VERTEX PHARMACEUTICALS INC / MA
Form 424B5
June 01, 2005

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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 June 1, 2005

PROSPECTUS SUPPLEMENT
(To prospectus dated April 25, 2005)

9,500,000 Shares

VERTEX PHARMACEUTICALS INCORPORATED

Common Stock

We are offering 9,500,000 shares of our Common Stock.

Our common stock is listed on the Nasdaq National Market under the symbol "VRTX." The last reported sale price of our common stock on the Nasdaq National Market on May 27, 2005 was $14.07 per share.

Investing in our common stock involves risks. See "Risk Factors" on page S-8 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 1,425,000 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 , 2005.

Merrill Lynch & Co.

JPMorgan **UBS Investment Bank**

The date of this prospectus supplement is , 2005.

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PROSPECTUS SUPPLEMENT

PROSPECTUS

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 "Where You Can Find More Information" 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; provided that 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 serious diseases, including HIV infection, chronic hepatitis C virus ("HCV") infection, inflammatory and autoimmune disorders, cancer, pain and bacterial infection, independently and with collaborators. Our principal focus at this time is on the development and commercialization of new treatments for viral diseases, inflammatory and autoimmune diseases and cancer. Our pipeline of potential products includes several drug candidates targeting chronic HCV infection, inflammatory and autoimmune diseases such as rheumatoid arthritis and psoriasis, and cancer. Two Vertex-discovered products for the treatment of HIV infection and AIDS, Agenerase and Lexiva/Telzir, have advanced to the market.

Our goal is to mature into a fully integrated pharmaceutical company with industry-leading capabilities in research, development and commercialization of products. We focus our efforts both on programs that we expect to control throughout the development and commercialization phases, and programs that we expect will be conducted principally by collaborators. We expect to continue to invest in our research and development capabilities as we advance our product candidates to market.

Recent Developments

Vertex HCV Drug Candidates

We are developing two drug candidates targeting HCV infection through different mechanisms. Our most advanced compound is the IMPDH inhibitor merimepodib, which targets HCV indirectly and currently is in Phase IIb development. IMPDH inhibitors appear to work additively or synergistically with other treatments for HCV, including ribavirin. Vertex's second HCV drug candidate, VX-950, is one of the most advanced of a new class of antiviral treatments in development for HCV infection. We believe VX-950 has the potential to change the treatment paradigm for HCV infection.

VX-950 investigational oral viral protease inhibitor for Hepatitis C

Our investigational oral protease inhibitor, VX-950, targets HCV directly, by inhibiting hepatitis C NS3-4A protease, an enzyme necessary for HCV replication. On May 10, 2005, we announced interim results indicating that VX-950 was well-tolerated and demonstrated potent antiviral activity in a Phase Ib clinical trial. Anti-viral activity and preliminary safety data were further presented by one of the clinical investigators on May 17, 2005 at the Digestive Disease Week scientific conference ("DDW").

The data presented at DDW showed that significant reductions in HCV-RNA were observed in HCV-infected patients taking VX-950 over a period of 14 days across three dose groups 450 milligrams every 8 hours, 1,250 milligrams every 12 hours, or 750 milligrams every 8 hours. After three days of treatment, the median reduction in HCV-RNA was greater than 3 log10, a reduction of at least 1,000-fold, in all three dose groups. In the dose group receiving 750 milligrams of VX-950 every 8 hours, there was a further reduction in viral levels between days 3 and 14 of treatment, with a median HCV-RNA reduction of 4.4 log10, a 25,000-fold reduction, at day 14. At the end of 14 days of treatment, 4 of 8 patients in the 750 milligrams dose group tested HCV-RNA negative in the

quantitative Roche COBAS TaqMan assay (<30 IU/mL), and 2 of these 4 patients tested undetectable in the qualitative Roche COBAS TaqMan assay (limit of detection 10 IU/mL). Initial pharmacokinetic analyses indicate that trough blood plasma concentrations of VX-950 in the 750 milligrams dose group were approximately 42% higher than in the 450 milligrams dose group and approximately 46% higher than the 1250 milligrams dose group. Patients in all three dose groups were HCV genotype I and predominantly non-responders to interferon-based therapy.

Across the three dose groups, a total of five of the 28 patients given VX-950 in the Phase Ib study tested HCV-RNA negative in the quantitative Roche COBAS TaqMan assay (<30 IU/mL), reaching this level between day 11 and day 14. Following completion of the 14-day dosing period, a slow increase in HCV-RNA levels was observed in these five patients during a 28-day post-dosing period. Twenty-eight days after receiving their last dose of VX-950, two patients still had viral levels that were more than 1 log10 below their pre-treatment levels.

Preliminary data indicate that across the three dose groups, VX-950 was well-tolerated, with no serious adverse events or treatment discontinuations reported. In addition, no elevations of the liver enzymes ALT/AST or other adverse clinical chemistry findings were reported. Complete safety and pharmacokinetic analyses of the data from the Phase Ib study, along with viral sequencing and viral kinetic analyses, are ongoing.

Based on the results of the Phase Ib clinical study, we plan to explore the development of VX-950 both as a monotherapy and in combination with other therapies for HCV infection. We currently are planning to initiate a 14-day Phase Ib combination clinical study with a limited number of patients involving VX-950 and pegylated interferon (one of the two drugs currently used in the standard treatment for HCV infection) before the end of the year. We also plan to consult with the FDA and European regulatory authorities on additional specific development plans. Pending these discussions and those with clinical experts in the field, we currently are further planning to initiate a Phase II combination clinical study before the end of the year involving VX-950 and pegylated interferon in patients who have not previously been treated for HCV infection. In addition, we are currently planning to initiate a Phase II study of VX-950 administered as a monotherapy. Major objectives of the Phase II program will be to evaluate dose, dose regimen and treatment duration required to obtain sustained virologic responses in treated patients. We anticipate treatment durations of both one and three months in the initial Phase II VX-950 and pegylated interferon combination clinical study, and a three month treatment duration in the initial Phase II monotherapy clinical study.

We expect to file an investigational new drug ("IND") application in the second half of 2005 to support Phase II clinical development of VX-950 in the United States. In anticipation of that IND filing, we are continuing our ongoing formulation and toxicology activities. The VX-950 formulation used in the Phase Ib study allowed us to achieve good exposure following oral dosing, but we have been working to improve the formulation for purposes of pharmacokinetic performance and other characteristics. Our formulation development work to date has identified prototype formulations that achieve higher blood concentrations in animals and lower variability than the formulation used in the Phase Ib clinical study. We are in the process of further scale-up and expect to produce a solid dosage formulation in the second half of 2005 for use in the Phase II clinical program. In addition, prior to filing an IND, we expect to complete a number of non-clinical toxicology studies in support of the treatment durations in the Phase II clinical studies.

Hepatitis C Virus Infection

HCV infection causes chronic inflammation in the liver. In a majority of patients, HCV infection can persist for decades and eventually lead to cirrhosis, liver failure and liver cancer. HCV infection represents a significant medical problem worldwide. Sources at the Centers for Disease Control have estimated that approximately 2.7 million Americans are chronically infected with HCV, and the World

Health Organization estimates that there are as many as 185 million chronic carriers of the virus worldwide.

The current standard treatment for HCV infection is a combination of pegylated interferon and ribavirin. Not only is this treatment regimen associated with significant side effects, including fatigue, flu-like symptoms, depression and anemia, but approximately 50% of patients infected with HCV genotype I, the most common HCV genotype in the United States, fail to show long-term sustained response to the therapy. As a result, new safe and effective treatment options for HCV infection are needed.

Rheumatoid Arthritis

VX-702- Investigational Oral p38 MAP Kinase Inhibitor for Rheumatoid Arthritis

On May 31, 2005, we began screening patients in our Phase II clinical study with VX-702. The study will help define the safety, tolerability and clinical activity of VX-702 in approximately 300 patients with moderate to severe rheumatoid arthritis treated for three months. The double-blind, randomized, placebo-controlled Phase II study will assess two doses of VX-702 compared to placebo. VX-702 will be dosed once-daily as monotherapy.

Commercial Products and Clinical Development Programs

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

Therapeutic Area, Product and Product Candidates	Clinical Indications	Development Phase	Company With Marketing Rights (Region)
Viral Diseases			
Lexiva/Telzir (fosamprenavir calcium)*	HIV infection	Marketed	GlaxoSmithKline (Worldwide)**
Merimepodib (VX-497)	Chronic hepatitis C virus infection	Phase II	Vertex (Worldwide)
VX-950	Chronic hepatitis C virus infection	Phase I	Mitsubishi (Far East); Vertex (Rest of World)
VX-385	HIV infection	Phase II	Vertex (Far East); GlaxoSmithKline (Rest of World)
Inflammatory and Autoimmune Diseases			
VX-765	Psoriasis and other autoimmune diseases	Phase II	Vertex (Worldwide)
VX-702	Rheumatoid arthritis and other inflammatory diseases	Phase II	Kissei (Far East); Vertex (Rest of World; Co-exclusive in certain Far East countries)
Pralnacasan (VX-740)	Rheumatoid arthritis and other inflammatory and autoimmune diseases	Phase II	Vertex (Worldwide)
Cancer			
VX-680	Oncology	Phase I	Merck (Worldwide)
VX-944	Oncology	Phase I	Avalon Pharmaceuticals (Worldwide)
VX-322	Oncology	Preclinical	Novartis (Worldwide)

* Fosamprenavir calcium is marketed under the trade names Lexiva in North America and Telzir in the European Union. Lexiva/Telzir, a prodrug of our first marketed HIV drug, Agenerase (amprenavir), also marketed by GlaxoSmithKline, is replacing Agenerase in world markets.

** Vertex has co-promotion rights in the United States and the European Union.

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:

Broadly advance our HCV portfolio. We are developing two drug candidates targeting HCV infection through different mechanisms. We plan to explore the development of VX-950 both as a

monotherapy and in combination with other therapies for HCV infection. We also are exploring the development of merimepodib as an additive anti-viral agent for use with both the current standard of care, and with other evolving therapies, to treat HCV infection. We believe that these drug candidates could form the basis of an exclusively oral therapy alternative for the treatment of HCV infection.

Maximize commercial opportunity for our products. We seek to develop and market breakthrough products and to advance the products ourselves in therapeutic areas where we believe commercialization can be effective with comparatively fewer resources, through the use of a specialist-focused sales force. We expect to retain control of the development of our HCV product candidates and certain of our other product candidates that are in areas where we currently believe we can compete effectively. 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. We expect to focus our Vertex-controlled commercialization efforts in North America, and to concentrate on identifying collaborative relationships for development of our HCV infection and inflammation product candidates outside of North America.

Continue existing and new collaborations to research, develop and commercialize products. 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 are currently seeking alliances for VX-409 and VX-692 under collaborative arrangements that would reinforce this strategy.

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 currently are collaborating with Novartis Pharma AG, GlaxoSmithKline plc, Merck & Co., Inc., Mitsubishi Pharma Corp., Kissei Pharmaceutical Co., Ltd., Cystic Fibrosis Foundation Therapeutics Incorporated 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. We believe our drug design approach integrates biology, chemistry, biophysics, automation and information technologies to make the drug discovery process more efficient and productive. In addition to our efforts to research and develop kinase inhibitors, we currently are conducting research programs in other areas, including the area of ion channel modulation.

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	9,500,000 shares
Common stock to be outstanding after the offering	90,703,170 shares
Overallotment option	1,425,000 shares
Use of proceeds	For general corporate purposes, which may include working capital, capital expenditures, research and development expenditures, clinical trial expenditures, acquisitions of new technologies, and investments. See "Use of Proceeds" on page S-20.
Nasdaq National Market symbol	VRTX

The information above is based on 81,203,170 shares of common stock outstanding as of March 31, 2005. It does not include:

- 16,538,000 shares of common stock issuable upon the exercise of stock options outstanding as of March 31, 2005 at a weighted average exercise price of $21.93 per share;
- 35,000 shares of common stock issuable upon the exercise of stock options granted to employees after March 31, 2005 at a weighted exercise price of $11.74 per share;
- 18,000 restricted shares of common stock issued to employees after March 31, 2005, at a purchase price of $0.01 per share; and
- 16,454,000 shares of common stock reserved for issuance upon conversion of our outstanding convertible 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 2005. We believe that operating losses will continue beyond 2005, 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 and developing our potential products. 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.

We do not know whether Lexiva/Telzir will continue to be competitive in the market for HIV protease inhibitors.

We currently receive royalties from sales of Lexiva/Telzir and Agenerase, two HIV protease inhibitors discovered in our collaboration with GlaxoSmithKline. Agenerase sales have decreased, which we attribute to the availability and acceptance of Lexiva/Telzir, and we anticipate that this trend will continue until Agenerase is largely replaced by Lexiva/Telzir in the market. Lexiva/Telzir's share of the worldwide protease inhibitor market may decrease due to competitive forces and market dynamics. Other HIV protease inhibitors and a number of other products, including Gilead Science's Viread, Bristol-Myers Squibb's Sustiva and GlaxoSmithKline's Ziagen, 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 and Boehringer Ingelheim, which may have better efficacy, fewer side effects, easier administration and/or lower costs than Lexiva/Telzir. Moreover, the growth in the worldwide market for HIV protease inhibitors 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 protease inhibitors. In addition, the clinical benefit of strategies used by clinicians to boost drug levels of Lexiva/Telzir by co-administering other antiretroviral agents may not prove to be effective, or may not result in increased revenues. As a result, the total market for protease inhibitors may decline, decreasing the sales potential of Lexiva/Telzir. Further, although we co-promote Lexiva/Telzir in the U.S. 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 upon any such termination. In such event, we may not be positioned to take over sales of Lexiva/Telzir or to license rights to Lexiva/Telzir to another company.

We may not successfully develop our drug pipeline.

All of the product candidates that we are pursuing independently and with collaborators will require extensive additional development, testing and investment, as well as regulatory approvals, prior to commercialization. Our product research and development efforts may not be successful. Our drug candidates may not enter preclinical, nonclinical or clinical studies as or when anticipated and may not receive required regulatory approvals. Moreover, our products, if introduced, may not be commercially successful. The results of nonclinical and initial clinical trials of products under development by us are not necessarily predictive of results that will be obtained from large-scale clinical testing. Clinical trials of products under development may not demonstrate the safety and efficacy of the products being tested or result in a marketable product. Findings in nonclinical studies conducted concurrently with clinical studies could adversely effect the development of our products. In addition, the administration, alone or in combination with other drugs, of any product developed by us may produce undesirable side effects in humans.

The failure to demonstrate adequately the safety and efficacy of a therapeutic drug under development, for the disease indication being targeted, could delay or prevent regulatory approval of the product and could have a material adverse effect on us. In addition, the FDA or regulatory authorities in other jurisdictions may require additional clinical or nonclinical studies, which could result in increased costs and significant delays in obtaining required marketing approvals and commercialization of a product. 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.

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 that 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 or not 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 constantly monitor the results of our discovery research and our nonclinical 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 delays in patient enrollment slow our development progress, we may lose competitive advantage or be unable to bring our drugs to market.

The rate of completion of clinical trials of our products is dependent upon, among other factors, the rate of patient accrual. Patient accrual is a function of many factors, including the size of the patient population, the proximity of patients to clinical sites, the eligibility criteria for the trial, the level of compliance by the clinical sites to clinical trial protocols, and the availability of clinical trial material. Delays in patient enrollment in clinical trials may result in increased costs, program delays, or both, which could have a material adverse effect on us. 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 that are not licensed to a collaborator. If our clinical trials are not completed, we may not be able to submit a new drug application. If we are able to file a new drug application, such application may not be reviewed and approved in a timely manner, if at all.

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 independently developing products for regulatory approval for the first time since the Company's 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 collaborations 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.

If we do not obtain regulatory approval for our products on a timely basis, or at all, our revenues will be negatively impacted.

The United States FDA and comparable agencies in foreign countries impose substantial requirements on the introduction of therapeutic pharmaceutical products through lengthy and detailed laboratory and clinical testing procedures, sampling activities and other costly and time-consuming procedures. Satisfaction of these requirements typically can take many years and may vary substantially based upon the type, complexity and novelty of the pharmaceutical product. Data obtained from preclinical, nonclinical and clinical activities are susceptible to varying interpretations, which could delay, limit or prevent regulatory approval. In addition, delays or rejections may be encountered based on changes in, or additions to, regulatory policies for drug approval during the period of product development and regulatory review. The effect of government regulation may be to delay or prevent the commencement of planned clinical trials for our drug candidates in clinical development. These regulations may also cause us to engage in complex and costly procedures that could result in a competitive advantage to companies more experienced in regulatory affairs that compete with us. Moreover, even if approval is granted, such approval may entail limitations on the indicated uses for which a product may be marketed.

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 and development 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 products. In exchange, we have given them technology, product and marketing rights relating

to those products. Some of our corporate collaborators, including GlaxoSmithKline, Merck and Novartis, 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 GlaxoSmithKline, Merck or Novartis were to terminate its relationship with us, or fail to meet its contractual obligations, it 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. For example, a significant portion of our overall research effort is conducted under our research collaborations with Novartis, Merck and CFFT, all of which are scheduled to conclude in the period between December 2005 and June 2006. If we are unable to enter into collaborative arrangements that would extend or replace these research collaborations, or to find other means of financing the effort currently devoted to these research programs, our ability to conduct our research, development and commercial activities could be adversely affected to a material degree. Even if we are able to establish acceptable collaborative arrangements in the future, they may not be successful.

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.

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 have received regulatory approval and currently are marketed. Many of our competitors, including major pharmaceutical companies such as Abbott Laboratories, GlaxoSmithKline, Merck, and Novartis, 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.

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 products are highly technical in nature, we require the services of highly qualified and trained scientists who have the skills necessary to develop our products. 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 the Company. 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 movement 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 has 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, in particular the Novartis, Merck and CFFT collaborations, 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 we fail to 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.

We depend on third-party manufacturers, and if we are unable to obtain contract manufacturing on reasonable terms, we may not be able to develop or commercialize our products.

Our ability to conduct clinical trials and our ability to commercialize our potential products will depend, in part, on our ability to manufacture our products on a large scale, either directly or through third parties, at a competitive cost and in accordance with regulatory requirements. We have no experience in manufacturing pharmaceuticals or other products, and we may not be able to develop such capabilities in the foreseeable future. In addition, some of our current corporate collaborators have manufacturing rights with respect to our products under development. We are, therefore, dependent on third-party manufacturers and our collaborators for the production of our drug candidates for preclinical and nonclinical research, clinical trial purposes and commercial production. Accordingly, if we are not able to obtain contract manufacturing from these third parties on commercially reasonable terms, we may not be able to conduct or complete clinical trials or

commercialize our products as planned. Further, commercial formulation and manufacturing processes have yet to be developed for our drug candidates other than Agenerase and Lexiva/Telzir. As a result, we or our collaborators may encounter difficulties developing commercial formulations and manufacturing processes for our drug candidates, which could result in delays in clinical trials, regulatory submissions, regulatory approvals and commercialization of our products.

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 United States 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 competing 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, even in those instances in which 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 consolidated financial position.

If we are not able to sublet our Kendall Square Facility on acceptable terms, or at all, we could be obligated to pay as much as the full amount due under the lease, as and when due under the lease agreement.

We have decided not to occupy a facility located in Kendall Square, Cambridge, Massachusetts that we lease under a 15-year agreement expiring in 2018. We have estimated our net ongoing obligations under this lease to be $52,305,000 as of March 31, 2005. This estimate is based on underlying estimates of the timing for executing subleases of the remaining space, the sublease rental terms we might expect to receive, and other assumptions and estimates we consider appropriate given current market conditions and other factors. To date, we have subleased 45,000 square feet of the 290,000 square foot facility. If we are unable to find a tenant or tenants willing to sublease the balance of the facility on the terms we have incorporated into our estimate, including the rental rate, timing and term of any such sublease(s), or if the market for specialized laboratory space in Cambridge, Massachusetts or other real estate fundamentals should change before we are able to sublease the remaining unoccupied space, or if any of our other assumptions or estimates are inaccurate or circumstances bearing upon the potential restructuring should change before we are able to sublease the facility, our estimated obligations could increase to as much as the full amount due under the lease. As of December 31, 2004, our future obligations under the lease could be as much as $312 million.

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 and undertake clinical trials of potential drugs resulting from such compounds. 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 anticipate that we will finance these substantial cash needs with:

- 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. 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.

Our sales and marketing experience is limited.

We have little 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. If 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 Agenerase and Lexiva/Telzir to GlaxoSmithKline worldwide (except for amprenavir in Japan, where Kissei holds rights under the name Prozei), for VX-702 to Kissei in certain countries in the Far East and for VX-680 and VX-322 to Merck and Novartis, respectively, worldwide. Avalon Pharmaceuticals has exclusive worldwide marketing rights to VX-944. Mitsubishi Pharma has exclusive marketing rights to VX-950 in Japan and certain Far East countries. Even though we retain some co-promotion rights, 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.

If we incur product liability expenses, our earnings could be negatively impacted.

Our business will expose us to potential product liability risks that arise from the testing, manufacturing and sales of our products. In addition to direct expenditures for damages, settlement and defense costs, there is the possibility of adverse publicity as a result of product liability claims. These risks will increase as our products receive regulatory approval and are commercialized. We currently carry $15 million of product liability insurance. This level of insurance may not be sufficient and it may not cover, in any event, all of the risks to which we are exposed in the course of conducting or sponsoring clinical trials. Moreover, we may not be able to maintain our existing levels of insurance or be able to obtain or maintain additional insurance that we may need in the future on acceptable terms.

In addition, our research and development activities may from time to time involve the controlled use of hazardous materials, including hazardous chemicals and radioactive materials. Accordingly, we are subject to federal, state and local laws governing the use, handling and disposal of these materials. Although we believe that our safety procedures for handling and disposing of hazardous materials comply with regulatory requirements, we cannot completely eliminate the risk that accidental contamination or injury from these materials could expose us to significant liability.

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

As of March 31, 2005, we had approximately $82.6 million in aggregate principal amount of 5% Convertible Subordinated Notes due in September 2007 and approximately $232.4 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 revenue depends, and will likely continue to depend, on a limited number of products.

We derive a portion of our revenue from royalties earned from the sale of our two marketed products. Accordingly, any factor either adversely affecting product sales or adversely affecting our expected royalties from product sales could also have a material adverse effect on our business, financial condition and results of operations.

Market acceptance of our products will be limited if users of our products are unable to obtain adequate reimbursement from third-party payors.

The commercial success of Lexiva/Telzir will depend in part on the availability of reimbursement from third-party payors, including government health administrators, managed care providers and private health insurers. Third-party payors are increasingly challenging the pricing of pharmaceutical products. Additionally, third-party payors may conclude that Lexiva/Telzir is less safe, less effective or less cost-effective than existing products. We cannot assure you that third-party payors will provide reimbursement for Lexiva/Telzir, in whole or in part. If third-party payors do not provide adequate reimbursement for Lexiva/Telzir, the sale of that product may not be profitable to GlaxoSmithKline,

which may stop selling Lexiva/Telzir, thus terminating the royalties we receive on sales of these products.

The recent Medicare prescription drug coverage legislation and future legislative or regulatory reform of the healthcare system may affect our collaborator's ability to sell Agenerase or Lexiva profitably.

In the United States, there have been a number of legislative and regulatory proposals to change the healthcare system in ways that could affect our collaborator's ability to market and sell Lexiva profitably. The Centers for Medicare and Medicaid Services, or CMS, the agency within the Department of Health and Human Services that administers Medicare and is responsible for reimbursement of the cost of drugs, has asserted the authority of Medicare to elect not to cover particular drugs if CMS determines that the drugs are not "reasonable and necessary" for Medicare beneficiaries, or to elect to cover a drug at a lower reimbursement rate similar to that of drugs that CMS considers to be "therapeutically comparable." Further federal and state proposals and healthcare reforms are likely and legislation and regulations affecting the pricing of pharmaceuticals may change in ways adverse to us. For example, the potential for importation of lower-priced drugs from foreign sources may limit or erode sales of Lexiva, negatively affecting the amount of royalties we receive.

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 any AWP cases where our collaborators or licensees are named as defendants, the outcome of the case could have an 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 March 31, 2005, our common stock traded between $8.00 and $12.05. 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 clinical or nonclinical 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; and

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

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 March 31, 2005, we had approximately 81,203,170 shares of common stock issued and outstanding, together with outstanding options to purchase approximately 16,538,000 shares of common stock with a weighted average exercise price of $21.93 per share, and notes convertible into approximately 16,454,000 shares of common stock with conversion prices of $14.94 and $92.26 per share and a weighted average conversion price of $19.15 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 $14.07 per share, if you purchase shares of common stock in this offering, you will suffer immediate and substantial dilution of $12.84 per share in the net tangible book value of the common stock. If the underwriters exercise their over-allotment option, you will experience additional dilution. See "Dilution" on page S-20 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 VX-950 has the potential to change the treatment paradigm for HCV infection and become a powerful option in future HCV therapy;

that the Company expects to explore development of VX-950 as a monotherapy and as part of a combination therapy;

that we plan to file an IND and initiate Phase Ib and Phase II combination clinical studies involving VX-950 before the end of the year;

that we plan to initiate a Phase II study of VX-950 as a monotherapy;

relating to the proposed objectives and treatment durations of our clinical studies;

that we expect to produce a solid dosage formulation of VX-950 in the second half of 2005;

that we expect to complete a number of non-clinical toxicology studies in support of the treatment durations in the Phase II clinical studies prior to filing the IND;

that VX-950 and merimepodib could form the basis of an exclusively oral therapy alternative for the treatment of HCV;

that we expect to retain control of the development of our HCV product candidates and certain other product candidates that are in areas where we currently believe we can compete effectively;

that we expect to focus our Vertex-controlled commercialization efforts in North America and concentrate on identifying collaborative relationships to develop our HCV infection and inflammation product candidates outside of North America;

that we intend to continue to pursue strategic transactions with collaborators to accelerate research, development and commercialization of our novel drug candidates, including VX-409 and VX-692, where we believe collaborators have the development and commercialization infrastructure to access therapeutic areas that would be more difficult for us to pursue;

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

that we believe our drug design approach makes the drug discovery process more efficient and productive; and

that we intend to opportunistically license and acquire technologies, resources and products that have the potential to strengthen our drug discovery platform, product pipeline and commercial capabilities.

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 $14.07 per share, will be approximately $125.3 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 $144.3 million. We intend to use the net proceeds from this offering for general corporate purposes, which may include working capital, capital expenditures, research and development expenditures, clinical trial expenditures, acquisitions of new technologies, and investments.

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 (deficit) 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 sheet at March 31, 2005.

Our net tangible book value (deficit) at March 31, 2005 was $(13.6) million, or $(0.17) per share, based on 81.2 million shares of our common stock outstanding. After giving effect to the sale of 9,500,000 shares of common stock by us at an assumed public offering price of $14.07 per share, less the underwriting discounts and commissions and our estimated offering expenses, our net tangible book value at March 31, 2005, would be $111.7 million, or $1.23 per share. This represents an immediate increase in net tangible book value of $1.40 per share to existing stockholders and an immediate dilution of $12.84 per share to investors in this offering. The following table illustrates this per share dilution:

Assumed public offering price per share		$ 14.07
Net tangible book value (deficit) per share as of March 31, 2005	$ (0.17)	
Increase per share attributable to new investors purchasing shares in this offering	$ 1.40	
Net tangible book value per share after this offering		$ 1.23
Dilution per share to new investors		$ 12.84

PRICE RANGE OF COMMON STOCK

Our common stock is listed on the Nasdaq National Market under the symbol "VRTX." The last reported sale price for our common stock on May 27, 2005 was $14.07 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, 2003:		
Quarter Ended:		
March 31, 2003	$ 16.36	$ 9.72
June 30, 2003	16.40	10.28
September 30, 2003	16.28	12.18
December 31, 2003	13.80	8.00
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 (through May 27, 2005)	14.55	8.83

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 March 31, 2005; and
- as adjusted 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 $14.07 per share, and after deducting the underwriting discounts and commissions and estimated offering expenses payable by us.

The table excludes the following shares:

- 16,538,000 shares of common stock issuable upon the exercise of stock options outstanding as of March 31, 2005 at a weighted average exercise price of $21.93 per share;
- 35,000 shares of common stock issuable upon the exercise of stock options granted to employees after March 31, 2005 at a weighted exercise price of $11.74 per share;
- 18,000 restricted shares of common stock issued to employees after March 31, 2005, at a purchase price of $0.01 per share; and
- 16,454,000 shares of common stock reserved for issuance upon conversion of our outstanding convertible notes.

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

	March 31, 2005 (Unaudited) (In thousands, except share data)	
	Actual	As Adjusted
Collaborator development loan	$ 19,997	$ 19,997
Convertible subordinated notes (due September 2007)	82,552	82,552
Convertible senior subordinated notes (due February 2011)	232,448	232,448
Stockholders' equity (deficit):		
Preferred stock, $0.01 par value; 1,000,000 shares authorized; none issued and outstanding at March 31, 2005		
Common stock, $0.01 par value; 200,000,000 shares authorized; 81,203,170 shares actual, 90,703,170 shares as adjusted, issued and outstanding at March 31, 2005	$ 812	$ 907
Additional paid-in capital	838,531	963,749
Deferred compensation, net	(14,354)	(14,354)
Accumulated other comprehensive loss	(2,593)	(2,593)
Accumulated deficit	(830,887)	(830,887)
Total stockholders' equity (deficit)	(8,491)	116,822
Total capitalization	$ 326,506	$ 451,819

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	
J. P. Morgan Securities Inc.	
UBS Securities LLC	
Total	9,500,000

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 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 1,425,000 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 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 without first obtaining the consent of Merrill Lynch. Specifically, 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 National Market

Our shares of common stock are traded on the Nasdaq National 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, 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 National 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.

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.

Filed Pursuant to Rule 424(b)(3)
Registration No. 333-123731

PROSPECTUS

VERTEX PHARMACEUTICALS INCORPORATED

$200,000,000

COMMON STOCK
PREFERRED STOCK
DEBT SECURITIES
WARRANTS

We may offer any combination of the securities described in this prospectus from time to time in amounts, at prices and on terms to be determined at or prior to the time of the offering. We will provide you with specific terms of the applicable offered securities in one or more supplements to this prospectus. The aggregate initial offering price of the securities that we may issue under this prospectus will not exceed $200,000,000.

We may sell these securities to or through underwriters and also to other purchasers or through agents. We will set forth the names of any underwriters or agents in the prospectus supplement that accompanies this prospectus.

This prospectus may not be used to sell securities unless accompanied by a prospectus supplement. Before you make your investment decision, we urge you to read this prospectus and the prospectus supplement carefully.

INVESTING IN OUR SECURITIES INVOLVES RISKS. SEE "RISK FACTORS" ON PAGE 1.

NEITHER THE SECURITIES AND EXCHANGE COMMISSION NOR ANY STATE SECURITIES COMMISSION HAS APPROVED OR DISAPPROVED OF THESE SECURITIES OR PASSED UPON THE ACCURACY OR ADEQUACY OF THIS PROSPECTUS. ANY REPRESENTATION TO THE CONTRARY IS A CRIMINAL OFFENSE.

This prospectus may not be used to consummate sales of securities unless it is accompanied by a prospectus supplement.

The date of this prospectus is April 25, 2005.

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RISK FACTORS

Investing in our securities is risky. Please see the risk factors described in our annual report on Form 10-K for the year ended December 31, 2004, which is incorporated by reference in this prospectus. Before making an investment decision, you should carefully consider these risks as well as other information we include or incorporate by reference in this prospectus. The risk and uncertainties we have described are not the only ones facing our company. Additional risks and uncertainties not presently known to us or that we currently deem immaterial may also affect our business operations.

ABOUT THIS PROSPECTUS

This prospectus is part of a registration statement that we filed with the Securities and Exchange Commission, or SEC, utilizing a "shelf" registration process. Under this shelf process, we may sell any combination of the securities described in this prospectus in one or more offerings up to a total dollar amount of $200,000,000. We have provided to you in this prospectus a general description of the securities we may offer. Each time we sell securities, we will provide a prospectus supplement that will contain specific information about the terms of that offering.

The following is only a summary. We urge you to read the entire prospectus, including the more detailed financial statements, notes to the financial statements and other information incorporated by reference from our other filings with the SEC.

VERTEX PHARMACEUTICALS INCORPORATED

We are a biotechnology company in the business of discovering, developing and commercializing small molecule drugs for serious diseases, independently and with collaborators. We have discovered two products that have advanced to the market, and have a pipeline of potential products at various stages of the drug development process.

Our goal is to mature into a profitable pharmaceutical company with industry-leading capabilities in research, development and commercialization of products. Our strategy is to continue building these capabilities as we advance our product candidates to market. We focus our efforts both on programs that we expect to control throughout the development and commercialization phases, and programs that we expect will be conducted principally by a collaborator. We expect to continue to invest in our research and development capabilities as we advance our product candidates to market.

Collaborations will continue to be a key component of our corporate strategy. 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 plan to continue to add promising potential products to our development pipeline through our continuing commitment to discovery research. Our drug design approach integrates biology, chemistry, biophysics, automation and information technologies to make the drug discovery process more efficient and productive. We believe that our drug discovery expertise is one of our distinguishing features. In addition to our efforts to research and develop kinase inhibitors, we currently are conducting a productive research program in the area of ion channel modulation. We expect that future development candidates from our programs will be focused on the treatment of a wide variety of diseases and conditions.

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.

We were incorporated in Massachusetts in 1989. Our principal executive offices are located at 130 Waverly Street, Cambridge, Massachusetts 02139. Our telephone number is (617) 444-6100. We maintain a web site on the Internet at *http://www.vrtx.com*. We do not intend for the information in our web site to be considered part of this prospectus.

SPECIAL NOTE REGARDING FORWARD-LOOKING STATEMENTS

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

our business strategy;

our predicted development and commercial timelines;

our financial outlook, including those contained in the reports we furnished to the SEC;

the establishment, development and maintenance of collaborative relationships;

our ability to identify and develop new potential products;

our ability to achieve commercial acceptance of our products;

our ability to scale up our manufacturing capabilities and facilities;

the potential for the acquisition of new and complementary technologies, resources and products;

our projected capital expenditures; and

our liquidity.

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 other information set forth in this prospectus and the documents incorporated by reference herein. 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.

RATIO OF EARNINGS TO FIXED CHARGES

The following table sets forth our dollar coverage deficiency. The ratio of earnings to fixed charges is not disclosed since it is a negative number in each year and period shown below. Any time we offer debt securities pursuant to this prospectus, we will provide an updated table setting forth our ratio of earnings to fixed charges on a historical basis in the applicable prospectus supplement, if required. Any

time we offer shares of preferred stock pursuant to this prospectus, we will provide a table setting forth our ratio of combined fixed charges and preferred stock dividends to earnings, if required.

Ratio of earnings to fixed charges	Year ended December 31,					
	1999	2000	2001	2002	2003	2004
	(1)	(1)	(1)	(1)	(1)	(1)

(1) Due to our loss from continuing operations for the years ended December 31, 1999, 2000, 2001, 2002, 2003, and 2004 earnings were insufficient to cover fixed charges by $47.6 million, $41.4 million, $79.6 million, $137.0 million, $266.4 million, and $166.2 million, respectively. For this reason, no ratios are provided.

USE OF PROCEEDS

Except as otherwise provided in the applicable prospectus supplement, we intend to use the net proceeds from the sale of the securities covered by this prospectus for general corporate purposes, which may include working capital, capital expenditures, research and development expenditures, clinical trial expenditures, acquisitions of new technologies, and investments. Additional information on the use of net proceeds from the sale of securities covered by this prospectus may be set forth in the prospectus supplement relating to the specific offering.

THE SECURITIES WE MAY OFFER

The descriptions of the securities contained in this prospectus, together with the applicable prospectus supplements, summarize all the material terms and provisions of the various types of securities that we may offer. We will describe in the applicable prospectus supplement relating to any securities the particular terms of the securities offered by that prospectus supplement. If we indicate in the applicable prospectus supplement, the terms of the securities may differ from the terms we have summarized below. We will also include in the prospectus supplement information, where applicable, about material United States federal income tax considerations relating to the securities, and the securities exchange, if any, on which the securities will be listed.

DESCRIPTION OF CAPITAL STOCK

The following description of our capital stock and certain provisions of our articles of organization and by-laws is a summary and is qualified in its entirety by the provisions of our articles of organization and by-laws.

Our authorized capital stock consists of 200,000,000 shares of common stock, $0.01 par value, and 1,000,000 shares of preferred stock, $0.01 par value.

Common Stock

Holders of common stock are entitled to one vote for each share held on all matters submitted to a vote of stockholders and do not have cumulative voting rights. Accordingly, holders of a majority of the shares of common stock entitled to vote in any election of directors may elect all of the directors standing for election. Holders of common stock are entitled to receive ratably such dividends, if any, as may be declared by the Board of Directors out of funds legally available therefor, subject to any preferential dividend rights of any outstanding preferred stock. Upon the liquidation, dissolution or winding up of Vertex, the holders of common stock are entitled to receive ratably the net assets of Vertex available after the payment of all debts and other liabilities and subject to any prior rights of any outstanding preferred stock. Holders of common stock have no preemptive, subscription, redemption or conversion rights. The rights, preferences and privileges of holders of common stock are

subject to, and may be adversely affected by, the rights of the holders of shares of any series of preferred stock that we may designate and issue in the future.

Preferred Stock

Our Board of Directors has the authority, without further action by the stockholders, to issue up to 1,000,000 shares of Preferred Stock in one or more series and to fix the rights, preferences, privileges and restrictions thereof, including dividend rights, conversion rights, voting rights, terms of redemption, liquidation preferences, sinking fund terms and the number of shares constituting any series or the designation of such series, without any further vote or action by stockholders. The issuance of Preferred Stock could adversely affect the voting power of holders of our common stock and the likelihood that such holders will receive dividend payments and payments upon liquidation and could have the effect of delaying, deferring or preventing a change in control.

Stockholders Rights Plan

Pursuant to our Stockholder Rights Plan, each share of common stock has an associated preferred share purchase right (each a "Right" and collectively, the "Rights"). Each Right entitles the holder to purchase from Vertex one half of one-hundredth of a share of Series A Junior Participating Preferred Stock, $.01 par value (the "Junior Preferred Stock"), of Vertex at a price of $135 per one half of one-hundredth of a share of the Junior Preferred Stock, subject to adjustment (the "Adjusted Purchase Price"). The Rights are not exercisable until after acquisition by a person or group of 15% or more of our outstanding common stock (an "acquiring person") or after the announcement of an intention to make or commencement of a tender offer or exchange offer the consummation of which would result in the beneficial ownership by a person or group of 15% or more of our outstanding common stock (the earlier of such dates being called the "Distribution Date"). Until the Distribution Date (or earlier redemption or expiration of the Rights), the Rights will be transferred with and only with the common stock. Until a Right is exercised, the Right will not entitle the holder thereof to any rights as a stockholder.

If any person or group becomes an acquiring person, each holder of a Right, other than Rights beneficially owned by the acquiring person, will thereafter have the right to receive upon exercise and payment of the Adjusted Purchase Price that number of shares of common stock having a market value of two times the Adjusted Purchase Price, and if Vertex is acquired in a business combination transaction or 50% or more of its assets are sold, each holder of a Right will thereafter have the right to receive upon exercise and payment of the Adjusted Purchase Price that number of shares of common stock of the acquiring company which at the time of the transaction will have a market value of two times the Adjusted Purchase Price.

At any time after any person becomes an acquiring person and prior to the acquisition by such person or group of 50% or more of the outstanding common stock, our Board of Directors may cause the Rights (other than Rights owned by such person or group) to be exchanged, in whole or in part, for common stock or junior preferred shares, at an exchange rate of one share of common stock per Right or one half of one-hundredth of a share of Junior Preferred Stock per Right.

At any time prior to the acquisition by a person or group of beneficial ownership of 15% or more of the outstanding common stock, our Board of Directors may redeem the Rights in whole at a price of $.01 per Right.

The Rights have certain anti-takeover effects, in that they will cause substantial dilution to a person or group that attempts to acquire a significant interest in Vertex on terms not approved by the Board of Directors.

Provisions of our articles of organization and by-laws relating to a change in control and certain provisions of Massachusetts law

Provisions of our articles of organization and by-laws and our Stockholder Rights Plan may discourage certain types of transactions involving an actual or potential change in control of Vertex that might be beneficial to the company or its stockholders. Our articles of organization provide 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.

We are subject to Chapter 110F of the Massachusetts General Laws, an anti-takeover law. In general, this statute prohibits a publicly-held Massachusetts corporation from engaging in a "business combination" with an "interested stockholder" for a period of three years after the date of the transaction in which the person becomes an interested stockholder, unless (i) the interested stockholder obtains the approval of the board of directors prior to becoming an interested stockholder, (ii) the interested stockholder acquires 90% of the outstanding voting stock of the corporation (excluding shares held by certain affiliates of the corporation) at the time it becomes an interested stockholder, or (iii) the business combination is approved by both the board of directors and the holders of two-thirds of the outstanding voting stock of the corporation (excluding shares held by the interested stockholder). Generally, an "interested stockholder" is a person who, together with affiliates and associates, owns (or at any time within the prior three years did own) 5% or more of the outstanding voting stock of the corporation. A "business combination" includes a merger, a stock or asset sale, and certain other transactions resulting in a financial benefit to the interested stockholders.

We are subject to Massachusetts General Laws Chapter 110D, entitled "Regulation of Control Share Acquisitions." In general, this statute provides that any stockholder of a corporation subject to this statute who acquires 20% or more of the outstanding voting stock of a corporation may not vote such stock unless the stockholders of the corporation so authorize. The board of directors may amend our By-laws to exclude us from this statute prospectively.

Our articles of organization provide that our directors will not be personally liable for monetary damages to us for breaches of their fiduciary duty as directors, unless they violated their duty of loyalty to us or our stockholders, acted in bad faith, knowingly or intentionally violated the law, authorized illegal dividends or redemptions, authorized a loan of any of our assets to one of our officers or directors which is not repaid or derived an improper personal benefit from their action as directors. This provision does not eliminate director liability under federal securities laws or preclude non-monetary relief under state law. In addition, our By-laws provide that we may indemnify our directors and officers against all liabilities and expenses incurred in connection with service for us or on our behalf.

Transfer agent and registrar

The Transfer Agent and Registrar for our common stock is EquiServe Trust Company. The Transfer Agent's address is P.O. Box 8040, Boston, Massachusetts 02266-8040, and its telephone number is (781) 575-3120.

DESCRIPTION OF DEBT SECURITIES

The following description, together with the additional information we include in any applicable prospectus supplements, summarizes the material terms and provisions of the debt securities that we may offer under this prospectus. While the terms we have summarized below will apply generally to any future debt securities we may offer pursuant to this prospectus, we will describe the particular terms of any debt securities that we may offer in more detail in the applicable prospectus supplement. If we indicate in a prospectus supplement, the terms of any debt securities we offer under that prospectus supplement may differ from the terms we describe below.

We may sell from time to time, in one or more offerings under this prospectus, debt securities, which may be senior or subordinated. We will issue any such senior debt securities under a senior indenture that we will enter into with a trustee to be named in the senior indenture. We will issue any such subordinated debt securities under a subordinated indenture, which we will enter into with a trustee to be named in the subordinated indenture. We have filed forms of these documents as exhibits to the registration statement, which includes this prospectus. We use the term "indentures" to refer to both the senior indenture and the subordinated indenture. The indentures will be qualified under the Trust Indenture Act. We use the term "debenture trustee" to refer to either the trustee or under the senior indenture or the trustee under the subordinated indenture, as applicable.

The following summaries of material provisions of the senior debt securities, the subordinated debt securities and the indentures are subject to, and qualified in their entirety by reference to, all the provisions of the indenture applicable to a particular series of debt securities.

We conduct some of our operations through our subsidiaries. Our rights and the rights of our creditors, including holders of debt securities, to the assets of any subsidiary of ours upon that subsidiary's liquidation or reorganization or otherwise would be subject to the prior claims of that subsidiary's creditors, except to the extent that we may be a creditor with recognized claims against the subsidiary. Our subsidiaries' creditors would include trade creditors, debt holders, secured creditors and taxing authorities. Except as we may provide in a prospectus supplement, neither the debt securities nor the indentures restrict us or any of our subsidiaries from incurring indebtedness or from imposing restrictions on the ability of our subsidiaries to pay dividends to us or others. Under this caption, the phrase "the Company" refers solely to Vertex Pharmaceuticals Incorporated.

General

Each indenture provides that debt securities may be issued from time to time in one or more series and may be denominated and payable in foreign currencies or units based on or relating to foreign currencies, including European Currency Units. Neither indenture limits the amount of debt securities that may be issued thereunder, and each indenture provides that the specific terms of any series of debt securities shall be set forth in, or determined pursuant to, an authorizing resolution and/or a supplemental indenture, if any, relating to such series.

We will describe in each prospectus supplement the following terms relating to a series of debt securities:

the title;

the aggregate principal amount and any limit on the amount that may be issued;

the currency or units based on or relating to currencies in which debt securities of such series are denominated and the currency or units in which principal or interest or both will or may be payable;

whether we will issue the series of debt securities in global form, the terms of any global securities and who the depositary will be;

the maturity date and the date or dates on which principal will be payable;

the interest rate, which may be fixed or variable, or the method for determining the rate and the date interest will begin to accrue, the date or dates interest will be payable and the record dates for interest payment dates or the method for determining such dates;

whether or not the debt securities will be secured or unsecured, and the terms of any secured debt;

the terms of the subordination of any series of subordinated debt;

the place or places where payments will be payable;

our right, if any, to defer payment of interest and the maximum length of any such deferral period;

the date, if any, after which, and the price at which, we may, at our option, redeem the series of debt securities pursuant to any optional redemption provisions;

the date, if any, on which, and the price at which we are obligated, pursuant to any mandatory sinking fund provisions or otherwise, to redeem, or at the holder's option to purchase, the series of debt securities;

whether the indenture will restrict our ability to pay dividends, or will require us to maintain any asset ratios or reserves;

whether we will be restricted from incurring any additional indebtedness;

a discussion on any material or special United States federal income tax considerations applicable to a series of debt securities;

the denominations in which we will issue the series of debt securities, if other than denominations of $1,000 and any integral multiple thereof; and

any other specific terms, preferences, rights or limitations of, or restrictions on, the debt securities.

We may issue debt securities that provide for an amount less than their stated principal amount to be due and payable upon declaration of acceleration of their maturity pursuant to the terms of the indenture. We will provide you with information on the federal income tax considerations and other special considerations applicable to any of these debt securities in the applicable prospectus supplement.

Conversion or Exchange Rights

We will set forth in the prospectus supplement the terms, if any, on which a series of debt securities may be convertible into or exchangeable for our common stock or other securities of ours. We will include provisions as to whether conversion or exchange is mandatory, at the option of the holder or at our option. We may include provisions pursuant to which the number of shares of our common stock or other securities of ours that the holders of the series of debt securities receive would be subject to adjustment.

Consolidation, Merger or Sale; No Protection in Event of a Change of Control or Highly Leveraged Transaction

The indentures do not contain any covenant that restricts our ability to merge or consolidate, or sell, convey, transfer or otherwise dispose of all or substantially all of our assets. However, any successor to or acquirer of such assets must assume all of our obligations under the indentures or the debt securities, as appropriate.

Unless we state otherwise in the applicable prospectus supplement, the debt securities will not contain any provisions that may afford holders of the debt securities protection in the event we have a change of control or in the event of a highly leveraged transaction (whether or not such transaction results in a change of control), which could adversely affect holders of debt securities.

Events of Default Under the Indenture

The following are events of default under the indentures with respect to any series of debt securities that we may issue:

- if we fail to pay interest when due and our failure continues for 90 days and the time for payment has not been extended or deferred;
- if we fail to pay the principal, or premium, if any, when due and the time for payment has not been extended or delayed;
- if we fail to observe or perform any other covenant relating to such series contained in the debt securities of such series or the applicable indentures, other than a covenant specifically relating to and for the benefit of holders of another series of debt securities, and our failure continues for 90 days after we receive written notice from the debenture trustee or holders of not less than a majority in aggregate principal amount of the outstanding debt securities of the applicable series; and
- if specified events of bankruptcy, insolvency or reorganization occur as to us.

No event of default with respect to a particular series of debt securities (except as to certain events of bankruptcy, insolvency or reorganization) necessarily constitutes an event of default with respect to any other series of debt securities. The occurrence of an event of default may constitute an event of default under any bank credit agreements we may have in existence from time to time. In addition, the occurrence of certain events of default or an acceleration under the indenture may constitute an event of default under certain of our other indebtedness outstanding from time to time.

If an event of default with respect to debt securities of any series at the time outstanding occurs and is continuing, then the trustee or the holders of not less than a majority in principal amount of the outstanding debt securities of that series may, by a notice in writing to us (and to the debenture trustee if given by the holders), declare to be due and payable immediately the principal (or, if the debt securities of that series are discount securities, that portion of the principal amount as may be specified in the terms of that series) of and premium and accrued and unpaid interest, if any, on all debt securities of that series. Before a judgment or decree for payment of the money due has been obtained with respect to debt securities of any series, the holders of a majority in principal amount of the outstanding debt securities of that series (or, at a meeting of holders of such series at which a quorum is present, the holders of a majority in principal amount of the debt securities of such series represented at such meeting) may rescind and annul the acceleration if all events of default, other than the non-payment of accelerated principal, premium, if any, and interest, if any, with respect to debt securities of that series, have been cured or waived as provided in the applicable indenture (including payments or deposits in respect of principal, premium or interest that had become due other than as a result of such acceleration). We refer you to the prospectus supplement relating to any series of debt securities that are discount securities for the particular provisions relating to acceleration of a portion of the principal amount of such discount securities upon the occurrence of an event of default.

Subject to the terms of the indentures, if an event of default under an indenture shall occur and be continuing, the debenture trustee will be under no obligation to exercise any of its rights or powers under such indenture at the request or direction of any of the holders of the applicable series of debt securities, unless such holders have offered the debenture trustee reasonable indemnity. The holders of a majority in principal amount of the outstanding debt securities of any series will have the right to direct the time, method and place of conducting any proceeding for any remedy available to the

debenture trustee, or exercising any trust or power conferred on the debenture trustee, with respect to the debt securities of that series, provided that:

- the direction so given by the holder is not in conflict with any law or the applicable indenture; and
- subject to its duties under the Trust Indenture Act, the debenture trustee need not take any action that might involve it in personal liability or might be unduly prejudicial to the holders not involved in the proceeding.

A holder of the debt securities of any series will only have the right to institute a proceeding under the indentures or to appoint a receiver or trustee, or to seek other remedies if:

- the holder previously has given written notice to the debenture trustee of a continuing event of default with respect to that series;
- the holders of at least a majority in aggregate principal amount of the outstanding debt securities of that series have made written request, and such holders have offered reasonable indemnity to the debenture trustee to institute the proceeding as trustee; and
- the debenture trustee does not institute the proceeding, and does not receive from the holders of a majority in aggregate principal amount of the outstanding debt securities of that series (or at a meeting of holders of such series at which a quorum is present, the holders of a majority in principal amount of the debt securities of such series represented at such meeting) other conflicting directions within 60 days after the notice, request and offer.

These limitations do not apply to a suit instituted by a holder of debt securities if we default in the payment of the principal, premium, if any, or interest on, the debt securities.

We will periodically file statements with the applicable debenture trustee regarding our compliance with specified covenants in the applicable indenture.

Modification of Indenture; Waiver

The debenture trustee and we may change the applicable indenture without the consent of any holders with respect to specific matters, including:

- to fix any ambiguity, defect or inconsistency in the indenture; and
- to change anything that does not materially adversely affect the interests of any holder of debt securities of any series issued pursuant to such indenture.

In addition, under the indentures, the rights of holders of a series of debt securities may be changed by us and the debenture trustee with the written consent of the holders of at least a majority in aggregate principal amount of the outstanding debt securities of each series (or, at a meeting of holders of such series at which a quorum is present, the holders of a majority in principal amount of the debt securities of such series represented at such meeting) that is affected. However, the debenture trustee and we may make the following changes only with the consent of each holder of any outstanding debt securities affected:

- extending the fixed maturity of the series of debt securities;

reducing the principal amount, reducing the rate of or extending the time of payment of interest, or any premium payable upon the redemption of any debt securities;

reduce the principal amount of discount securities payable upon acceleration of maturity;

make the principal of or premium or interest on any debt security payable in currency other than that stated in the debt security; or

reducing the percentage of debt securities, the holders of which are required to consent to any amendment or waiver.

Except for certain specified provisions, the holders of at least a majority in principal amount of the outstanding debt securities of any series (or, at a meeting of holders of such series at which a quorum is present, the holders of a majority in principal amount of the debt securities of such series represented at such meeting) may on behalf of the holders of all debt securities of that series waive our compliance with provisions of the indenture. The holders of a majority in principal amount of the outstanding debt securities of any series may on behalf of the holders of all the debt securities of such series waive any past default under the indenture with respect to that series and its consequences, except a default in the payment of the principal of, premium or any interest on any debt security of that series or in respect of a covenant or provision, which cannot be modified or amended without the consent of the holder of each outstanding debt security of the series affected; *provided, however,* that the holders of a majority in principal amount of the outstanding debt securities of any series may rescind an acceleration and its consequences, including any related payment default that resulted from the acceleration.

Discharge

Each indenture provides that we can elect to be discharged from our obligations with respect to one or more series of debt securities, except for obligations to:

register the transfer or exchange of debt securities of the series;

replace stolen, lost or mutilated debt securities of the series;

maintain paying agencies;

hold monies for payment in trust;

compensate and indemnify the trustee; and

appoint any successor trustee.

In order to exercise our rights to be discharged with respect to a series, we must deposit with the trustee money or government obligations sufficient to pay all the principal of, any premium, if any, and interest on, the debt securities of the series on the dates payments are due.

Form, Exchange, and Transfer

We will issue the debt securities of each series only in fully registered form without coupons and, unless we otherwise specify in the applicable prospectus supplement, in denominations of $1,000 and any integral multiple thereof. The indentures provide that we may issue debt securities of a series in temporary or permanent global form and as book-entry securities that will be deposited with, or on behalf of, The Depository Trust Company or another depositary named by us and identified in a prospectus supplement with respect to that series. See "Legal Ownership of Securities" for a further description of the terms relating to any book-entry securities.

At the option of the holder, subject to the terms of the indentures and the limitations applicable to global securities described in the applicable prospectus supplement, the holder of the debt securities of any series can exchange the debt securities for other debt securities of the same series, in any authorized denomination and of like tenor and aggregate principal amount.

Subject to the terms of the indentures and the limitations applicable to global securities set forth in the applicable prospectus supplement, holders of the debt securities may present the debt securities for exchange or for registration of transfer, duly endorsed or with the form of transfer endorsed thereon duly executed if so required by us or the security registrar, at the office of the security registrar

or at the office of any transfer agent designated by us for this purpose. Unless otherwise provided in the debt securities that the holder presents for transfer or exchange or in the applicable indenture, we will make no service charge for any registration of transfer or exchange, but we may require payment of any taxes or other governmental charges.

We will name in the applicable prospectus supplement the security registrar, and any transfer agent in addition to the security registrar, that we initially designate for any debt securities. We may at any time designate additional transfer agents or rescind the designation of any transfer agent or approve a change in the office through which any transfer agent acts, except that we will be required to maintain a transfer agent in each place of payment for the debt securities of each series.

If we elect to redeem the debt securities of any series, we will not be required to:

issue, register the transfer of, or exchange any debt securities of that series during a period beginning at the opening of business 15 days before the day of mailing of a notice of redemption of any debt securities that may be selected for redemption and ending at the close of business on the day of the mailing; or

register the transfer of or exchange any debt securities so selected for redemption, in whole or in part, except the unredeemed portion of any debt securities we are redeeming in part.

Information Concerning the Debenture Trustee

The debenture trustee, other than during the occurrence and continuance of an event of default under the applicable indenture, undertakes to perform only those duties as are specifically set forth in the applicable indenture. Upon an event of default under an indenture, the debenture trustee under such indenture must use the same degree of care as a prudent person would exercise or use in the conduct of his or her own affairs. Subject to this provision, the debenture trustee is under no obligation to exercise any of the powers given it by the indentures at the request of any holder of debt securities unless it is offered reasonable security and indemnity against the costs, expenses and liabilities that it might incur.

Payment and Paying Agents

Unless we otherwise indicate in the applicable prospectus supplement, we will make payment of the interest on any debt securities on any interest payment date to the person in whose name the debt securities, or one or more predecessor securities, are registered at the close of business on the regular record date for the interest.

We will pay principal of and any premium and interest on the debt securities of a particular series at the office of the paying agents designated by us, except that unless we otherwise indicate in the applicable prospectus supplement, will we make interest payments by check which we will mail to the holder. Unless we otherwise indicate in a prospectus supplement, we will designate the corporate trust office of the debenture trustee in the City of New York as our sole paying agent for payments with respect to debt securities of each series. We will name in the applicable prospectus supplement any other paying agents that we initially designate for the debt securities of a particular series. We will maintain a paying agent in each place of payment for the debt securities of a particular series.

All money we pay to a paying agent or the debenture trustee for the payment of the principal of or any premium or interest on any debt securities which remains unclaimed at the end of two years after such principal, premium or interest has become due and payable will be repaid to us, and the holder of the security thereafter may look only to us for payment thereof.

Governing Law

The indentures and the debt securities will be governed by and construed in accordance with the laws of the State of New York, except to the extent that the Trust Indenture Act is applicable.

Subordination of Subordinated Debt securities

The obligations of the company pursuant to any subordinated debt securities will be unsecured and will be subordinate and junior in priority of payment to certain of our other indebtedness to the extent described in a prospectus supplement. The subordinated indenture does not limit the amount of senior indebtedness we may incur. It also does not limit us from issuing any other secured or unsecured debt.

DESCRIPTION OF WARRANTS

The following description, together with the additional information we may include in any applicable prospectus supplements, summarizes the material terms and provisions of the warrants that we may offer under this prospectus and the related warrant agreements and warrant certificates. While the terms summarized below will apply generally to any warrants that we may offer, we will describe the particular terms of any series of warrants in more detail in the applicable prospectus supplement. If we indicate in the prospectus supplement, the terms of any warrants offered under that prospectus supplement may differ from the terms described below. Specific warrant agreements will contain additional important terms and provisions and will be incorporated by reference as an exhibit to the registration statement that includes this prospectus.

General

We may issue warrants for the purchase of common stock, preferred stock and/or debt securities in one or more series. We may issue warrants independently or together with common stock, preferred stock and/or debt securities, and the warrants may be attached to or separate from these securities.

We will evidence each series of warrants by warrant certificates that we will issue under a separate agreement. We will enter into the warrant agreement with a warrant agent. Each warrant agent will be a bank that we select which has its principal office in the United States. We will indicate the name and address of the warrant agent in the applicable prospectus supplement relating to a particular series of warrants.

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

- the offering price and aggregate number of warrants offered;
- the currency for which the warrants may be purchased;
- if applicable, the designation and terms of the securities with which the warrants are issued and the number of warrants issued with each such security or each principal amount of such security;
- if applicable, the date on and after which the warrants and the related securities will be separately transferable;
- in the case of warrants to purchase debt securities, the principal amount of debt securities purchasable upon exercise of one warrant and the price at, and currency in which, this principal amount of debt securities may be purchased upon such exercise;
- in the case of warrants to purchase common stock or preferred stock, the number of shares of common stock or preferred stock, as the case may be, purchasable upon the exercise of one warrant and the price at which these shares may be purchased upon such exercise;

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- the effect of any merger, consolidation, sale or other disposition of our business on the warrant agreement and the warrants;
- the terms of any rights to redeem or call the warrants;
- any provisions for changes to or adjustments in the exercise price or number of securities issuable upon exercise of the warrants;
- the dates on which the right to exercise the warrants will commence and expire;
- the manner in which the warrant agreement and warrants may be modified;
- federal income tax consequences of holding or exercising the warrants;
- the terms of the securities issuable upon exercise of the warrants; and
- any other specific terms, preferences, rights or limitations of or restrictions on the warrants.

Before exercising their warrants, holders of warrants will not have any of the rights of holders of the securities purchasable upon such exercise, including:

- in the case of warrants to purchase debt securities, the right to receive payments of principal of, or premium, if any, or interest on, the debt securities purchasable upon exercise or to enforce covenants in the applicable indenture; or
- in the case of warrants to purchase common stock or preferred stock, the right to receive dividends, if any, or, payments upon our liquidation, dissolution or winding up or to exercise voting rights, if any.

Exercise of Warrants

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

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

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

Enforceability of Rights By Holders of Warrants

Each warrant agent will act solely as our agent under the applicable warrant agreement and will not assume any obligation or relationship of agency or trust with any holder of any warrant. A single bank or trust company may act as warrant agent for more than one issue of warrants. A

warrant agent

will have no duty or responsibility in case of any default by us under the applicable warrant agreement or warrant, including any duty or responsibility to initiate any proceedings at law or otherwise, or to make any demand upon us. Any holder of a warrant may, without the consent of the related warrant agent or the holder of any other warrant, enforce by appropriate legal action its right to exercise, and receive the securities purchasable upon exercise of, its warrants.

LEGAL OWNERSHIP OF SECURITIES

We can issue securities in registered form or in the form of one or more global securities. We describe global securities in greater detail below. We refer to those persons who have securities registered in their own names on the books that any applicable trustee or we maintain for this purpose as the "holders" of those securities. These persons are the legal holders of the securities. We refer to those persons who, indirectly through others, own beneficial interests in securities that are not registered in their own names, as "indirect holders" of those securities. As we discuss below, indirect holders are not legal holders, and investors in securities issued in book-entry form or in street name will be indirect holders.

Book-Entry Holders

We may issue securities in book-entry form only, as we will specify in the applicable prospectus supplement. This means securities may be represented by one or more global securities registered in the name of a financial institution that holds them as depositary on behalf of other financial institutions that participate in the depositary's book-entry system. These participating institutions, which are referred to as participants, in turn, hold beneficial interests in the securities on behalf of themselves or their customers.

Only the person in whose name a security is registered is recognized as the holder of that security. Securities issued in global form will be registered in the name of the depositary or its participants. Consequently, for securities issued in global form, we will recognize only the depositary as the holder of the securities, and we will make all payments on the securities to the depositary. The depositary passes along the payments it receives to its participants, which in turn pass the payments along to their customers who are the beneficial owners. The depositary and its participants do so under agreements they have made with one another or with their customers; they are not obligated to do so under the terms of the securities.

As a result, investors in a book-entry security will not own securities directly. Instead, they will own beneficial interests in a global security, through a bank, broker or other financial institution that participates in the depositary's book-entry system or holds an interest through a participant. As long as the securities are issued in global form, investors will be indirect holders, and not holders, of the securities.

Street Name Holders

We may terminate a global security or issue securities in non-global form. In these cases, investors may choose to hold their securities in their own names or in "street name." Securities held by an investor in street name would be registered in the name of a bank, broker or other financial institution that the investor chooses, and the investor would hold only a beneficial interest in those securities through an account he or she maintains at that institution.

For securities held in street name, we will recognize only the intermediary banks, brokers and other financial institutions in whose names the securities are registered as the holders of those securities, and we will make all payments on those securities to them. These institutions pass along the payments they receive to their customers who are the beneficial owners, but only because they agree to do so in their customer agreements or because they are legally required to do so. Investors who hold securities in street name will be indirect holders, not holders, of those securities.

Legal Holders

Our obligations, as well as the obligations of any applicable trustee and of any third parties employed by us or a trustee, run only to the legal holders of the securities. We do not have obligations to investors who hold beneficial interests in global securities, in street name or by any other indirect means. This will be the case whether an investor chooses to be an indirect holder of a security or has no choice because we are issuing the securities only in global form.

For example, once we make a payment or give a notice to the holder, we have no further responsibility for the payment or notice even if that holder is required, under agreements with depositary participants or customers or by law, to pass it along to the indirect holders but does not do so. Similarly, we may want to obtain the approval of the holders to amend an indenture, to relieve us of the consequences of a default or of our obligation to comply with a particular provision of the indenture or for other purposes. In such an event, we would seek approval only from the holders, and not the indirect holders, of the securities. Whether and how the holders contact the indirect holders is up to the holders.

Special Considerations for Indirect Holders

If you hold securities through a bank, broker or other financial institution, either in book-entry form or in street name, you should check with your own institution to find out:

how it handles securities payments and notices;

whether it imposes fees or charges;

how it would handle a request for the holders' consent, if ever required;

whether and how you can instruct it to send you securities registered in your own name so you can be a holder, if that is permitted in the future;

how it would exercise rights under the securities if there were a default or other event triggering the need for holders to act to protect their interests; and

if the securities are in book-entry form, how the depositary's rules and procedures will affect these matters.

Global Securities

A global security is a security held by a depositary that represents one or any other number of individual securities. Generally, all securities represented by the same global securities will have the same terms.

Each security issued in book-entry form will be represented by a global security that we deposit with and register in the name of a financial institution or its nominee that we select. The financial institution that we select for this purpose is called the depositary. Unless we specify otherwise in the applicable prospectus supplement, The Depository Trust Company, New York, New York, known as DTC, will be the depositary for all securities issued in book-entry form.

A global security may not be transferred to or registered in the name of anyone other than the depositary, its nominee or a successor depositary, unless special termination situations arise. We describe those situations below under " Special Situations When a Global Security Will Be Terminated." As a result of these arrangements, the depositary, or its nominee, will be the sole registered owner and holder of all securities represented by a global security, and investors will be permitted to own only beneficial interests in a global security. Beneficial interests must be held by means of an account with a broker, bank or other financial institution that in turn has an account with the depositary or with another institution that does. Thus, an investor whose security is represented by

a global security will not be a holder of the security, but only an indirect holder of a beneficial interest in the global security.

If the prospectus supplement for a particular security indicates that the security will be issued in global form only, then the security will be represented by a global security at all times unless and until the global security is terminated. If termination occurs, we may issue the securities through another book-entry clearing system or decide that the securities may no longer be held through any book-entry clearing system.

Special Considerations for Global Securities

As an indirect holder, an investor's rights relating to a global security will be governed by the account rules of the investor's financial institution and of the depositary, as well as general laws relating to securities transfers. We do not recognize an indirect holder as a holder of securities and instead deal only with the depositary that holds the global security.

If securities are issued only in the form of a global security, an investor should be aware of the following:

An investor cannot cause the securities to be registered in his or her name, and cannot obtain non-global certificates for his or her interest in the securities, except in the special situations we describe below;

An investor will be an indirect holder and must look to his or her own bank or broker for payments on the securities and protection of his or her legal rights relating to the securities, as we describe under " Legal Ownership of Securities" above;

An investor may not be able to sell interests in the securities to some insurance companies and to other institutions that are required by law to own their securities in non-book-entry form;

An investor may not be able to pledge his or her interest in a global security in circumstances where certificates representing the securities must be delivered to the lender or other beneficiary of the pledge in order for the pledge to be effective;

The depositary's policies, which may change from time to time, will govern payments, transfers, exchanges and other matters relating to an investor's interest in a global security. Any applicable trustee and we have no responsibility for any aspect of the depositary's actions or for its records of ownership interests in a global security. We and the trustee also do not supervise the depositary in any way;

The depositary may, and we understand that DTC will, require that those who purchase and sell interests in a global security within its book- entry system use immediately available funds, and your broker or bank may require you to do so as well; and

Financial institutions that participate in the depositary's book-entry system, and through which an investor holds its interest in a global security, may also have their own policies affecting payments, notices and other matters relating to the securities. There may be more than one financial intermediary in the chain of ownership for an investor. We do not monitor and are not responsible for the actions of any of those intermediaries.

Special Situations When a Global Security will be Terminated

In a few special situations described below, the global security will terminate and interests in it will be exchanged for physical certificates representing those interests. After that exchange, the choice of whether to hold securities directly or in street name will be up to the investor. Investors must consult their own banks or brokers to find out how to have their interests in securities transferred to their own

name, so that they will be direct holders. We have described the rights of holders and street name investors above.

The global security will terminate when the following special situations occur:

- if the depositary notifies us that it is unwilling, unable or no longer qualified to continue as depositary for that global security and we do not appoint another institution to act as depositary within 90 days;
- if we notify any applicable trustee that we wish to terminate that global security; or
- if an event of default has occurred with regard to securities represented by that global security and has not been cured or waived.

The prospectus supplement may also list additional situations for terminating a global security that would apply only to the particular series of securities covered by the prospectus supplement. When a global security terminates, the depositary, and not we or any applicable trustee, is responsible for deciding the names of the institutions that will be the initial direct holders.

PLAN OF DISTRIBUTION

We may sell the securities being offered hereby in one or more of the following ways from time to time:

- through dealers or agents to the public or to investors;
- to underwriters for resale to the public or to investors;
- directly to investors; or
- through a combination of such methods.

In addition, we may issue the securities as a dividend or distribution or in a subscription rights offering or in other transactions to our existing security holders. In some cases, we or dealers acting with us or on our behalf may also purchase securities and reoffer them to the public by one or more of the methods described above. This prospectus may be used in connection with any offering of our securities through any of these methods or other methods described in the applicable prospectus supplement.

We may determine the price or other terms of the securities offered under this prospectus by use of an electronic auction. We will describe how any auction will determine the price or other terms, how potential investors may participate in the auction and the nature of the underwriter's obligations in the related supplement to this prospectus.

We will set forth in a prospectus supplement the terms of the offering of securities, including:

- the name or names of any agents, dealers or underwriters;
- the purchase price of the securities being offered and the proceeds we will receive from the sale;
- any over-allotment options under which underwriters may purchase additional securities from us;

any agency fees or underwriting discounts and other items constituting agents' or underwriters' compensation;

any discounts or concessions allowed or reallowed or paid to dealers; and

any securities exchanges on which such securities may be listed.

Underwriters

Underwriters, dealers and agents that participate in the distribution of the securities may be deemed to be underwriters as defined in the Securities Act and any discounts or commissions they receive from us and any profit on their resale of the securities may be treated as underwriting discounts and commissions under the Securities Act. We will identify in the applicable prospectus supplement any underwriters, dealers or agents and will describe their compensation. We may have agreements with the underwriters, dealers and agents to indemnify them against specified civil liabilities, including liabilities under the Securities Act. Underwriters, dealers and agents may engage in transactions with or perform services for us or our subsidiaries in the ordinary course of their businesses.

If we offer securities in a subscription rights offering to our existing security holders, we may enter into a standby underwriting agreement with dealers, acting as standby underwriters. We may pay the standby underwriters a commitment fee for the securities they commit to purchase on a standby basis. If we do not enter into a standby underwriting arrangement, we may retain a dealer-manager to manage a subscription rights offering for us.

Trading Markets and Listing of Securities

Unless otherwise specified in the applicable prospectus supplement, each class or series of securities will be a new issue with no established trading market, other than our common stock, which is listed on the Nasdaq National Market. We may elect to list any other class or series of securities on any exchange, but we are not obligated to do so. It is possible that one or more underwriters may make a market in a class or series of securities, but the underwriters will not be obligated to do so and may discontinue any market making at any time without notice. We cannot give any assurance as to the liquidity of the trading market for any of the securities.

Stabilization Activities

Certain persons that participate in the distribution of the securities may engage in transactions that stabilize, maintain or otherwise affect the price of the securities, including over-allotment, stabilizing and short-covering transactions in such securities, and the imposition of penalty bids, in connection with an offering. Over-allotment involves sales in excess of the offering size, which creates a short position. Stabilizing transactions involve bids to purchase the underlying security so long as the stabilizing bids do not exceed a specified maximum. Syndicate short covering transactions involve purchases of securities in the open market after the distribution has been completed in order to cover syndicate short positions. Penalty bids permit the underwriters to reclaim selling concessions from dealers when the securities originally sold by the dealers are purchased in covering transactions to cover syndicate short positions. These transactions may cause the price of the securities sold in an offering to be higher than it would otherwise be. These transactions, if commenced, may be discontinued by the underwriters at any time.

Passive Market Making

Certain persons may also engage in passive market making transactions as permitted by Rule 103 of Regulation M. Passive market makers must comply with applicable volume and price limitations and must be identified as passive market makers. In general, a passive market maker must display its bid at a price not in excess of the highest independent bid for such security; if all independent bids are lowered below the passive market maker's bid, however, the passive market maker's bid must then be lowered when certain purchase limits are exceeded.

LEGAL MATTERS

Mintz, Levin, Cohn, Ferris, Glovsky and Popeo, P.C., Boston, Massachusetts, will provide us with an opinion as to the legal matters in connection with the securities we are offering.

EXPERTS

The financial statements and management's assessment of the effectiveness of internal control over financial reporting (which is included in Management's Report on Internal Control over Financial Reporting) incorporated in this Prospectus by reference to the Annual Report on Form 10-K for the year ended December 31, 2004 have been so incorporated in reliance on the report of PricewaterhouseCoopers LLP, an independent registered public accounting firm, given on the authority of said firm as experts in auditing and accounting.

WHERE YOU CAN FIND MORE INFORMATION

We are a public company and file annual, quarterly and current reports, proxy statements and other information with the Securities and Exchange Commission. You may read and copy any document we file at the SEC's Public Reference Room at 450 Fifth Street, N.W., Washington, D.C. 20549. You can request copies of these documents by writing to the SEC and paying a fee for the copying cost. Please call the SEC at 1-800-SEC-0330 for more information about the operation of the public reference room. Our SEC filings are also available to the public at the SEC's web site at "http://www.sec.gov." In addition, our stock is listed for trading on the Nasdaq National Market. You can read and copy reports and other information concerning us at the offices of the National Association of Securities Dealers, Inc. located at 1735 K Street, Washington, D.C. 20006. You may also access our filings with the Securities and Exchange Commission and obtain other information about us through the website maintained by Vertex, which is http://www.vrtx.com. The information contained in that website is not incorporated by reference into this prospectus.

This prospectus is only part of a Registration Statement on Form S-3 that we have filed with the SEC under the Securities Act and therefore omits certain information contained in the Registration Statement. We have also filed exhibits and schedules with the Registration Statement that are excluded from this prospectus, and you should refer to the applicable exhibit or schedule for a complete description of any statement referring to any contract or other document. You may:

inspect a copy of the Registration Statement, including the exhibits and schedules, without charge at the public reference room or,

obtain a copy from the SEC upon payment of the fees prescribed by the SEC.

INCORPORATION OF DOCUMENTS BY REFERENCE

The SEC allows us to "incorporate by reference" the information we file with it, which means that we can disclose important information to you by referring you to those documents. The information incorporated by reference is considered to be part of this prospectus and information we file later with the SEC will automatically update and supersede this information. We incorporate by reference the documents listed below and any future filings made with the SEC under Sections 13(a), 13(c), 14 or 15(d) of the Exchange Act. The documents we are incorporating by reference are:

Our annual report on Form 10-K for the fiscal year ended December 31, 2004 (filing date March 16, 2005: Commission File No. 000-19319);

Our current reports on Form 8-K dated March 14, 2005 (filing date March 18, 2005), February 3, 2005 (filing date February 9, 2005) and February 7, 2005 (filing date February 9, 2005);

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The portions of our definitive proxy statement on Schedule 14A that are deemed "filed" with the SEC under the Exchange Act (filing date March 29, 2005); and

The description of our common stock and our outstanding Rights contained in our registration statement on Form 8-A, as that description is amended from time to time (filing date May 30, 1991: Commission File No. 000-19319).

You may request, orally or in writing, a copy of these documents, which will be provided to you at no cost, by contacting:

Vertex Pharmaceuticals Incorporated, 130 Waverly Street, Cambridge, Massachusetts 02139, (617) 444-6100, Attention: Investor Relations.

9,500,000 Shares

VERTEX PHARMACEUTICALS INCORPORATED

Common Stock

PROSPECTUS SUPPLEMENT

Merrill Lynch & Co.

JPMorgan

UBS Investment Bank

, 2005