, among other things, the price of shares available for purchase in the open market as compared to the price at which they may purchase shares through the overallotment option. "Naked" short sales are any sales in excess of such option. The underwriters must close out any naked short position by purchasing stock in the open market. A naked short position is more likely to be created if the underwriters are concerned that there may be downward pressure on the price of our common stock in the open market after pricing that could adversely affect investors who purchase in the offering. Stabilizing transactions consist of various bids for or purchases of common stock made by the underwriters in the open market prior to the completion of the offering.

The underwriters may also impose a penalty bid. This occurs when a particular underwriter repays to the underwriters a portion of the underwriting discount received by it because the representative has repurchased shares sold by or for the account of such underwriter in stabilizing or short covering transactions.

Similar to other purchase transactions, the underwriters' purchases to cover the syndicate short sales may have the effect of raising or maintaining the market price of our common stock or preventing or retarding a decline in the market price of our common stock. As a result, the price of our common stock may be higher than the price that might otherwise exist in the open market. Neither we nor any of the underwriters make any representation or prediction as to the direction or magnitude of any effect that the transactions described above may have on the price of the common stock. In addition, neither we nor the underwriters make any representation that the underwriters will engage in these transactions or that these transactions, once commenced, will not be discontinued without notice.

Passive Market Making

In connection with this offering, underwriters and selling group members may engage in passive market making transactions in our common stock on the Nasdaq Global Select Market in accordance with Rule 103 of Regulation M under the Exchange Act during a period before the commencement of offers or sales of our common stock and extending through completion of the distribution. A passive market maker must display its bid at a price not in excess of the highest independent bid of that security. However, if all independent bids are lowered below the passive market maker's bid, that bid must then be lowered when specified purchase limits are exceeded.

Electronic Distribution

A prospectus in electronic format will be made available on the website maintained by Merrill Lynch. Other than the electronic prospectus, the information on the website is not part of this prospectus supplement. Merrill Lynch may agree to allocate a number of shares for sale to their online brokerage account holders.

Other Relationships

The underwriters and their affiliates have provided investment and commercial banking and financial advisory services from time to time to us in the ordinary course of business, for which they have received customary fees. Any of the underwriters or their respective affiliates may in the future engage in investment banking or other transactions of a financial nature with us or our affiliates, including the provision of advisory services and the making of loans to us or our affiliates, for which they would receive customary fees or other payments.

VALIDITY OF COMMON STOCK

The validity of the shares of common stock offered hereby will be passed upon for us by Mintz, Levin, Cohn, Ferris, Glovsky and Popeo, P.C., Boston, Massachusetts. Certain legal matters will be passed upon for the underwriters by Cleary Gottlieb Steen & Hamilton LLP, New York, New York.

8,000,000 Shares

VERTEX PHARMACEUTICALS INCORPORATED

Common Stock

PROSPECTUS SUPPLEMENT

Merrill Lynch & Co.

Morgan Stanley

UBS Investment Bank

, 2006