VERTEX PHARMACEUTICALS INC / MA
Form 424B5
September 18, 2008

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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 we are not soliciting an offer to buy these securities in any jurisdiction where the offer or sale is not permitted.

Subject to Completion
Preliminary Prospectus Supplement dated September 17, 2008

PROSPECTUS SUPPLEMENT
(To prospectus dated September 17, 2008)

7,000,000 Shares

VERTEX PHARMACEUTICALS INCORPORATED

Common Stock

Our common stock is listed on the Nasdaq Global Select Market under the symbol "VRTX". The last reported sale price of our common stock on the Nasdaq Global Select Market on September 17, 2008 was $26.57 per share.

Investing in our common stock involves risks. See "Risk Factors" beginning on page S-8 of this prospectus supplement.

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 accompanying prospectus is truthful or complete. Any representation to the contrary is a criminal offense.

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

To the extent that the underwriter sells more than 7,000,000 shares of common stock, the underwriter has the option to purchase up to an additional 1,050,000 shares from Vertex at the initial price to public less the underwriting discount.

The shares will be ready for delivery on or about , 2008.

Goldman, Sachs & Co.

The date of this prospectus is , 2008.

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Prospectus Supplement

Prospectus

This document is in two parts. The first part is this prospectus supplement, which describes the specific terms of this common stock offering and also adds to and updates information contained in the accompanying prospectus and the documents incorporated by reference into the prospectus. The second part, the accompanying prospectus, gives more general information, some of which does not apply to this offering. If the description of the offering varies between this prospectus supplement and the accompanying prospectus, you should rely on the information contained in this prospectus supplement. However, if any statement in one of these documents is inconsistent with a statement in another document having a later date for example, a document incorporated by reference in the accompanying prospectus the statement in the document having the later date modifies or supersedes the earlier statement. 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 captions "Where You Can Find More Information" and "Incorporation by Reference" in the prospectus.

We are offering to sell, and are seeking offers to buy, the common stock only in jurisdictions where such 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.

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

Business Overview

We are in the business of discovering, developing and commercializing small molecule drugs for the treatment of serious diseases. Telaprevir, our lead drug candidate, is an oral hepatitis C protease inhibitor and one of the most advanced of a new class of antiviral treatments in clinical development that targets hepatitis C virus, or HCV, infection, a life-threatening disease. In March 2008, we began a Phase 3 clinical trial of telaprevir to evaluate 24-week telaprevir-based treatment regimens in treatment-naïve patients with genotype 1 HCV, and, with our collaborator Tibotec, we are initiating a Phase 3 clinical trial of telaprevir to evaluate telaprevir-based treatment in patients with genotype 1 HCV who failed prior treatment.

We have built a drug discovery capability that integrates biology, pharmacology, biophysics, chemistry, automation and information technologies in a coordinated manner, with the goal of more efficiently identifying promising drug candidates to address significant unmet medical needs. Using this drug discovery capability we have identified, among other drug candidates: telaprevir; VX-770 and VX-809, two novel drug candidates targeting cystic fibrosis, or CF; VX-500 and VX-813, two second generation HCV protease inhibitors; and VX-509, a novel Janus Kinase 3, or JAK3, inhibitor that targets immune-mediated inflammatory diseases, or IMID. We have a number of other compounds in clinical trials, preclinical studies or research programs, which are being investigated either by us or in collaboration with other pharmaceutical companies. We co-discovered fosamprenavir calcium, an HIV protease inhibitor that is being marketed by GlaxoSmithKline plc as Lexiva in the United States and Telzir in Europe. We are building our drug development, supply chain management and commercialization organizations to prepare for the potential commercial launch of telaprevir and to support the development of other drug candidates in our pipeline.

Telaprevir (VX-950) (investigational oral HCV protease inhibitor for the treatment of chronic HCV infection)

We are conducting a comprehensive global clinical development program for telaprevir in collaboration with Janssen Pharmaceutica, N.V., or Janssen, a Johnson & Johnson company, and Mitsubishi Tanabe Pharma Corporation. This program is designed to support potential registration of telaprevir by us in North America and our collaborators in international markets for treatment-naïve and treatment-experienced patients across a range of HCV genotypes.

Telaprevir Clinical Development

In March 2008, we began our international three-arm Phase 3 clinical trial of telaprevir in treatment-naïve patients infected with genotype 1 HCV, which we refer to as the ADVANCE trial. This clinical trial was the first Phase 3 clinical trial initiated for an HCV protease inhibitor. The ADVANCE

trial is designed to enroll approximately 1,050 treatment-naïve patients with genotype 1 HCV and is focused on 24-week telaprevir-based treatment regimens utilizing rapid viral response criteria to determine which patients will complete all treatment after 24 weeks. In addition, in the third quarter of 2008, we expect to begin enrollment in a clinical trial that will include evaluation of 24-week and 48-week telaprevir-based treatment regimens. This clinical trial is expected to enroll approximately 450 treatment-naïve patients with genotype 1 HCV. We expect to complete enrollment in both of these trials during the fourth quarter of 2008 and to have sustained viral response, or SVR, data from them in the first half of 2010.

In August 2008, we reached agreement with regulatory authorities in the United States and the European Union to proceed with the REALIZE trial, a pivotal Phase 3 clinical trial with telaprevir in combination therapy for patients with chronic HCV infection who failed to achieve a SVR with prior therapy. The trial will be conducted in the United States and the European Union and will enroll approximately 650 patients with genotype 1 HCV who failed prior treatment with pegylated-interferon, or peg-IFN, and ribavirin, or RBV. The trial is designed to evaluate two 48-week telaprevir-based regimens in comparison with a 48-week control arm. Telaprevir will be dosed for 12 weeks.

The REALIZE trial will be conducted by Tibotec Pharmaceuticals Ltd., or Tibotec, at more than 100 centers in the United States and the European Union. Tibotec expects to complete enrollment of the REALIZE trial in the first quarter of 2009. The trial will include the following patient groups:

null responders who are patients who achieved less than a 2 log reduction in HCV RNA levels at week 12 of prior therapy;

partial responders who are patients who achieved at least a 2 log reduction at week 12, but failed to achieve undetectable HCV RNA levels by week 24 of prior therapy; and

relapsers who are patients who had undetectable HCV RNA at the completion of at least 42 weeks of prior treatment, but relapsed during follow-up.

The REALIZE trial will dose telaprevir in combination with peg-IFN and RBV. The REALIZE trial will enroll three 48-week trial arms:

telaprevir dosed at three-times daily for 12 weeks in combination with peg-IFN and RBV, followed by 36 weeks of treatment with peg-IFN and RBV alone;

peg-IFN and RBV alone for 4 weeks of treatment, followed by telaprevir dosed three-times daily for 12 weeks in combination with peg-IFN and RBV, followed by another 32 weeks of peg-IFN and RBV alone; and

peg-IFN and RBV alone dosed for 48 weeks, which is the control arm.

Telaprevir Clinical Data

In April 2008, we presented data from our PROVE 1 and PROVE 2 clinical trials at the 43rd annual meeting of the European Association for the Study of the Liver, or EASL. PROVE 1 and PROVE 2 were two Phase 2b clinical trials of telaprevir-based combination therapy in patients with genotype 1 HCV that enrolled an aggregate of approximately 580 treatment-naïve patients. On an intent-to-treat basis, in the 24-week telaprevir-based treatment arms of PROVE 1 and PROVE 2, 61% and 68%, respectively, of patients achieved SVR. Our criteria for SVR require that the patients have undetectable HCV RNA levels less than 10 IU/mL as measured by the Roche TaqMan® assay 24 weeks post-treatment. In the control arm of PROVE 1, on an intent-to-treat basis, 41% of patients achieved SVR, and in the control arm of PROVE 2, on an intent-to-treat basis, 48% of patients achieved undetectable HCV RNA levels at 12 weeks post-treatment.

In June 2008, we reported results of an interim analysis from PROVE 3, a randomized, double-blind, placebo-controlled Phase 2b clinical trial of telaprevir-based combination therapy in patients with genotype 1 HCV who did not achieve SVR with a previous treatment with peg-IFN and RBV. In the interim analysis of 115 patients, 52% of the patients who received treatment with a 24-week telaprevir-based regimen 12 weeks of telaprevir-based treatment followed by an additional 12 weeks of peg-IFN and RBV treatment had undetectable HCV RNA levels 12 weeks post-treatment. Of the 115 patients, 66 were non-responders patients who never achieved undetectable HCV RNA during prior treatment, including null responders and partial responders; 40 were prior relapsers; and 9 were prior breakthroughs patients who had viral rebound during prior treatment. Among patients receiving the 24-week telaprevir-based regimen, 41% (27 of 66) of the prior non-responders, 73% (29 of 40) of prior relapsers, and 44% (4 of 9) of prior breakthroughs had undetectable HCV RNA levels 12 weeks post-treatment.

In the control arm, which is evaluating 48 weeks of peg-IFN and RBV only, available data indicate that on an intent-to-treat basis 8% of the 114 patients had undetectable HCV RNA at week 12, and 30% had undetectable HCV RNA at week 36. In prior studies of peg-IFN and RBV in treatment-failure patients, the proportion of patients who had undetectable HCV RNA at week 36 of treatment has been significantly higher than the proportion who ultimately achieved SVR. End-of-treatment and post-treatment data including SVR rates are not yet available for this clinical trial arm in PROVE 3.

In addition to the 24-week telaprevir-based regimen that includes RBV and the 48 week control arm described above, two other treatment regimens are being evaluated in PROVE 3: a 24-week telaprevir treatment arm without RBV, and a 48-week treatment arm that includes 24 weeks of telaprevir dosing in combination with peg-IFN and RBV. The interim PROVE 3 analysis supports the inclusion of RBV in future studies of telaprevir-based regimens in treatment-failure patients, similar to earlier observations in our clinical trials with treatment-naïve subjects. In addition, available on-treatment results from PROVE 3 suggest that additional dosing of telaprevir beyond 12 weeks does not confer additional benefit to patients. Patient dosing has now been completed in PROVE 3 and all patients are now being followed post-treatment. We expect that PROVE 3 data will be the subject of a presentation at a medical conference later in 2008.

In our Phase 2 clinical trials, more than 700 patients with genotype 1 HCV received a telaprevir-based combination treatment with peg-IFN and RBV. The adverse event profile has been generally consistent across these clinical trials. The most common adverse events reported more frequently in patients receiving telaprevir have been gastrointestinal events, skin events rash and pruritus and anemia. There have been reports of severe rashes in clinical trials involving telaprevir-based treatments. In our Phase 2 clinical trials, the most common reason for discontinuation among patients receiving a telaprevir-based treatment regimen was rash, which has resulted in treatment discontinuations in 7% of patients in the telaprevir-based treatment arms. Other adverse events reported in our Phase 2 clinical trials were similar in type and frequency to those seen with peg-IFN and RBV treatment.

Additional Telaprevir Trials

In the PROVE, ADVANCE and REALIZE clinical trials, the patients in the telaprevir-based treatment arms are being dosed with 750 mg of telaprevir three times daily. In order to explore the safety and antiviral activity of a twice-daily dosing regimen of telaprevir, Tibotec is conducting a four-arm Phase 2a clinical trial the C208 clinical trial that enrolled approximately 160 treatment-naïve patients infected with genotype 1 HCV, to explore the safety and antiviral activity of a twice-daily dosing regimen of telaprevir 1,125 mg every 12 hours in combination with peg-IFN and RBV, as compared to a three-times daily dosing regimen 750 mg every 8 hours in combination with peg-IFN and RBV. Dosing through 12 weeks of treatment in all arms of the

C208 clinical trial is complete. An interim analysis conducted at week 12 of treatment showed that greater than 80% of patients, on an intent-to-treat basis, achieved undetectable HCV RNA levels at weeks 4 and 12 in both the twice-daily and three-times daily dosing arms of telaprevir given in combination with pegylated interferon alfa-2a (PEGASYS) and RBV. After 12 weeks of treatment, the type and frequency of adverse events across the clinical trial arms generally were consistent with those observed in previous clinical trials of telaprevir. No substantial differences in safety profile between twice-daily and three-times daily dosing regimens were observed. We believe these data support continued clinical evaluation of twice-daily dosing of telaprevir. We expect that a complete analysis will be performed upon the conclusion of this clinical trial in 2009 and that more detailed interim data will be presented at a medical conference later in 2008.

Tibotec also is conducting two clinical trials of telaprevir in patients with different HCV genotypes. Tibotec has completed an interim analysis of one of these trials, which we refer to as the C209 clinical trial. C209 is a clinical trial exploring the viral kinetics of telaprevir in approximately 50 patients with genotype 2 or genotype 3 HCV infection. The interim analysis was conducted after all subjects had completed 2 weeks of telaprevir dosing in combination with peg-IFN and RBV. Preliminary viral kinetic results at the end of week 2 of dosing suggest that telaprevir has potent antiviral activity against genotype 2 HCV. Analyses of viral dynamics are underway to further characterize the potency of telaprevir against genotype 2 HCV. Preliminary viral kinetic results at the end of week 2 do not support further investigation of telaprevir in patients with genotype 3 HCV infection. In the second of these clinical trials, Tibotec is evaluating telaprevir-based treatment regimens in patients infected with genotype 4 HCV.

VX-500 and VX-813 (second generation investigational oral HCV protease inhibitors for the treatment of chronic HCV infection)

We have completed a Phase 1a clinical trial of VX-500, an investigational HCV protease inhibitor, and expect to initiate a Phase 1b clinical trial of VX-500 in patients with HCV in the third quarter of 2008. We expect to initiate a Phase 1a clinical trial of another second-generation HCV protease inhibitor, VX-813, in the fourth quarter of 2008.

VX-770 (investigational oral CFTR potentiator for the treatment of cystic fibrosis)

We are evaluating VX-770 in a Phase 2a clinical trial. VX-770 is an investigational potentiator compound designed to enhance the activity of cystic fibrosis transmembrane regulator, or CFTR, proteins in patients with the G551D CF mutation, which leads to "gating defects". In March 2008, we announced interim results from Part 1 of the Phase 2a clinical trial of VX-770, which involved 20 patients with the G551D CF mutation. These data showed that patients in the trial receiving the highest dose of VX-770 over 14 days had a 10.1% improvement in lung function as measured by an increase in FEV(1), the lung function test most commonly used to monitor progression of airway disease in patients with CF. Patients receiving placebo showed a slight decrease in FEV(1). In addition, patients showed improved function of the CFTR protein, as measured by changes in sweat chloride levels, and by changes in chloride ion transport in the upper airway as measured by nasal potential difference. In patients receiving the highest dose of VX-770, sweat chloride levels decreased from a mean of 95.5 mmol/L at baseline to 53.2 mmol/L over the 14-day dosing period, and sweat chloride levels were reduced to below 60 mmol/L, which is the standard diagnostic cutoff for CF, in 6 of the 8 patients receiving the highest dose of VX-770. There was no notable change in sweat chloride levels in patients receiving placebo. In Part 1 of the Phase 2a clinical trial, VX-770 appeared to be well-tolerated over the 14-day duration of dosing, with observed adverse events being similar across both the VX-770 and placebo arms of the clinical trial.

We have completed dosing in Part 2 of this Phase 2a clinical trial, in which 18 patients with the G551D mutation on at least one allele were dosed with VX-770 for up to 28 days. We expect

that data from Part 2 of this clinical trial will be available by the end of 2008. Depending on the results of this clinical trial, and based on discussions to date with regulatory authorities, we believe that we could reach agreement with those authorities on the initiation of a registration program for VX-770 in 2009.

VX-809 (investigational oral CFTR corrector compound for the treatment of cystic fibrosis)

We are evaluating VX-809, an investigational corrector compound designed to increase the concentration of CFTR proteins on the cell surface in patients with CF trafficking defects. We are conducting two Phase 1 clinical trials of VX-809 in healthy volunteers. The first clinical trial is a single and multiple-dose trial. The second is a single-dose clinical trial examining the pharmacokinetics and safety of a solid dosage form of VX-809. Depending on the results from these Phase 1 trials, we plan to initiate a single-dose pharmacokinetics and safety trial of VX-809 in patients with CF in the second half of 2008.

VX-509 (investigational oral JAK3 inhibitor for the treatment of IMID indications)

VX-509 is a novel oral JAK3 inhibitor that we believe has the potential to be used in multiple IMID indications. We began a Phase 1a clinical trial of VX-509 in the second quarter of 2008.

Corporate Information

We were incorporated in Massachusetts in 1989. Our principal executive offices are located at 130 Waverly Street, Cambridge, Massachusetts 02139, and we have research sites located in San Diego, California, Iowa City, Iowa and Milton Park, U.K. Our telephone number is (617) 444-6100, and 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, the accompanying prospectus or the documents incorporated by reference in the accompanying prospectus.

"Vertex" and the Vertex logo in the form appearing on the cover page of this prospectus supplement are registered trademarks of Vertex. "Lexiva" and "Telzir" are registered trademarks of GlaxoSmithKline plc. Other brands, names and trademarks contained in this prospectus supplement, the accompanying prospectus or the documents incorporated by reference in the prospectus are the property of their respective owners.

The Offering

Unless otherwise indicated, all information in this prospectus supplement assumes that the underwriter does not exercise its option to purchase additional shares.

Common stock offered by us	7,000,000 shares
Common stock to be outstanding after this offering	148,119,323 shares
Option to purchase additional shares	1,050,000 shares
Use of proceeds	We intend to use the net proceeds from this offering for general corporate purposes, which we expect to include investment in the development and commercialization of telaprevir and VX-770, and the development of our other drug candidates, research expenditures, manufacture and supply of drug substances, and which may include capital expenditures, investments and potentially acquisitions. See "Use of Proceeds" on page S-27.
Risk factors	See "Risk Factors" beginning on page S-8 and other information included in this prospectus supplement for a discussion of factors you should carefully consider before deciding to invest in shares of our common stock.
Nasdaq Global Select Market symbol	VRTX

The information above is based on 141,119,323 shares of common stock outstanding as of June 30, 2008. It does not include:

16,515,634 shares of common stock issuable upon the exercise of stock options outstanding as of June 30, 2008 at a weighted-average exercise price of $28.02 per share;

1,459,950 shares of common stock issuable upon the exercise of stock options granted to employees after June 30, 2008 and on or before September 15, 2008 at a weighted-average exercise price of $32.06 per share;

204,645 restricted shares of common stock issued to employees after June 30, 2008 and on or before September 15, 2008; and

12,424,916 shares of common stock that are issuable upon the conversion of the 4.75% Convertible Senior Subordinated Notes due 2013.

Summary Consolidated Financial Data

The following unaudited summary consolidated financial data for each of the three years in the period ended December 31, 2007 are derived from our audited consolidated financial statements incorporated by reference in the accompanying prospectus. The following unaudited summary consolidated financial data for each of the six months in the periods ended June 30, 2008 and 2007 are derived from our unaudited condensed consolidated financial statements incorporated by reference in the accompanying prospectus. The data should be read in conjunction with our audited consolidated financial statements and related notes and "Management's Discussion and Analysis of Financial Condition and Results of Operations" that are incorporated by reference into the accompanying prospectus from our Annual Report on Form 10-K for the year ended December 31, 2007, as filed with the Securities and Exchange Commission, or SEC, on February 11, 2008, and our unaudited condensed consolidated financial statements and related notes and "Management's Discussion and Analysis of Financial Condition and Results of Operations" that are incorporated by reference into the accompanying prospectus from our Quarterly Report on Form 10-Q for the quarter ended June 30, 2008, as filed with the SEC on August 11, 2008.

	Year Ended December 31,			Six Months Ended June 30,	
	2007	2006	2005	2008	2007
	(In thousands, except per share amounts)				
Consolidated Statements of Operations Data:					
Revenues:					
Royalty revenues	$ 47,973	$ 41,208	$ 32,829	$ 20,592	$ 20,763
Collaborative and other research and development revenues	151,039	175,148	128,061	90,492	86,243
Total revenues	199,012	216,356	160,890	111,084	107,006
Costs and expenses:					
Royalty expenses	13,904	12,170	10,098	7,277	6,670
Research and development expenses	513,054	371,713	248,540	241,714	268,765
Sales, general and administrative expenses	84,727	57,860	43,990	50,512	39,859
Restructuring expense	7,119	3,651	8,134	1,798	5,961
Total costs and expenses	618,804	445,394	310,762	301,301	321,255
Loss from operations	(419,792)	(229,038)	(149,872)	(190,217)	(214,249)
Other income/(expense)	28,513	21,101	(53,545)	2,742	15,754
Cumulative effect of a change in accounting principle SFAS 123(R)		1,046			
Net loss	$ (391,279)	$ (206,891)	$ (203,417)	$ (187,475)	$ (198,495)
Basic and diluted net loss per common share	$ (3.03)	$ (1.83)	$ (2.28)	$ (1.37)	$ (1.56)
	128,986	113,221	89,241	136,607	127,527

	Year Ended December 31,			Six Months Ended June 30,	
Basic and diluted weighted-average number of common shares outstanding					

	June 30, 2008	
	Actual	As Adjusted(1)
	(In thousands)	
Consolidated Balance Sheet Data:		
Cash, cash equivalents and marketable securities	$ 832,062	$ 1,014,862
Other current assets	25,566	25,566
Restricted cash	30,258	30,258
Property and equipment, net	66,630	66,630
Other non-current assets	16,289	16,289
Total assets	$ 970,805	$ 1,153,605
Deferred revenues	$ 267,581	$ 267,581
Accrued restructuring expense	34,490	34,490
Other liabilities	141,309	141,309
Convertible Senior Subordinated Notes due 2013	287,500	287,500
Stockholders' equity	239,925	422,725
Total liabilities and stockholders' equity	$ 970,805	$ 1,153,605

(1) Reflects the sale of our common stock offered hereby at an assumed offering price of $26.57 per share, after deducting estimated underwriting discount and offering expenses.

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, including net losses of $391.3 million, $206.9 million and $203.4 million during 2007, 2006 and 2005, respectively, and a net loss of $187.5 million in the six months ended June 30, 2008. We expect to continue to incur a significant operating loss for the remainder of 2008. We believe that operating losses will continue beyond 2008, because we are planning to make significant investments in research and development and in building commercial supply of telaprevir to prepare for the potential launch of telaprevir, and because we will incur significant selling, general and administrative expenses in the course of researching, developing and commercializing our drug candidates, particularly telaprevir. We are investing significant research and development resources across a relatively broad array of therapeutic areas, due in part to the high risks associated with the biotechnology and pharmaceutical business and the relatively high potential for failure of any specific effort. This diversification strategy requires more significant financial resources than would be required if we pursued a more limited approach or focused exclusively on telaprevir. In particular, in 2008 we expect to invest significant resources in order to advance the development of VX-770, VX-809, VX-500, VX-813 and VX-509. Our net losses have had and will continue to have an adverse effect on, among other things, our stockholders' equity, total assets and working capital. 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 depend heavily on the success of our lead drug candidate, telaprevir, which is still under development. If we are unable to commercialize telaprevir, or experience delays in doing so, our business will be materially harmed.

We are investing a significant portion of our time, personnel and financial resources in the development of telaprevir. The clinical development and commercial success of telaprevir will depend on several factors, including the following:

- successful completion and favorable outcomes of clinical trials;
- ongoing discussions with the FDA and comparable foreign authorities regarding the scope and design of our clinical trials, the quality of our manufacturing process for telaprevir and our clinical trial results;
- receipt and timing of marketing approvals for telaprevir from the United States Food and Drug Administration, or FDA, and similar foreign regulatory authorities;
- receipt and timing of marketing approvals from the FDA and similar foreign regulatory authorities for products being developed for the treatment of HCV by our competitors;

our ability to conduct clinical trials with respect to telaprevir in a timely manner to support a potential new drug application, or NDA, for marketing approval;

establishing and maintaining commercial manufacturing arrangements for telaprevir with third-party manufacturers that are subject to extensive regulation by the FDA;

launching commercial sales of telaprevir by us and our collaborators;

the efficacy and other characteristics of telaprevir relative to existing and future treatments for HCV;

our ability to increase awareness of the benefits of early treatment for HCV if telaprevir is approved; and

acceptance of telaprevir, if approved, in the medical community and with third-party payors.

If the data from our ongoing clinical trials or non-clinical studies regarding the safety or efficacy of telaprevir are not favorable, we may be forced to delay or terminate the clinical development of telaprevir, which would materially harm our business. Further, even if we gain marketing approvals from the FDA and comparable foreign regulatory authorities in a timely manner, we cannot be sure that telaprevir will be commercially successful in the pharmaceutical market. We are investing significant amounts of cash in the development and commercialization process, and any significant delay in realizing a return on the investment would require us to engage in additional financing activities to recoup that investment, which may not be available on satisfactory terms, if at all. If the results of clinical trials of telaprevir, the anticipated or actual timing of marketing approvals for telaprevir, or the market acceptance of telaprevir, if approved, do not meet the expectations of investors or public market analysts, the market price of our common stock would likely decline.

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

We expect to incur substantial research and development and related supporting expenses as we design and develop existing and future compounds, undertake clinical trials of drug candidates resulting from such compounds, and build our drug supply, regulatory, development and commercial capabilities. We also expect to incur substantial administrative and commercialization expenses in the future. We are making significant capital investments in building our drug product supply chain and creating pre-launch inventory of telaprevir and may need to make additional significant capital investments for one or more of our other drug candidates. We anticipate that we will finance these substantial cash needs with:

public offerings or private placements of our debt or equity securities or other methods of financing;

cash received from our existing collaborative agreements;

cash received from new collaborative agreements or from the sale of existing assets;

existing cash reserves, together with interest earned on those reserves; or

future product sales to the extent that we market drugs directly.

While we believe that our current cash, cash equivalents and marketable securities, in addition to amounts we expect to receive from our collaborators under existing contractual obligations, will be sufficient to fund our operations for at least the next twelve months, we may raise additional capital through public offerings or private placements of our securities, securing new collaborative agreements, or other methods of financing. Any such capital raising transactions may or may not be similar to transactions in which we have engaged in the past. Any equity financings could result in dilution to our then-existing security holders. Any debt financing may be on terms that, among other things, restrict our ability to pay interest and dividends although we do not intend to pay

dividends for the foreseeable future. If adequate funds are not available on acceptable terms, or at all, we may be required to curtail significantly or discontinue one or more of our research, drug discovery or development programs, including clinical trials, incur significant cash exit costs, or attempt to obtain funds through arrangements with collaborators or others that may require us to relinquish rights to certain of our technologies, drugs or drug candidates. Additional financing may not be available on acceptable terms, if at all.

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

The success of our business depends primarily upon our ability, and our collaborators' ability, to develop and commercialize our drug candidates, including telaprevir, successfully. Due to the development efforts of our competitors, in order to develop a successful franchise in a therapeutic area it is often necessary to develop follow-on compounds and/or develop new combination therapies. Our drug candidates are in various stages of development and must satisfy rigorous standards of safety and efficacy before they can be approved by the FDA or other regulatory authorities for sale. To satisfy these standards, we and/or our collaborators must allocate our resources among our various development programs and must engage in expensive and lengthy testing of our drug candidates. These discovery and development efforts for a new pharmaceutical product, including follow-on compounds, are lengthy and resource- intensive, and may take 10 to 15 years or more. Despite our efforts, our drug candidates may not:

offer therapeutic or other improvement over existing competitive drugs;

be proven safe and effective in clinical trials;

meet applicable regulatory standards;

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

if approved for commercial sale, be successfully commercialized.

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

We and many other companies in the pharmaceutical and biotechnology industries have suffered significant setbacks in late-stage clinical trials even after achieving promising results in early-stage development. Accordingly, the results from the completed preclinical studies and clinical trials and ongoing clinical trials for our drug candidates may not be predictive of the results we may obtain in later stage trials, and may not be predictive of the likelihood of approval of a drug candidate for commercial sale. In addition, from time to time, we report interim data from our clinical trials, including the PROVE clinical trials of telaprevir. Interim data is subject to change as final data are confirmed, and there can be no assurances that interim data will be confirmed upon the analysis of final data.

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

Our drug candidates are subject to extensive governmental regulations relating to their development, clinical trials, manufacturing and commercialization. Rigorous preclinical testing and

clinical trials and an extensive regulatory approval process are required in the United States and in most other countries prior to the commercial sale of our drug candidates. Satisfaction of these and other regulatory requirements is costly, time consuming, uncertain and subject to unanticipated delays. It is possible that none of the drug candidates we are developing independently, or in collaboration with others, will be approved for marketing.

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

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

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

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

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

- ongoing discussions with the FDA or comparable foreign authorities regarding the scope or design of our clinical trials and the number of clinical trials we must conduct;
- delays in receiving or the inability to obtain required approvals from institutional review boards at one or more of the institutions at which a clinical trial is conducted or other reviewing entities at clinical sites selected for participation in our clinical trials;
- delays in enrolling volunteers or patients into clinical trials;
- a lower than anticipated retention rate of volunteers or patients in clinical trials;
- the need to repeat clinical trials as a result of inconclusive results or unforeseen complications in testing;
- inadequate supply or deficient quality of drug candidate materials or other materials necessary for the conduct of our clinical trials;

unfavorable FDA inspection and review of a manufacturing facility for a drug candidate or its relevant manufacturing records or a clinical trial site or records of any clinical or preclinical investigation;

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

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

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

We, our collaborators, the FDA or other applicable regulatory authorities may suspend clinical trials of a drug candidate at any time if we or they believe the subjects or patients participating in such clinical trials are being exposed to unacceptable health risks or for other reasons. Any such suspension could materially adversely impact the development of a particular drug candidate and our business.

In addition, it is impossible to predict whether legislative changes will be enacted, or whether FDA regulations, guidance or interpretations will be changed, or what the impact of such changes, if any, may be. If we experience any such problems, we may not have the financial resources to continue development of the drug candidate that is affected or the development of any of our other drug candidates.

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

Our drug candidates in development may not be able to compete effectively with drugs that are currently on the market or new drugs that may be developed by others. No assurance can be given that telaprevir will be approved for marketing prior to competing therapies, or at all. There are many other companies developing drugs for the same indications that we are pursuing in development in particular for the treatment of HCV infection. In order to compete successfully in these areas, we must demonstrate improved safety, efficacy and ease of manufacturing and gain market acceptance over competing drugs that may receive regulatory approval before or after our drug candidates, and over those that currently are marketed. Many of our competitors, including major pharmaceutical companies such as GlaxoSmithKline, Wyeth, Pfizer, Roche, Amgen, Novartis, Johnson & Johnson and Schering-Plough possess substantially greater financial, technical and human resources than we possess. In addition, many of our competitors have significantly greater experience than we have in conducting preclinical and nonclinical testing and human clinical trials of drug candidates, scaling up manufacturing operations and obtaining regulatory approvals of drugs and manufacturing facilities. Accordingly, our competitors may succeed in obtaining regulatory approval for drugs more rapidly than we do. If we obtain regulatory approval and launch commercial sales of our drug candidates, we also will compete with respect to manufacturing efficiency and sales and marketing capabilities, areas in which we currently have limited experience.

We believe that the first company that is able to successfully develop and obtain marketing approval for a new treatment for chronic HCV infection with significant advantages over the current standard of care may have a significant competitive advantage over later-approved therapies for HCV infection. We are aware of a number of companies that are developing new treatments for HCV infection including protease inhibitor compounds like telaprevir, polymerase inhibitor compounds and advanced interferons. Even if we are able to obtain marketing approval for telaprevir, it is possible that one or more of these therapies could be approved prior to or shortly after we obtain such approval for telaprevir, which we believe could negatively impact telaprevir sales.

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

We currently are developing drug candidates for regulatory approval for the first time since our inception, and are in the process of implementing regulated processes and systems required to obtain and maintain regulatory approval for our drug 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 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, or if compliance issues are identified at any point in the development and approval process, we may experience delays in filing for regulatory approval for our drug candidates, or delays in obtaining regulatory approval after filing. In addition, any later discovery of previously unknown problems or safety issues with approved drugs or manufacturing processes, or failure to comply with regulatory requirements, may result in restrictions on such drugs or manufacturing processes, withdrawal of drugs 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 agreements that transfer responsibility for complying with specified regulatory requirements, such as filing and maintenance of marketing authorizations and safety reporting or compliance with manufacturing requirements, to our collaborators and third-party manufacturers. If our collaborators or third-party manufacturers do not fulfill these regulatory obligations, any drugs 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 obtain regulatory approvals, our drug candidates will be subject to ongoing regulatory review. If we fail to comply with continuing United States and applicable foreign regulations, we could lose those approvals, and our business would be seriously harmed.

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

suspension or withdrawal of regulatory approval, product recalls and seizures, operating restrictions and criminal prosecutions.

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

Small molecule drug discovery and development involve, initially, the identification of chemical compounds 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 humans. Our ultimate objective is to determine whether the drug candidates have physical characteristics, both intrinsically and in animal and human systems, and 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 investigation process for a particular drug candidate, could result in uncertainty over the proper course to pursue, or could result in the termination of further drug development efforts with respect to the compound being evaluated. We monitor the results of our discovery research and our nonclinical studies and clinical trials and regularly evaluate and re-evaluate our portfolio investments with the objective of balancing risk and potential return in view of new data and scientific, business and commercial insights. This process can result in relatively abrupt changes in focus and priority as new information comes to light and we gain additional insights into ongoing programs and potential new programs.

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

We have granted development and commercialization rights to telaprevir to Janssen (worldwide other than North America and Far East) and to Mitsubishi Tanabe (Far East). We expect to receive significant financial support under our Janssen collaboration agreement, as well as meaningful technical and manufacturing contributions to the telaprevir program. The success of some of our key in-house programs, such as for telaprevir, is dependent upon the continued financial and other support that our collaborators have agreed to provide.

For some drug candidates on which we are not currently focusing our development efforts, we have granted worldwide rights to a collaborator, as in our collaborations with Merck and Avalon.

The success of our collaborations depends on the efforts and activities of our collaborators. Each of our collaborators has significant discretion in determining the efforts and resources that it will apply to the collaboration. Our existing collaborations may not be scientifically or commercially successful, and we may fail in our attempts to establish further collaborations to develop our drug candidates on acceptable terms.

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

Our collaboration agreements are subject to termination under various circumstances, including, as in the case of our agreements with Janssen and Merck, termination without cause. Any such termination could have an adverse material effect on our financial condition and/or delay the development and commercial sale of our drug candidates, including telaprevir.

Our collaborators may change the focus of their development and commercialization efforts. Pharmaceutical and biotechnology companies historically have re-evaluated their development and commercialization priorities following mergers and consolidations, which have been common in recent years in these industries. The ability of some of our drug

candidates to reach their potential could be limited if our collaborators decrease or fail to increase development or commercialization efforts related to those drug candidates.

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

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

If we are unable to attract and retain collaborators for the development and commercialization of our drugs and drug candidates, we may not be able to fund our development and commercialization activities.

Our collaborators have agreed to fund portions of our pharmaceutical development programs and/or to conduct the development and commercialization of specified drug candidates and, if they are approved, drugs. In exchange, we have given them technology, sales and marketing rights relating to those drugs and drug candidates. Some of our corporate collaborators have rights to control the planning and execution of drug development and clinical programs including for our Aurora Kinase inhibitor drug candidates, MK-5108 (VX-689) and AVN-944 (VX-944). Our collaborators may exercise their control rights in ways that may negatively affect the timing and success of those programs. Our collaborations are subject to termination rights by the collaborators. If any of our collaborators were to terminate its relationship with us, or fail to meet its contractual obligations, that action could have a material adverse effect on our ability to develop, manufacture and market any drug candidates being developed under the collaboration. We expect to seek additional collaborative arrangements, which may not be available to us on favorable terms, or at all, to develop and commercialize our drug candidates in the future. We plan to seek a collaborator for our oral MAP kinase inhibitor VX-702 for the treatment of rheumatoid arthritis and other inflammatory diseases. No assurance can be given that these efforts will be successful. Even if we are able to establish acceptable collaborative arrangements in the future, these collaborations may not be successful.

Our investment in the clinical development and manufacture of a commercial supply of telaprevir may not result in any benefit to us if telaprevir is not approved for commercial sale.

We are investing significant resources in the clinical development of telaprevir. In 2006 and 2007, we increased our investment in telaprevir to support our Phase 2b clinical development program and in 2008 and 2009 we have been and will be investing in our global registration program, including our Phase 3 clinical trial. Telaprevir is the first drug candidate for which we expect to perform all activities related to late-stage development, drug supply, registration and commercialization in a major market. We are planning for and investing significant resources now in preparation for application for marketing approval, commercial supply and sales and marketing. We also expect to incur significant costs for the remainder of 2008 and in 2009 to manufacture registration batches and invest in telaprevir commercial supply. Our engagement in these resource-intensive activities could make it more difficult for us to maintain our portfolio focus, and puts significant investment at risk if we do not obtain regulatory approval and successfully commercialize telaprevir in North America. There is no assurance that our development of telaprevir will lead successfully to regulatory approval, or that obtaining regulatory approval will lead to commercial success. If telaprevir is not approved for commercial sale or if its development is delayed for any reason, our full investment in telaprevir may be at risk, we may face significant costs to dispose of unusable inventory, and our business and financial condition could be materially adversely affected.

We depend on third-party manufacturers, including sole source suppliers, to manufacture clinical trial materials for clinical trials and expect to continue to rely on them to meet our commercial supply needs for any drug candidate that is approved for sale. We may not be able to establish or maintain these relationships and could experience disruptions outside of our control.

We currently are relying on a worldwide network of third-party manufacturers to manufacture and distribute our drug candidates for clinical trials, and we expect that we will continue to do so to meet our commercial supply needs for these drugs, including telaprevir, if they are approved for sale. As a result of our reliance on these third-party manufacturers and suppliers, including sole source suppliers of certain components of our drug candidates, we may be subject to significant supply disruptions outside of our control.

We will be responsible for supplying telaprevir for sale in North America if we are successful in obtaining marketing approval. Establishing the commercial supply chain for telaprevir is a multi-step international endeavor involving the purchase of several raw materials, the application of certain manufacturing processes requiring significant lead times, the conversion of active pharmaceutical ingredient to tablet form and the packaging of tablets for distribution. We expect to source raw materials, drug substance and drug product, including finished packaging, from third parties located in China, the European Union, Japan and the United States, and we currently are establishing and expanding those third-party relationships. Establishing and providing quality assurance for this global supply chain requires a significant financial commitment, experienced personnel and the creation or expansion of numerous third-party contractual relationships. While we believe that there are multiple third parties that are capable of providing the materials and services that we need in order to manufacture and distribute telaprevir, if it is approved for sale, some of these services are in high demand and capacity is constrained. Because of the significant lead times involved in the manufacture and supply of telaprevir, we may have less flexibility to adjust our supply in response to changes in demand than if we had shorter lead times. There can be no assurance that we will be able to establish and maintain this commercial supply chain on commercially reasonable terms in order to support a timely launch of telaprevir or at all.

We plan to identify and enter into commercial relationships with multiple third-party manufacturers in order to reduce the risk of supply chain disruption by limiting our reliance on any one manufacturer. In addition, we are in the process of transferring technical information regarding the manufacture of telaprevir to Janssen so that Janssen will be able to manufacture telaprevir, if approved, for sale in Janssen's territories and as a secondary source for us. There is no assurance, however, that we will be able to establish second sources for each stage of manufacturing of telaprevir, or any other drug or drug candidate, or that any second source will be able to produce sufficient quantities in the required timeframe to avoid a supply chain disruption if there is a problem with one of our suppliers.

Even if we successfully establish arrangements with third-party manufacturers, supply disruptions may result from a number of factors including shortages in product raw materials, labor or technical difficulties, regulatory inspections or restrictions, shipping or customs delays or any other performance failure by any third-party manufacturer on which we rely.

Any supply disruptions could impact the timing of our clinical trials and the commercial launch of any approved drugs. Furthermore, we may be required to modify our production methods to permit us to economically manufacture our drugs for commercial launch and sale. These modifications may require us to reevaluate our resources and the resources of our third-party manufacturers, which could result in abrupt changes in our production methods and supplies. Upon approval of a drug candidate for sale, if any, we similarly may be at risk of supply chain disruption for our commercial drug supply. In the course of its services, a contract manufacturer may develop process technology related to the manufacture of our drug candidates that the manufacturer owns,

either independently or jointly with us. This would increase our reliance on that manufacturer or require us to obtain a license from that manufacturer in order to have our products manufactured by other suppliers utilizing the same process.

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

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

If we are unable to develop independent sales and marketing capabilities or establish third-party relationships for the commercialization of our drug candidates, we will not be able to successfully commercialize our drug candidates even if we are able to obtain regulatory approval.

We currently have limited experience as a company in sales and marketing or with respect to pricing and obtaining adequate third-party reimbursement for drugs. We will need to either develop marketing capabilities and an independent sales force or enter into arrangements with third parties to sell and market any of our drug candidates if they are approved for sale by regulatory authorities.

In order to market telaprevir in North America if it is approved, we intend to build a marketing organization and a direct sales force, which will require substantial efforts and significant management and financial resources. During 2008, we have committed and intend to continue to commit significant personnel and financial resources to this effort, staging our commitments to the extent possible in consideration of the ongoing telaprevir development timeline. We will need to devote significant effort, in particular, to recruiting individuals with experience in the sales and marketing of pharmaceutical products. Competition for personnel with these skills is intense and may be particularly difficult for us since telaprevir is still an investigational drug candidate and we will be competing with companies that are currently marketing successful drugs. As a result, we may not be able to successfully develop our own marketing capabilities or independent sales force for telaprevir in North America in order to support an effective launch of telaprevir if it is approved for sale.

We have granted commercialization rights to other pharmaceutical companies with respect to certain of our drug candidates in specific geographic locations, including telaprevir (Janssen worldwide except for North America and the Far East, and Mitsubishi Tanabe in the Far East), Aurora kinase inhibitors (Merck worldwide) and AVN-944 (VX-944) (Avalon worldwide). To the extent that our collaborators have commercial rights to our drugs, any revenues we receive from any approved drugs will depend primarily on the sales and marketing efforts of others. We do not know whether we will be able to enter into additional third-party sales and marketing arrangements with respect to any of our other drug candidates on acceptable terms, if at all, or whether we will be able to leverage the sales and marketing capabilities we intend to build for telaprevir in order to market and sell any other drug candidate if it is approved for sale.

Risks associated with our international business relationships could materially adversely affect our business.

We have manufacturing, collaborative and clinical trial relationships, and we and our collaborators are seeking approval for our drug candidates, outside the United States. In addition, we expect that if telaprevir is approved for commercial sale, a significant portion of our commercial supply chain, including sourcing of raw materials and manufacturing, will be located in China, Japan and the European Union. Consequently, we are, and will continue to be, subject to risks related to operating in foreign countries. Risks associated with conducting operations in foreign countries include:

- differing regulatory requirements for drug approvals in foreign countries;
- unexpected changes in tariffs, trade barriers and regulatory requirements;
- economic weakness, including inflation, or political instability in particular foreign economies and markets;
- compliance with tax, employment, immigration and labor laws for employees living or traveling abroad;
- foreign taxes, including withholding of payroll taxes;
- foreign currency fluctuations, which could result in increased operating expenses or reduced revenues, and other obligations incident to doing business or operating a subsidiary in another country;
- workforce uncertainty in countries where labor unrest is more common than in the United States;
- production shortages resulting from any events affecting raw material supply or manufacturing capabilities abroad; and
- business interruptions resulting from geo-political actions, including war and terrorism.

These and other risks associated with our international operations could materially adversely affect our business.

If we are unable to realize the expected benefits of our drug discovery capabilities and other technologies, we may not be able to compete in the marketplace.

The pharmaceutical research field is characterized by rapid technological progress and intense competition. As a result, we may not realize the expected benefits from our integrated drug discovery capabilities and 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, or at all, our business could be adversely affected.

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

We expect that if our clinical drug 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. For example, the number of our full-time employees increased by 20% in 2007, and we expect to experience significant growth in the future. Our ability to commercialize our drug candidates, 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.

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

We face intense competition for our personnel from our competitors, our collaborators and other companies throughout our industry. Moreover, the growth of local biotechnology companies and the expansion of major pharmaceutical companies into the Boston area have increased competition for the available pool of skilled employees, especially in technical fields, and the high cost of living in the Boston and San Diego areas makes it difficult to attract employees from other parts of the country to these areas. A failure to retain, as well as hire, train and effectively integrate into our organization a sufficient number of qualified scientists, professionals and sales personnel would negatively affect our business and our ability to grow our business.

If our patents do not protect our drugs, or our drugs 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 drugs, their uses and our processes, to preserve our trade secrets and to operate without infringing the proprietary rights of third parties. We do not know whether any patents will issue from any of our patent applications or, even if patents issue or have issued, that the issued claims will provide us with any significant protection against competitive products or otherwise be valuable commercially. Legal standards relating to the validity of patents and the proper scope of their claims in the pharmaceutical field are still evolving, and there is no consistent law or policy regarding the valid breadth of claims in biopharmaceutical patents or the effect of prior art on them. If we are not able to obtain adequate patent protection, our ability to prevent competitors from making, using and selling similar drugs will be limited. Furthermore, our activities may infringe the claims of patents held by third parties.

Defense and prosecution of infringement or other intellectual property claims, as well as participation in other inter-party proceedings, can be expensive and time-consuming, regardless of whether or not the outcome is favorable to us. If the outcome of any such litigation or proceeding were adverse, we could be subject to significant liabilities to third parties, could be required to obtain licenses from third parties or could be required to cease sales of affected drugs, any of which outcomes could have a material adverse effect on our business.

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

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

the timing of the market introduction of competitive drugs;

lower demonstrated clinical safety and efficacy compared to other drugs;

lack of cost-effectiveness;

lack of availability of reimbursement from third-party payors;

convenience and ease of administration;

prevalence and severity of adverse side effects;

other potential advantages of alternative treatment methods; and

ineffective marketing and distribution support.

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

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

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

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

in the United States. Such legislation, or similar regulatory changes or relaxation of laws that restrict imports of drugs from other countries, could reduce the net price we receive for our marketed drugs.

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

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

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

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

We have adopted anti-takeover provisions and are subject to Massachusetts corporate laws that may frustrate any attempt to remove or replace our current management.

Our articles of organization and by-laws, Massachusetts state laws and our stockholder rights plan may discourage certain types of transactions involving an actual or potential change of control of Vertex that might be beneficial to us or our security holders. 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. 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. Massachusetts state law prohibits us from engaging in specified business combinations, unless the combination is approved or consummated in a prescribed manner, and prohibits voting by any stockholder who acquires 20% or more of our voting stock without stockholder approval. As a result, stockholders or other parties may find it more difficult to remove or replace our current management.

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

Market prices for securities of companies such as Vertex are highly volatile. From January 1, 2007 to July 30, 2008, our common stock traded between $13.84 and $41.42 per share. 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 trials or nonclinical studies relating to our drug candidates or those of our competitors;
- announcements of financial results and other operating performance measures, or capital structuring or financing activities;
- technological innovations or the introduction of new drugs by our competitors;
- government regulatory action;
- public concern as to the safety of drugs developed by others;
- developments in patent or other intellectual property rights or announcements relating to these matters;
- developments in domestic and international governmental policy or regulation, for example relating to intellectual property rights; and
- developments relating specifically to other companies and market conditions for pharmaceutical and biotechnology stocks or stocks in general.

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

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

Government investigations or litigation against our collaborators could adversly affect our business.

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

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

As of June 30, 2008, we had outstanding $287.5 million in aggregate principal amount of 4.75% Convertible Senior Subordinated Notes due 2013. The level of our indebtedness could 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 substantial cash to service the semi-annual interest payments on our outstanding debt, thereby reducing the amount of cash available for other purposes.

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 restricted common stock or common stock upon exercise of any outstanding option would be dilutive, and may cause the market price for a share of our common stock to decline. As of June 30, 2008, we had 141,119,323 shares of common stock outstanding. We also had outstanding options to purchase 16,515,634 shares of common stock with a weighted-average exercise price of $28.02 per share. Outstanding options may be exercised if the market price of our common stock exceeds the applicable exercise price. We may issue additional common stock or restricted securities in the future as part of our financing activities and any such issuances may have a dilutive effect on existing shareholders. Although we and our officers and directors have agreed to lock-up restrictions for a 90-day period, with respect to us, and a 60-day period, with respect to our directors and officers, following the offering, these restrictions are subject to waiver by the underwriter.

Risks Related to Our Common Stock and This Offering

We 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 from this offering 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 management may use the net proceeds for corporate purposes that may not yield profitable results or increase our market value.

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 $26.57 per share, if you purchase shares of common stock in this offering, you will suffer immediate and substantial dilution of $23.81 per share in the net tangible book value of the common stock. If the underwriter exercises its option to purchase additional shares, you will experience additional dilution. See "Dilution" on page S-28 for a more detailed discussion of the dilution you will incur in this offering.

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 regarding:

- our expectations regarding clinical trials, development timelines and regulatory authority filings for telaprevir, VX-770 and other drug candidates under development by us and our collaborators;
- our expectations regarding the number of patients that will be evaluated, the trial design that will be utilized, the anticipated date by which enrollment will be commenced and/or completed and the expected date by which SVR data, interim data and/or final data will be available and/or publicly announced for our ADVANCE Phase 3 clinical trial, the REALIZE Phase 3 clinical trial, the other ongoing or planned clinical trials of telaprevir, the ongoing Phase 2a clinical trial of and the potential registration program for VX-770, the Phase 1a clinical trials and planned clinical trial of VX-809, the Phase 1b clinical trial of VX-500 and the Phase 1a clinical trial of VX-813, and the clinical trials being conducted by our collaborators of drug candidates for the treatment of cancer;
- expectations regarding our net loss, revenues and costs and expenses in future periods as compared to previous periods;
- the data that will be generated by ongoing and planned clinical trials, and the ability to use that data for the design and initiation of further clinical trials and to support regulatory filings, including potentially an NDA for telaprevir;
- our beliefs that we could reach agreement with regulatory authorities on the initiation of a registration program for VX-770 in 2009;
- the design of our global clinical program for telaprevir and our ability to potentially register telaprevir for marketing across a range of genotypes and patient populations;
- our expectations regarding the future market demand and medical need for telaprevir and our other drug candidates;
- our ability to retain greater development control of, and commercial rights to, drug candidates by funding a greater portion of our research programs;
- our beliefs regarding the support provided by clinical trials and preclinical and nonclinical studies of our drug candidates for further investigation, clinical trials or potential use as a treatment of those drug candidates;
- our ability to capitalize on the advances in our telaprevir clinical program by building our drug development, supply chain management and commercialization organizations in order to prepare for the potential commercial launch of telaprevir and to support the development of our other drug candidates;
- the focus of our drug development efforts;
- the establishment, development and maintenance of collaborative relationships;
- our ability to use our research programs to identify and develop new drug candidates to address serious diseases and significant unmet medical needs;

our ability to increase our headcount and scale up our drug development and commercialization capabilities;

our estimates regarding obligations associated with a lease of a facility in Kendall Square, Cambridge, Massachusetts; and

our liquidity and our expectations regarding our needs for additional capital.

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, the accompanying prospectus and in the documents incorporated by reference in the accompanying prospectus. 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 $26.57 per share, will be approximately $182.8 million (or $210.3 million if the underwriter exercises its option to purchase additional shares in full), after deducting the estimated underwriting discount and offering expenses. It is possible that, based on market conditions, we may increase or decrease the number of shares offered hereby.

We intend to use the net proceeds from this offering for general corporate purposes, which we expect to include investment in the development and commercialization of telaprevir, clinical trial expenditures and other development expenses for telaprevir and VX-770 and our other drug candidates, and investment in our research programs and manufacture and supply of drug substances, and which may include capital expenditures, investments and potentially acquisitions. 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 commitments or agreements with respect to any acquisitions and may not make any acquisitions. Pending application of the net proceeds as described above, we intend to invest the net proceeds of the offering in short-term, investment-grade, interest-bearing securities.

DILUTION

If you purchase our common stock in this offering, your interest will be diluted to the extent of the difference between the public offering price per share and the net tangible book value per share of our common stock after this offering. We calculate net tangible book value per share by subtracting our total liabilities from our total tangible assets and dividing the difference by the number of outstanding shares of our common stock. Total tangible assets excludes deferred debt issuance costs and royalty sale transaction expenses included in other assets on our condensed consolidated balance sheet at June 30, 2008.

Our net tangible book value at June 30, 2008 was $225.5 million, or $1.60 per share, based on 141.1 million shares of our common stock outstanding. After giving effect to the sale of 7.0 million shares of common stock by us at an assumed public offering price of $26.57 per share, less the estimated underwriting discount and offering expenses, our net tangible book value at June 30, 2008 would be $408.3 million, or $2.76 per share. This represents an immediate increase in net tangible book value of $1.16 per share to existing stockholders and an immediate dilution of $23.81 per share to investors in this offering. The following table illustrates this per share dilution:

Assumed public offering price per share		$ 26.57
Net tangible book value per share as of June 30, 2008	$ 1.60	
Increase per share attributable to new investors purchasing shares in this offering	$ 1.16	
Net tangible book value per share after this offering		2.76
Dilution per share to new investors		$ 23.81

A $1.00 increase in the assumed public offering price of $26.57 per share would increase our net tangible book value per share after this offering to $2.80 per share, representing an immediate increase in net tangible book value of $1.20 per share to existing stockholders and an immediate dilution of $24.77 per share to investors in this offering, assuming that the number of shares offered by us, as set forth on the cover page of this prospectus supplement, remains the same and after deducting the estimated underwriting discount and offering expenses. A $1.00 decrease in the assumed public offering price of $26.57 per share would decrease our net tangible book value per share after this offering to $2.71 per share, representing an immediate increase in net tangible book value of $1.11 per share to existing stockholders, and an immediate dilution of $22.86 per share to investors in this offering, assuming that the number of shares offered by us, as set forth on the cover page of this prospectus supplement, remains the same and after deducting the estimated underwriting discount and offering expenses. The information discussed above is illustrative only and will adjust based on the actual offering price and other terms of this offering determined at pricing.

If the underwriter exercises its option to purchase additional shares in full, the net tangible book value per share after this offering would be $2.92 per share, representing an increase to existing stockholders of $1.32 per share, and there would be an immediate dilution of $23.65 per share to new investors.

PRICE RANGE OF COMMON STOCK

Our common stock is listed on the Nasdaq Global Select Market under the symbol "VRTX". The last reported sale price for our common stock on September 17, 2008 was $26.57 per share. The table below sets forth information on the range of high and low prices for our common stock during the periods indicated.

	Price Range of Common Stock	
	High	**Low**
Fiscal Year ended December 31, 2006		
First quarter	$ 44.71	$ 26.50
Second quarter	40.00	29.00
Third quarter	37.10	29.75
Fourth quarter	45.38	32.50
Fiscal Year ended December 31, 2007		
First quarter	$ 38.95	$ 26.98
Second quarter	32.51	25.61
Third quarter	41.42	27.55
Fourth quarter	39.48	22.80
Fiscal Year ending December 31, 2008		
First quarter	$ 24.67	$ 13.84
Second quarter	34.97	23.40
Third quarter (through September 17, 2008)	35.00	25.35

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.

UNDERWRITING

We intend to offer the shares of common stock through Goldman, Sachs & Co. as underwriter. Subject to the terms and conditions described in an underwriting agreement between us and the underwriter, we have agreed to sell to the underwriter, and the underwriter has agreed to purchase from us, 7,000,000 shares.

The underwriter has agreed to purchase all of the shares sold under the underwriting agreement if any of these shares are purchased.

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

The underwriter is offering the shares, subject to prior sale, when, as and if issued to and accepted by it, subject to approval of legal matters by its counsel, including the validity of the shares, and other conditions contained in the underwriting agreement, such as the receipt by the underwriter of officers' certificates and legal opinions. The underwriter reserves the right to withdraw, cancel or modify offers to the public and to reject orders in whole or in part.

The underwriter has advised us that it proposes 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 underwriter 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 underwriter of its option to purchase additional shares.

	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 option to purchase additional shares), are estimated at $400,000 and are payable by us.

We have granted an option to the underwriter to purchase up to 1,050,000 additional shares at the public offering price listed on the cover page of this prospectus, less the underwriting discount. The underwriter may exercise this option for 30 days from the date of this prospectus.

We, our directors and our executive officers have agreed, with certain exceptions, not to sell or transfer any common stock for 90 days, with respect to us, and 60 days, with respect to our directors and officers, after the date of the underwriting agreement (the "lock-up period") without first obtaining the written consent of the underwriter. Specifically, we and these directors and officers have agreed, subject to such exceptions, not to directly or indirectly:

- offer, pledge, sell or contract to sell any common stock or any securities convertible into or exchangeable or exercisable for our common stock (the "lock-up securities");
- sell any option or contract to purchase any lock-up securities;
- purchase any option or contract to sell any lock-up securities;
- grant any option, right or warrant for the sale of any lock-up securities;

otherwise dispose of or transfer any lock-up securities;

file, or cause to be filed, any registration statement under the Securities Act of 1933, as amended, with respect to any lock-up securities; 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 lock-up securities, whether any such swap or transaction is to be settled by delivery of common stock or other securities, in cash or otherwise.

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

Until the distribution of our shares is completed, SEC rules may limit the underwriter from bidding for and purchasing our common stock. However, the underwriter 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 underwriter creates a short position in the common stock in connection with the offering, i.e., if it sells more shares than are listed on the cover page of this prospectus, the underwriter may reduce that short position by purchasing shares in the open market. The underwriter may also elect to reduce any short position by exercising all or part of the option to purchase additional shares 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 underwriter's option to purchase additional shares from us in the offering. The underwriter may close out any covered short position by either exercising its 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 underwriter will consider, among other things, the price of shares available for purchase in the open market as compared to the price at which it may purchase shares through the option to purchase additional shares. "Naked" short sales are any sales in excess of such option. The underwriter 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 underwriter is 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 underwriter in the open market prior to the completion of the offering.

Similar to other purchase transactions, the underwriter's purchases to cover the 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 the underwriter 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 underwriter make any representation that the underwriter will engage in these transactions or that these transactions, once commenced, will not be discontinued without notice.

In connection with this offering, the underwriter may engage in passive market making transactions in our common stock on the Nasdaq Global Select Market in accordance with Rule 103 of Regulation M under the Securities Exchange Act of 1934, as amended, 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.

The underwriter and its 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 underwriter or its 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.

LEGAL MATTERS

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 underwriter by Cleary Gottlieb Steen & Hamilton LLP, New York, New York.

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PROSPECTUS

VERTEX PHARMACEUTICALS INCORPORATED

Common Stock

This prospectus will allow us to issue shares of our common stock from time to time at prices and on terms to be determined at or prior to the time of the offering. We will provide specific terms of any offering in one or more supplements to this prospectus filed with the Securities and Exchange Commission.

We may sell the common stock to or through one or more underwriters, dealers and agents, or directly to purchasers, on a continued or delayed basis. We will set forth the names of any underwriters, dealers or agents and their compensation in the accompanying prospectus supplement.

This prospectus may not be used to sell any shares of common stock unless accompanied by a prospectus supplement.

Our common stock is listed on the Nasdaq Global Select Market under the symbol "VRTX." The last reported sale price of our common stock on the Nasdaq Global Select Market on September 16, 2008 was $28.15 per share. Prospective purchasers of our securities are urged to obtain current information as to the market prices of our common stock.

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

The date of this prospectus is September 17, 2008.

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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 shares of our common stock in one or more offerings. Each time our common stock is offered under this prospectus, we will provide a prospectus supplement that will contain specific information about the terms of that offering.

This prospectus does not contain all of the information included in the registration statement. For a more complete understanding of any offering of our common stock pursuant to this prospectus, you should refer to the registration statement, including its exhibits. The prospectus supplement may also add, update or change information contained in this prospectus. You should read both this prospectus and the applicable prospectus supplement together with additional information under the headings "Where You Can Find More Information" and "Incorporation by Reference." To the extent there are inconsistencies between any prospectus supplement, this prospectus and any documents incorporated by reference, the document with the most recent date will control.

You should rely only on information contained in, or incorporated by reference into, this prospectus and any prospectus supplement. We have not authorized anyone to provide you with information different from that contained in this prospectus or incorporated by reference in this prospectus. We are not making offers to sell our common stock in any jurisdiction in which such an offer or solicitation is not authorized or in which the person making such offer or solicitation is not qualified to do so or to anyone to whom it is unlawful to make such offer or solicitation.

The information contained in this prospectus is accurate only as of the date on the front cover of the prospectus and information we have incorporated by reference in this prospectus is accurate only as of the date of the document incorporated by reference. You should not assume that the information contained in, or incorporated by reference into, this prospectus is accurate as of any other date.

WHERE YOU CAN FIND MORE INFORMATION

We are a public company and are required to file annual, quarterly and current reports, proxy statements and other information with the SEC pursuant to the Securities Exchange Act of 1934, as amended, or the Exchange Act. You may read and copy any document we file at the SEC's public reference room at 100 F Street, N.E., 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 on the SEC's website at *www.sec.gov*. The information on the SEC's website is not part of this prospectus, and any references to this website or any other website are inactive textual references only.

We filed a registration statement on Form S-3 under the Securities Act of 1933, as amended, or the Securities Act, with the SEC with respect to the common stock being offered pursuant to this prospectus. This prospectus is only part of the registration statement and omits certain information contained in the registration statement, as permitted by the SEC. You should refer to the registration statement, including the exhibits, for further information about us and the common stock being offered pursuant to this prospectus. Statements in this prospectus regarding the provisions of certain documents filed with, or incorporated by reference in, the registration statement are not necessarily complete and each statement is qualified in all respects by that reference. You may:

- inspect a copy of the registration statement, including the exhibits and schedules, without charge at the public reference room;
- obtain a copy from the SEC upon payment of the fees prescribed by the SEC; or
- obtain a copy from the SEC's website.

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Our internet address is *www.vrtx.com*. Our Annual Reports on Form 10-K, Quarterly Reports on Form 10-Q, Current Reports on Form 8-K, and all amendments to those reports are also available to you free of charge through the "Finances/Investor Info" section of our website as soon as reasonably practicable after those materials have been electronically filed with, or furnished to, the SEC. Other than the documents filed with the SEC and incorporated by reference into this prospectus, the information contained on our website does not constitute a part of this prospectus.

INCORPORATION BY REFERENCE

The SEC allows us to "incorporate by reference" information that we file with them. Incorporation by reference allows us to disclose important information to you by referring you to those other documents. The information incorporated by reference is an important part of this prospectus, and any information incorporated by reference is considered part of this prospectus. Any reports filed by us with the SEC after the date of this prospectus and before the date that the offering of common stock by means of this prospectus is terminated will automatically update and, where applicable, supersede any information contained in this prospectus or incorporated by reference in this prospectus. We incorporate by reference into this prospectus the following documents or information filed with the SEC (other than, in each case, documents or information therein deemed to have been furnished and not filed in accordance with SEC rules):

(a) Our Annual Report on Form 10-K for the year ended December 31, 2007 (filing date February 11, 2008: Commission File No. 000-19319);

(b) Our Quarterly Reports on Form 10-Q for the quarters ended March 31, 2008 and June 30, 2008 (filing dates May 12, 2008 and August 11, 2008: Commission File No. 000-19319);

(c) Our Current Reports on Form 8-K filed on February 14, 2008 (Items 1.01 and 9.01), February 25, 2008 (Items 1.01, 2.03 and 9.01), March 31, 2008 (Items 8.01 and 9.01), May 16, 2008 (Items 1.01, 1.02 and 9.01), June 4, 2008 (Items 1.01 and 2.01), June 18, 2008 (Item 5.02) and September 12, 2008 (Item 5.02) (Commission File No. 000-19319);

(d) The portions of our definitive proxy statement on Schedule 14A that are deemed "filed" with the SEC under the Exchange Act (filing date April 8, 2008: Commission File No. 000-19319); and

(e) The description of our common stock and the outstanding series A junior participating preferred stock purchase rights contained in our Registration Statement on Form 8-A, including any amendment or report filed for the purpose of updating such description (filing date May 30, 1991: Commission File No. 000-19319).

In addition, all documents filed by us pursuant to Section 13(a), 13(c), 14 or 15(d) of the Exchange Act on or after the date of this prospectus and before the termination of offerings under this prospectus are deemed to be incorporated by reference into, and to be a part of, this prospectus.

Our SEC filings are available to the public on the SEC's website at *www.sec.gov*. You also may request, orally or in writing, a copy of these documents, which will be provided to you at no cost, by contacting us at:

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

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USE OF PROCEEDS

Except as otherwise provided in the applicable prospectus supplement, we intend to use the net proceeds from this offering for general corporate purposes, which we expect to include investment in the development and commercialization of telaprevir, clinical trial expenditures and other development expenses for telaprevir and our other drug candidates, and investment in our research programs and manufacture and supply of drug substances, and which may include capital expenditures, investments and potentially acquisitions. 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.

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 300,000,000 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 our 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 our net assets 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 or exchange rights. The rights, powers, preferences and terms 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, powers, preferences and terms thereof, including dividend rights, conversion or exchange rights, voting rights, terms of redemption, liquidation preferences, sinking fund terms, the number of shares constituting any series or the designation of such series and any restrictions on the issue or reissue of any additional shares of such series or another 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, $0.01 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

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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 $0.01 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 and Massachusetts Law Relating to a Change in Control and Indemnification

Provisions of our articles of organization and by-laws and our Stockholder Rights Plan may discourage specific types of transactions involving an actual or potential change in control of Vertex that might be beneficial to Vertex or our 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

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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 to us or our stockholders for monetary damages for breach of fiduciary duty as a director except for (i) any breach of such director's duty of loyalty to us or our stockholders, (ii) acts or omissions not in good faith or which involve intentional misconduct or a knowing violation of laws, (iii) the authorization of illegal dividends or redemptions, or the authorization of a loan of any of our assets to one of our officers or directors that is not repaid, or (iv) any transactions from which such director derived an improper personal benefit. 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

Computershare Investor Services is the transfer agent and registrar for our common stock.

LEGAL MATTERS

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.

EXPERTS

The consolidated financial statements of Vertex Pharmaceuticals Incorporated appearing in Vertex Pharmaceuticals Incorporated's Annual Report (Form 10-K) for the year ended December 31, 2007, have been audited by Ernst & Young LLP, independent registered public accounting firm, as set forth in their report thereon, included therein, and incorporated herein by reference. Such consolidated financial statements are incorporated herein by reference in reliance upon such report given on the authority of such firm as experts in accounting and auditing.

7,000,000 Shares

VERTEX PHARMACEUTICALS INCORPORATED

Common Stock

PROSPECTUS SUPPLEMENT

Goldman, Sachs & Co.

, 2008