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.

	Year ended December 31,					
1999	2000	2001	2002	2003	2004	
(1)	(1)	(1)	(1)	(1)	(1)	
		<u>1999</u> <u>2000</u>	$\begin{array}{c ccccccccccccccccccccccccccccccccccc$	$\begin{array}{c ccccccccccccccccccccccccccccccccccc$	$\begin{array}{c ccccccccccccccccccccccccccccccccccc$	

(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 are entitled 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 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" 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 debt securities 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 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 a majority in principal amount of the outstanding debt security and 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;

- 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);



- 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.