

SYNAPTIC PHARMACEUTICAL CORP
Form 424B3
February 27, 2003

Filed pursuant to Rule 424(b)(3)
Registration Statement No. 333-71026

PROSPECTUS

SYNAPTIC PHARMACEUTICAL CORPORATION

7,564,584 Shares of Common Stock

This prospectus relates to the offer and sale, from time to time, of up to 7,564,584 shares of our common stock by the selling stockholders listed on page 12.

Our common stock is traded on the National Market tier of the Nasdaq Stock Market under the trading symbol "SNAP." On February 12, 2002, the last reported sale price for our common stock on the Nasdaq National Market was \$6.55 per share.

INVESTING IN OUR COMMON STOCK INVOLVES RISKS.
SEE "RISK FACTORS" BEGINNING ON PAGE 2.

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

The information in this prospectus is not complete and may be changed. We may not sell these securities until the registration statement filed with the Securities and Exchange Commission is effective. The prospectus is not an offer to sell these securities and it is not soliciting an offer to buy these securities in any state where the offer is not permitted.

The date of this prospectus is February 14, 2002.

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You should rely only on the information incorporated by reference or provided in this prospectus or any supplement to this prospectus. We have not authorized anyone else to provide you with different information. Neither the delivery of this prospectus nor any distribution of the shares of our common stock shall, under any circumstances, create any implication that there has been no change in our affairs since the date of this prospectus.

ABOUT SYNAPTIC PHARMACEUTICAL CORPORATION

We are a drug discovery company using our patented portfolio of G protein-coupled receptors ("GPCRs") as the basis for developing new drugs for the treatment of a variety of human disorders. GPCRs represent a class of human receptors that is believed to comprise over 1,000 different human receptors which, in turn, cause a broad range of physiological functions in the body. Human receptors are protein molecules that exist on the surface membrane of all cells and affect cell activity. They are associated with physiological functions and, sometimes, disorders. We and our licensees conduct research to discover the function of specific GPCRs in the human body and physiological disorders with which they may be associated. We use this information to design compounds that attach to and change the function of these GPCRs and that have the potential to be developed into drugs to treat disorders with which the GPCRs are associated. Our goal is to develop the compounds we design into commercially viable drugs.

We were incorporated in the state of Delaware in 1987. Our principal executive offices are located at 215 College Road, Paramus, New Jersey 07652, and our telephone number is (201) 261-1331. References in this prospectus to "we," "us," and "our" refer to Synaptic Pharmaceutical Corporation.

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RISK FACTORS

An investment in our securities involves a high degree of risk. You should carefully consider the risks and uncertainties and other information in this prospectus and in the documents incorporated by reference in this prospectus before deciding to buy any of the securities being offered to you. Our business, financial condition and results of operations could be harmed were any the following risks or uncertainties to develop into actual events. In such case, the value of our securities could decline and you might lose all or part of your investment.

OUR PRODUCTS ARE IN AN EARLY STAGE OF DEVELOPMENT, AND WE MAY NEVER DEVELOP ANY COMMERCIALY VIABLE PRODUCTS.

It generally takes at least twelve years to discover and develop a new drug. To date, neither we nor any of our licensees have developed any drugs using our technology. We currently have approximately 30 GPCRS in various stages of research or pre-clinical testing. We plan to initiate clinical testing of one new compound each year commencing in the first quarter of 2002, when we began Phase I clinical trials in our depression program. We believe that it will take a minimum of five years, and perhaps longer, from the beginning of clinical trials for any program to develop an approved drug, assuming the clinical trials produce favorable results. We have no means of predicting when, or if, any of our licensees will develop commercially available drugs using our GPCRS; however, to our knowledge, none of our licensees are currently engaged in

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clinical trials on any compounds developed with our technology.

Numerous factors may preclude any of our products from being developed into marketable drugs or any drugs we do develop from being commercially successful. Any of these factors could require us to abandon any particular product at any stage of development, notwithstanding the expenditure of large amounts of time and money on the product. These factors include the following:

Adverse Test Results. Research may show that a product is ineffective or that it has harmful side effects during either pre-clinical testing or clinical trials. The safety and efficacy of a therapeutic product under development must be supported by extensive data from clinical trials. The results of preclinical studies and initial clinical trials are not necessarily predictive of results that will be obtained from later large-scale clinical trials, and there can be no assurance that clinical trials of any product under development will demonstrate the safety and efficacy of the product or will result in a marketable product.

Manufacturing Difficulties. Because the products that we and our licensees are attempting to develop are at a very early stage of development, we cannot now predict whether they can be manufactured at a cost or in quantities necessary to support all of our future development efforts or to achieve commercial viability. We have no manufacturing facilities and rely on third parties to produce compounds for development, preclinical and clinical purposes. Because each compound is unique, the cost and difficulty of producing any particular compound can only be determined on a case-by-case basis for each stage of development. If we are unable to contract for a sufficient supply of compounds on acceptable terms, or if we should encounter difficulties in our relationships with third party manufacturers, our preclinical and clinical testing schedule would be delayed. If clinical trials of a product were successful, we might consider shifting production of that product from a contract manufacturer to a large pharmaceutical company for mass production. Such a transfer would entail numerous technical difficulties, and, because none of our potential products are sufficiently developed to consider mass production, we cannot be certain that such a transfer could be arranged successfully or on terms acceptable to the company.

Marketing and Sales Capacity. Although we do not currently have any marketable products, our ability to produce revenue ultimately depends on our or our licensees ability to sell our products if and when they are approved by the FDA. We currently have no marketing experience, sales force or distribution capabilities. If we are unable to establish direct or indirect sales and distribution capabilities, or are unsuccessful in gaining market acceptance for licensing arrangements, we will not be able to generate revenue from our products, even if they prove to be effective. If we enter into co-promotion or licensing arrangements, our revenues will be dependent on the efforts of third parties, and at this early stage of our product development, we cannot predict whether any of these arrangements would be obtainable on acceptable terms or would be successful.

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Acceptance by Health Care Community. Any product we develop will be successful only if it is accepted by the health care community. The degree of acceptance of any product we develop by the health care community will depend on a variety of factors, including the following:

- our establishment and demonstration to the medical community of the clinical efficacy and safety of the product;

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- our ability to demonstrate that the product is superior to alternatives then on the market; and
- the reimbursement policies of government and third-party payers with respect to the product.

WE HAVE A HISTORY OF OPERATING LOSSES AND WE EXPECT OUR LOSSES TO INCREASE AS A RESULT OF OUR STRATEGY OF INCREASING OUR INTERNAL DRUG DEVELOPMENT EFFORTS.

We have incurred significant operating losses since our inception in January 1987. At September 30, 2001, our accumulated deficit was \$80,136,000. We incur losses because our research and development and general and administrative expenses exceed the revenue we generate from our operating activities and investments. Our net loss for the last three fiscal years and the interim period, in thousands of dollars, was as follows:

| | YEAR ENDED DECEMBER 31, | | | NINE MONTHS ENDED SEPTEMBER 30, | |
|---------|-------------------------|----------|---------|---------------------------------|--|
| 1998 | 1999 | 2000 | 2000 | 2001 | |
| ---- | ---- | ---- | ---- | ---- | |
| \$6,493 | \$15,121 | \$13,859 | \$9,796 | \$15,347 | |

The rate at which we incur losses has increased over the past year as we have increased our internal drug development efforts. We expect our rate of loss to increase further as these efforts continue to result in increased expenses from pre-clinical and clinical testing and reduced revenues from collaborative arrangements. Our research and development expenses increased by \$2,232,000 for the nine months ended September 30, from \$10,545,000 in 2000 to \$12,777,000 in 2001, due primarily to increases in pre-clinical testing costs associated with our depression program. Costs for this program may increase further as it moves into clinical trials in early 2002, and costs for other programs will also increase as we accelerate our development efforts. At this stage of product development, we cannot accurately predict how large these increases will be, but we expect that they will be at least as much as, and probably more than, the increases seen to date in our depression program.

To date, our only material sources of operating revenue have been license revenue, which generally has come in the form of one-time payments, and contract revenue, which comes from collaborative arrangements. License revenue is unpredictable, as it depends on the research activities and needs of potential third party licensees, about which we have little knowledge. We do not currently plan to enter into any new collaborative arrangements and therefore do not expect any material increase in contract revenue for the foreseeable future. The table below shows our license and contract revenue, in thousands of dollars, for the past three fiscal years and the interim period:

| | YEAR ENDED DECEMBER 31, | | | NINE MONTHS ENDED SEPTEMBER 30, | |
|------------------|-------------------------|---------|---------|---------------------------------|------|
| | 1998 | 1999 | 2000 | 2000 | 2001 |
| | ---- | ---- | ---- | ---- | ---- |
| Contract Revenue | \$7,202 | \$1,855 | \$1,086 | \$ 804 | \$86 |
| License Revenue | \$2,000 | -- | \$2,750 | \$2,667 | \$25 |

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We don't expect to achieve sufficient revenue to become profitable unless and until we realize revenue from the sale of commercially successful new drugs. This will not happen unless we or our licensees successfully complete clinical trials with respect to a drug candidate, obtain regulatory approval for that drug candidate and

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commercialize the resulting drug. As discussed above in the preceding risk factor, this will not occur for a significant number of years and may never occur.

IF WE ARE UNABLE TO OBTAIN ADDITIONAL FINANCING IN THE FUTURE, WE MAY NOT BE ABLE TO SUSTAIN OUR BUSINESS.

As discussed above, we must expend capital to fund our operations, and we expect our rate of capital expenditure to increase in the future. As of September 30, 2001, we had \$58,478,000 in cash, cash equivalents and marketable securities, which we believe will be sufficient to fund operations at least through the end of the year 2002. However, it is likely that we will need to raise additional capital to fund our operations beyond that time. Because of the uncertainties inherent in capital markets, we cannot be sure that additional funds will be available on favorable terms or at all, or whether any funds raised would be sufficient to permit us to continue to conduct our operations or achieve profitability. Any further equity financing we do obtain could result in additional dilution to our then existing stockholders. If adequate funds are not available when we need them, we may never become profitable and we may be required to curtail significantly or eliminate one or more of our drug development programs, or to discontinue our operations all together.

IF WE ARE UNABLE TO OBTAIN AND MAINTAIN PATENT PROTECTION FOR OUR INTELLECTUAL PROPERTY, WE WILL BE UNABLE TO GROW OUR BUSINESS OR BECOME PROFITABLE.

Our success depends, in part, on our ability to establish, protect and enforce our proprietary rights relating to our intellectual property. Our policy is to seek, when appropriate, protection for our gene and compound discoveries and other proprietary technology by filing patent applications in the United States and in other countries. As of December 31, 2001, we had been granted 149 patents. Patent law as it relates to inventions in the biotechnology field is still evolving, and involves complex legal and factual questions for which legal principles are not firmly established. Accordingly, we cannot be certain that patents will be granted with respect to any of our patent applications currently pending in the United States or in other countries, or with respect to applications filed by us in the future. If we do not receive patents on the genes and compounds we develop, or if we are unable to enforce the patents we have been granted, then our ability to profit from these developments may be materially diminished.

There is no clear policy regarding the breadth of claims allowed in patents or the degree of protection they afford. We therefore cannot predict the breadth or enforceability of claims allowed in the patents that have been issued to us or in patents that may be issued to us in the future, nor can we be sure that claims in our patents, either as initially allowed by the United States Patent and Trademark Office or any of its non-United States counterparts or as subsequently interpreted by courts inside or outside the United States, will be sufficiently broad to allow us to profit from the genes and compounds we discover.

Patents issued to us may be infringed, invalidated or circumvented by

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others, or the rights granted under our patents may not be commercially valuable or provide competitive advantages to us or our licensees. A number of pharmaceutical companies, biotechnology companies, universities and research institutions have significantly expanded their gene discovery efforts in recent years and have filed patent applications or received patents covering their gene discoveries. Some of these applications or patents may be competitive with our applications or conflict in certain respects with claims made under our applications. We cannot predict whether, in the event of any conflict, we will be in a priority position with respect to inventorship on any of these applications. If we are not, then our ability to exploit the patents subject to the conflict would be materially diminished.

In some cases, litigation or other proceedings may be necessary to assert infringement claims against others, to defend against claims of infringement, to enforce patents issued to us, to protect trade secrets, our know-how or other intellectual property rights, or to determine the scope and validity of the proprietary rights of third parties. An adverse outcome in any litigation or proceeding could subject us to significant liabilities, require us to cease using the subject technology or require us to license the subject technology from a third party, all of which could cause our costs to increase and our revenues or potential revenues to decline. Any litigation could result in substantial costs and divert our resources from drug development activities.

In June 2000, we filed suit against M.D.S. Panlabs, Inc., a Washington corporation, and Panlabs Taiwan Ltd., a Taiwanese corporation, alleging that Panlabs had infringed several U.S. patents owned by us. In October

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2001, we amended this complaint to name Euroscreen, S.A., a Belgian corporation, as a defendant, alleging that Euroscreen has been selling products that infringe our patents and conspired with Panlabs to infringe our patents. An unfavorable outcome in this litigation may have an adverse effect on our business.

OUR DRUG DEVELOPMENT AND COMMERCIALIZATION EFFORTS MAY BE IMPAIRED BY THE INTELLECTUAL PROPERTY RIGHTS OF THIRD PARTIES.

Our future success depends, in part, on our ability to operate without infringing patents and proprietary rights of third parties. We are aware of a large number of patents and patent applications of third parties that contain claims to genes that code for G protein-coupled receptors or compounds that interact with G protein-coupled receptors. Patents issued to others may preclude us from using or licensing our technology or may preclude us and our licensees from commercializing drugs developed with our technology. We have acquired licenses to use certain technologies covered by patents owned by Stanford University and the University of California, jointly, and by Columbia University, and may be required to obtain additional licenses to patents or other proprietary rights of other parties in order to pursue our own technologies. We cannot be sure that, if required, we would be able to obtain any additional licenses on acceptable terms, if at all. The failure to obtain needed licenses could result in delays in our development efforts or those of our licensees, or could preclude the development, manufacture or sale of some products.

OBTAINING AND MAINTAINING OUR PATENT RIGHTS IS EXPENSIVE AND COULD LEAD TO HIGHER EXPENSES AND LARGER LOSSES.

Our patents and patent applications may be challenged by way of interference proceedings or opposed by third parties, and we may need to participate in interference proceedings or oppose the patents or patent

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applications of third parties in order to protect our rights. Interference and opposition proceedings can be expensive to prosecute and defend. We are currently involved in an interference proceeding at the United States Patent and Trademark Office between one of our patent applications and an issued patent of a third party. We cannot predict the outcome of the interference proceeding. If the outcome is unfavorable to us, then we might not be able to practice the subject matter of the relevant patent application in the United States. Accordingly, an unfavorable outcome in the interference proceeding could have an adverse effect on the company. Even if the eventual outcome of the interference proceeding is favorable to us, our participation in will have resulted in substantial costs to us.

OUR COMPETITIVE POSITION WILL BE IMPAIRED IF WE ARE UNABLE TO MAINTAIN THE CONFIDENTIALITY OF OUR TRADE SECRETS AND OTHER PROPRIETARY INFORMATION.

We rely upon trade secrets, proprietary know-how and continuing technological advances to develop and maintain our competitive position. Our business strategy requires us to share this information among our employees and those of our licensees. If this confidential information becomes known to third parties, whether through inadvertent disclosure or breach of a confidentiality agreement or otherwise, the value of the information to us may be diminished as well as our ability to develop competitive processes and products.

WE FACE SUBSTANTIAL COMPETITION FROM MANY COMPANIES THAT HAVE SIGNIFICANTLY GREATER RESOURCES THAN WE DO.

We operate in a field in which new developments occur and are expected to continue to occur at a rapid pace. Competition from biotechnology and pharmaceutical companies, joint ventures, academic and other research institutions and others is intense, and we expect it to increase. Because the research and pre-clinical stages of the drug development process are highly secretive processes, we cannot be certain of who our competitors are or where our drug discoveries stand in relation to theirs; however we believe many other pharmaceutical and biotechnology companies, including Merck, Pfizer and Eli Lilly, currently employ elements of our human receptor-targeted drug design technology in their drug discovery efforts, we are aware that many pharmaceutical and biotechnology companies including Arena Pharmaceuticals, 7TM Pharma, and Norsk Biosciences are engaged in efforts to develop compounds that interact with G protein-coupled receptor subtypes, including receptor subtypes with which we are working. Our competitors include large biotechnology companies and multinational pharmaceutical companies, including, in addition to those identified above, GlaxoSmithxline, Schering-Plough, and Bristol-Myers Squibb, who may gain a competitive advantage over us because they employ greater financial and other resources, including

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larger research and development staffs and more extensive marketing and manufacturing organizations, than are available to us. We expect our competition to increase, as many large pharmaceutical companies are now routinely performing the types of research and services that have historically been performed by smaller companies such as ours.

We believe that every major pharmaceutical company, and numerous other drug development companies, are attempting to develop drugs to treat the disorders for which we are attempting to develop drugs. For example, Eli Lilly, Merck, and Pfizer have announced that they are attempting to develop drugs to combat obesity, depression, incontinence and diabetes. We believe that many of these companies have products that are closer to market than ours. For example, Merck has announced the commencement of clinical trials on a drug which, if

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successful, will be used to treat depression. Our competitors will achieve a significant competitive advantage if they complete clinical trials, obtain required regulatory approvals or commence commercial sales of their drugs before we achieve that stage of development with our products. Moreover, our competitors may be able to develop technologies that circumvent our technology or that are more effective than those that we develop or that render our technology or drugs less competitive or obsolete. Our competitors may also be able to obtain patent protection or other intellectual property rights that would limit our ability to use or license our own technology or commercialize the drugs we or our licensees develop.

THE STRINGENT REGULATORY APPROVAL PROCESS FOR NEW DRUGS CREATES SIGNIFICANT EXPENSES AND MAKES IT UNCERTAIN WHETHER ANY DRUGS WE OR OUR LICENSEES MAY DEVELOP WOULD BE APPROVED FOR COMMERCIAL USE.

The development, manufacturing and marketing of drugs are subject to regulation by numerous Federal, state and local governmental authorities in the United States, the principal one of which is the FDA, and by similar agencies in other countries in which we may test and market the drugs we develop. The FDA and comparable regulatory agencies in other countries impose mandatory procedures and standards for the conduct of preclinical testing and clinical trials and the production and marketing of drugs for human therapeutic use. Product development and approval of a new drug are likely to take many years and involve the expenditure of substantial resources.

The steps required by the FDA before new drugs may be marketed in the United States include:

- preclinical studies;
- the submission to the FDA of a request for authorization to conduct clinical trials on an investigational new drug (IND);
- adequate and well-controlled clinical trials, including Phase I, Phase II and Phase III trials, to establish the safety and efficacy of the drug for its intended use;
- submission to the FDA of a New Drug Application (NDA); and
- review and approval of the NDA by the FDA before the drug may be shipped or sold commercially.

In the United States in particular, timetables for the various phases of clinical trials and NDA approval cannot be predicted with any certainty. We, our licensees or the FDA may suspend clinical trials at any time if it is believed that individuals participating in the trials are being exposed to unacceptable health risks. Even assuming that clinical trials are completed and that an NDA is submitted to the FDA, there can be no assurance that the NDA will be reviewed by the FDA in a timely manner or that once reviewed, the NDA will be approved. The approval process is affected by numerous factors, including the severity of the targeted indications, the availability of alternative treatments and the risks and benefits demonstrated in clinical trials. The FDA may deny an NDA if applicable regulatory criteria are not satisfied, or may require additional testing or information with respect to the investigational drug. Data obtained from preclinical and clinical activities are susceptible to varying interpretations that could also delay, limit or prevent regulatory agency approval. Even if initial FDA approval is obtained, further studies, including post-market studies, may be required in order to provide additional data on safety and will be required in order to gain approval for the use of a product as a treatment for clinical indications other than those for which the product was initially tested. The FDA will also require post-market reporting and may require surveillance programs to monitor the side effects of the drug. Results

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of post-marketing programs may limit further marketing of the drug. Further, if there are any modifications to the drug, including changes in indication, manufacturing process

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or labeling, an NDA supplement may be required to be submitted to the FDA. Finally, delays or rejections may be encountered based upon changes in regulatory agency policy during the period of drug development or the period of review of any application for regulatory agency approval of a drug. Moreover, because our present licensees are, and future licensees may be, responsible for preclinical testing, clinical trials, regulatory approvals, manufacturing and commercialization of some drugs, the ability to obtain and the timing of regulatory approvals for these drugs may not always be within our control.

Prior to the commencement of marketing a product in any other country, approval by regulatory agencies in that country is required, regardless of whether FDA approval has been obtained for the product. The requirements governing the conduct of clinical trials and product approvals vary widely from country to country, and the time required for approval may be longer or shorter than the time required for FDA approval. Although there are procedures for unified filings for some European countries, in general each country has its own procedures and requirements.

Delays in obtaining regulatory agency approvals could adversely affect the marketing of any drugs we or our licensees develop, impose costly procedures upon our activities, diminish any competitive advantages that we may attain and adversely affect our ability to receive revenues or royalties. Because there are numerous reasons that regulatory approval of any given product may be denied at any stage of the development process, there is a material risk that, even after the expenditure of significant time and money on a product, we will not obtain all required regulatory agency approvals for that product. Moreover, even if regulatory agency approval for a product is granted, the approval may entail limitations on the indicated uses for which the product may be marketed. Further, approved drugs and their manufacturers are subject to continual review, and discovery of previously unknown problems with a drug or its manufacturer may result in restrictions on the drug or manufacturer, including withdrawal of the drug from the market. Regulatory agency approval of prices is required in many countries, which could limit the revenues that we are able to realize from any particular product.

At present, none of our compounds have progressed beyond pre-clinical studies. We submitted an IND application to the FDA for our depression program in the fourth quarter of 2001 and began Phase I clinical trials on this program in February 2002.

WE COULD FACE PRODUCT LIABILITY CLAIMS THAT EXCEED OUR ABILITY TO PAY THEM.

Product liability risks are inherent in the testing, manufacturing and marketing of human therapeutic products. The compounds we and our licensees are investigating could prove to be injurious to humans. We are covered by clinical trial insurance coinciding with the commencement of Phase I clinical trials of the depression compound. If we are unable to obtain appropriate liability insurance coverage for drugs developed by us or our licensees, we may be exposed to product liability claims that we do not have the resources to pay. Large liability claims could result in substantial losses and potentially force us to discontinue operations.

WE WILL NOT BE SUCCESSFUL IF WE ARE UNABLE TO ATTRACT AND RETAIN

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SUFFICIENT QUALIFIED PERSONNEL.

We rely on our management and scientific staff. We face intense competition for personnel from, among others, biotechnology and pharmaceutical companies, as well as academic and other research institutions. In addition, our new business strategy requires us to hire employees with drug development expertise and to manage aspects of the drug development process that we formerly relied on our licensees to manage. If we lose the services of any key personnel, or are unable to hire additional personnel with the right knowledge and skills, then our drug development efforts may be delayed or disrupted.

In November 2001, Robert Spence, our Chief Financial Officer for the past twelve years, retired from the company effective January 2, 2002. Mr. Edmund M. Caviasco, C.P.A., the Company's Controller, has assumed the responsibilities of principal accounting officer from Mr. Spence.

In November 2001, our board of directors implemented a CEO succession plan pursuant to which it appointed a special committee to recruit a new President and Chief Executive Officer. Kathleen P. Mullinix, the

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founder of the company, resigned as Chairman of the Board and will retire as President, Chief Executive Officer and a Director upon the hiring of her successor.

Our business may experience some disruptions as we seek to hire and transition to new senior management.

OUR USE OF RADIOACTIVE MATERIALS EXPOSES US TO POTENTIAL LIABILITIES AND SANCTIONS THAT COULD DISRUPT OUR OPERATIONS.

Our activities involve the controlled use of radioactive compounds. We are subject to local, state and Federal laws and regulations relating to occupational safety, laboratory practices, the use, handling and disposition of radioactive materials, environmental protection and hazardous substance control. While complying with these requirements does not represent a material cost, we do not maintain insurance for this particular risk and, despite compliance with these requirements, we can not completely eliminate the risk of accidental contamination or injury from the use, storage, handling or disposal of radioactive compounds. Any accidental contamination or injury from these materials could expose us to liability for damages or result in sanctions that require us to delay or discontinue some or all of our operations.

OUR STOCK PRICE IS HIGHLY VOLATILE, AND YOU COULD LOSE MONEY INVESTING IN OUR STOCK EVEN IF WE MEET OUR PERFORMANCE GOALS.

Historically, the market price for our common stock has been highly volatile and subject to significant fluctuations both related and unrelated to our operating performance. Relatively small purchases or sales of our common stock can result in relatively large fluctuations in our stock price. In addition, future announcements or events concerning us or our industry may have a significant impact on the market price of our stock. Such announcements and events could include, but are not limited to, the following:

- the results of research, development testing, or technological innovations, either by us or others,
- the introduction of new commercial products, whether by us or others,

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- new government regulations or enforcement actions,
- developments in the protection of proprietary rights,
- litigation or the results of litigation,
- public concern as to the safety of our products or those of others in our industry,
- the failure of operating results to meet expectations of investors or public market analysts,
- fluctuations in our results of operations,
- changes in health care policy in the United States or other countries,
- changes in analysts' recommendations regarding our stock, and
- changes in the pharmaceutical or biotechnology industry generally.

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The table below sets forth the high and low last trade prices for our common stock as reported by The Nasdaq Stock Market for the periods indicated.

| | 1999 | | 2000 | | 2001 | |
|-------------|--------------|------------|--------------|------------|--------------|------------|
| | HIGH ---- | LOW --- | HIGH ---- | LOW --- | HIGH ---- | LOW --- |
| 1st Quarter | 19.2500 | 6.1667 | 16.5000 | 5.8125 | 6.7500 | 3.6875 |
| 2nd Quarter | 7.5000 | 4.5000 | 8.0000 | 4.5000 | 6.8000 | 3.8125 |
| 3rd Quarter | 9.0000 | 4.5000 | 7.3750 | 5.0938 | 6.4000 | 4.4600 |
| 4th Quarter | 7.2500 | 4.0000 | 7.3750 | 5.0000 | 6.0400 | 4.4000 |

OUR RIGHTS PLAN AND PROVISIONS IN OUR CHARTER MAKE IT DIFFICULT FOR STOCKHOLDERS TO REPLACE OUR EXISTING BOARD, WHICH COULD PREVENT A SALE OF OUR COMPANY THAT IS DESIRABLE TO OUR STOCKHOLDERS.

In November 1995, we adopted a stockholders' rights plan pursuant to which one right to purchase 1/1000th of a share of our Series A Junior Participating Preferred Stock is attached to each share of outstanding common stock. The rights detach from the common stock and become exercisable on the tenth business day following (i) the acquisition by a person or group of 15% or more of our outstanding common stock or (ii) the announcement by a person or group of an intention to acquire through tender or exchange offer 18% or more of our outstanding common stock, in either case without the prior approval of our board of directors.

Our certificate of incorporation provides for our board of directors to be divided into three classes of approximately equal size, with each class to be elected for a three-year term at the annual meeting of stockholders at which that class of directors term expires. Directors can be removed by the stockholders only for cause and only with a vote of 60% of the outstanding

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voting power. Accordingly, it would require two years to replace a majority of the board of directors without cause. Any amendment or repeal of any of the provisions of the certificate of incorporation which relate to the classified board of directors or the removal of directors requires the affirmative vote of at least 80% of the outstanding voting power of our stock and a majority of our board of directors.

Our certificate of incorporation and by-laws require approval of a majority of the board of directors to call a special meeting of stockholders, prohibit the stockholders from taking action by written consent and require advance notice by stockholders of an intention to nominate persons for election to the board of directors. In addition, the board of directors is authorized to issue preferred stock without stockholder approval with whatever rights and preferences the board may determine to be appropriate. The rights of the holders of common stock will be subject to, and could be adversely affected by, the rights of the holders of any preferred stock issued in the future.

Our rights plan has the effect of making an acquisition of the company prohibitively expensive for any potential acquiror not approved by the board of directors. Under Delaware law, the board of directors has broad discretion in determining whether or not to sell the company, even in circumstances where stockholders consider a sale to be desirable. Thus, an acquiror not approved by the board could be prevented from acquiring the company unless a majority of the company's stockholders voted to replace a majority of the board with directors that did approve the acquisition. As discussed above, it would take years to replace a majority of the board of directors without cause. It would therefore be very difficult for any third party to acquire our company without the consent of our board, even in a transaction that stockholders believe to be favorable. This could have the effect of depriving the owners of our common stock of the opportunity to sell their shares at a premium over prevailing market prices in a transaction proposed by a third party, where our board favors an alternative transaction or believes that a sale of the company is not desirable.

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WARBURG PINCUS, WHOSE INTERESTS MAY DIFFER FROM YOURS, EXERCISES SUBSTANTIAL INFLUENCE OVER OUR MANAGEMENT AND POLICIES AND COULD PREVENT A SALE OF THE COMPANY.

Warburg Pincus Private Equity VIII, LP, our largest shareholder, holds approximately 34.68% of the voting power of our outstanding capital stock. Warburg Pincus has the right to appoint two of the nine members of our board of directors and to approve the selection of a third member in consultation with company management and the rest of the board. Warburg Pincus' interests may differ from your interests, and Warburg Pincus may be in a position to influence us to act in a way that is inconsistent with the interests of the public holders of our common stock. Because of its large equity position, it is unlikely that any transaction requiring shareholder approval, such as a sale of the company or its assets or the election of directors, would be approved without Warburg Pincus' consent. As the holder of a majority of our outstanding Series B and Series C Convertible Preferred Stock, Warburg Pincus also has the right to veto any future issuance of preferred stock that is senior to or at parity with our Series B and Series C Preferred Stock. This could give Warburg Pincus the ability to prevent us from raising capital in a private financing on terms favorable to the holders of common stock.

THE SALE OF SHARES BY THE SELLING SHAREHOLDERS COULD CAUSE A DECLINE IN THE MARKET PRICE OF OUR COMMON STOCK.

Sales or the potential for sales of a substantial number of shares of

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our common stock in the public market could adversely affect its market price. Upon the effectiveness of the registration statement of which this prospectus is a part, there will be no restrictions on the right of the selling shareholders to convert their preferred stock to common stock and sell it in the open market. If all shares of our outstanding Series B and Series C Convertible Preferred Stock were converted to common stock, we would have 18,517,187 shares of common stock outstanding, of which 7,564,584 shares, or approximately 47%, would be held by the selling shareholders.

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CAUTIONARY STATEMENT REGARDING FORWARD-LOOKING STATEMENTS

This prospectus contains forward-looking statements that involve risk and uncertainties. The statements contained in this prospectus that are not purely historical are forward-looking statements within the meaning of Section 27A of the Securities Act of 1933, as amended (the "Securities Act") and Section 21E of the Securities Exchange Act of 1934, as amended (the "Exchange Act"). When used in this prospectus, or in the documents incorporated by reference into this prospectus, the words "anticipate," "believe," "estimate," "intend" and "expect" and similar expressions are intended to identify such forward-looking statements. These forward-looking statements involve known and unknown risks, uncertainties and other important factors that may cause our actual results, performance, achievements, plans and objectives to differ materially from any future results, performance, achievements, plans and objectives expressed or implied by these forward-looking statements. Such risks, uncertainties and other factors include those described under the heading "Risk Factors."

You should not place undue reliance on any such forward-looking statements. Further, any forward-looking statement speaks only as of the date on which it is made. New factors emerge from time to time, and it is not possible for us to predict what factors will arise or when. In addition, we cannot assess the impact of each factor on our business or the extent to which any factor, or combination of factors, may cause actual results to differ materially from those contained in any forward-looking statements.

For a discussion of important risks of an investment in our securities, including factors that could cause actual results to differ materially from results referred to in the forward-looking statements, see "Risk Factors." You should carefully consider the information set forth under the caption "Risk Factors." In light of these risks, uncertainties and assumptions, the forward-looking events discussed in or incorporated by reference in this prospectus might not occur.

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USE OF PROCEEDS

This prospectus relates to shares of our common stock being offered and sold for the accounts of the selling stockholders named in this prospectus. We will not receive any proceeds from the sale of common stock by the selling stockholders in this offering, but will pay certain expenses related to the registration of the shares of the Common Stock. See "Plan of Distribution."

SELLING STOCKHOLDERS

Based upon information available to us as of January 31, 2002, the

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table below sets forth the name of each selling stockholder, and with respect to each selling stockholder, the number of shares owned, the number of shares being offered by this prospectus and the number and percent of outstanding shares that will be owned after the sale of the registered shares, assuming all of the shares are sold.

The shares of common stock listed in the table represent shares of common stock issuable upon conversion of shares of Series B Convertible Preferred Stock and Series C Convertible Preferred Stock that we issued to the selling shareholders in a private placement pursuant to a stock purchase agreement dated August 2, 2001. In the stock purchase agreement, we agreed to file, within ten days after the final closing under the stock purchase agreement, a registration statement to enable the resale by the selling stockholders of all shares of common stock issuable upon conversion of the share of preferred stock acquired from us in the private placement, and to use our reasonable best efforts to have the registration statement declared effective by the Securities and Exchange Commission within 60 days after filing and to keep it effective, subject to certain blackout periods, for a period of two years or, if earlier, until all shares have been sold by the selling stockholders or can be sold without the volume restrictions of Section 144 (e) of the Securities Act.

| Name ----- | Shares Beneficially Owned Prior to the Offering ----- | Shares Being Offered ----- |
|---|--|----------------------------------|
| Warburg Pincus Private Equity VIII, L.P. (1) | 6,429,923 (2) | 6,429,923 |
| Ziff Asset Management, L.P. (3) | 1,107,015 (4) | 1,107,015 |
| David Hirsh (5) | 27,646 (6) | 27,646 |

* Less than 1%.

- (1) Warburg, Pincus & Co. is the sole general partner of Warburg Pincus Private Equity VIII, L.P. ("WP VIII"). WP VIII is managed by Warburg Pincus LLC. Lionel I. Pincus is the managing partner of Warburg Pincus & Co. and the managing member of Warburg Pincus LLC and may be deemed to control both entities. Jonathan S. Leff, a member of our board of directors, is a general partner of Warburg, Pincus & Co. and a managing director of Warburg Pincus LLC. Stewart J. Hen, a member of our board of directors, is a vice president of Warburg Pincus LLC. Messrs. Leff and Hen disclaim beneficial ownership (within the meaning of Rule 16a-1 under the Exchange Act) of all shares held by Warburg Pincus.
- (2) Represents shares of common stock issuable upon conversion of 9,398 shares of our Series B Convertible Preferred Stock and 25,452 shares of our Series C Convertible Preferred Stock.
- (3) Ziff Asset Management, L.P. is controlled by PBK Holdings, Inc., its general partner, which is controlled by Philip B. Korsant. Ziff Asset Management, L.P. is the sole investor in BVF Investments, L.L.C. BVF Investments, L.L.C. is controlled by BVF Inc. BVF Inc., through controlled affiliates including BVF Investments, beneficially owns approximately 14.8% of our outstanding common stock. Ziff Asset Management has no control of the voting or disposition of the shares held by BVF Investments or any other affiliate of BVF Inc. and disclaims beneficial ownership of all such shares.

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- (4) Represents shares of common stock issuable upon conversion of 1,618 shares of our Series B Convertible Preferred Stock and 4,382 shares of our Series C Convertible Preferred Stock.
- (5) David Hirsh is a member of the technical advisory board of Warburg Pincus LLC.
- (6) Represents shares of common stock issuable upon conversion of 40 shares of our Series B Convertible Preferred Stock and 4,382 shares of our Series C Convertible Preferred Stock.

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PLAN OF DISTRIBUTION

The shares of our common stock offered pursuant to this prospectus may be offered and sold from time to time by the selling shareholders, or their donees, transferees, pledgees or other successors in interest that receive such shares as a gift or other non-sale related transfer. Each selling shareholder will act independently of us in making decisions with respect to the timing, manner and size of each sale. All or a portion of the common stock offered by this prospectus may be offered for sale from time to time on The Nasdaq National Market or on one or more exchanges, or otherwise at prices and terms then obtainable, or in negotiated transactions. The distribution of these securities may be effected in one or more transactions that may take place on the over-the-counter market, including, among others, ordinary brokerage transactions, privately negotiated transactions or through sales to one or more dealers for resale of such securities as principals, at market prices prevailing at the time of sale, at prices related to such prevailing market prices or at negotiated prices. Usual and customary or specifically negotiated brokerage fees or commissions may be paid by the selling shareholders.

We will not receive any part of the proceeds from the sale of common stock. The selling shareholders and intermediaries through whom such securities are sold may be deemed "underwriters" within the meaning of the Securities Act, in which event commissions received by such intermediaries may be deemed to be underwriting commissions under the Securities Act. We will pay all expenses of the registration of securities covered by this prospectus. The selling shareholders will pay any applicable underwriters' commissions and expenses, brokerage fees or transfer taxes. A selling shareholder may, in the future, also sell the shares of common stock offered pursuant to this prospectus in accordance with Rule 144 under the Securities Act, or other available exemption, rather than pursuant to this prospectus.

LEGAL MATTERS

The validity of the common stock offered hereby has been passed upon for us by Baker Botts L.L.P., New York, New York.

EXPERTS

Ernst & Young LLP, independent auditors, have audited our financial statements included in our Annual Report on Form 10-K for the year ended December 31, 2000, as set forth in their report, which is incorporated by reference in this prospectus and elsewhere in the registration statement. Our financial statements are incorporated by reference in reliance on Ernst & Young LLP's report, given on their authority as experts in accounting and auditing.

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WHERE YOU CAN FIND MORE INFORMATION

We file annual, quarterly and special reports, proxy statements and other information with the SEC. Our SEC filings are available to the public over the Internet at the SEC's web site at <http://www.sec.gov>. You may also read and copy any document we file at the SEC's public reference room at 450 Fifth Street, N.W., Washington, D.C. 20549. You may obtain information on the operation of the Public Reference Room by calling the SEC at 1-800-SEC-0330.

This prospectus, which constitutes a part of a registration statement on Form S-3 filed by us with the SEC under the Securities Act, omits certain of the information set forth in the registration statement. Accordingly, you should refer to the registration statement and its exhibits for further information with respect to us and our common stock. Copies of the registration statement and its exhibits are on file at the offices of the SEC. Furthermore, statements contained in this prospectus concerning any document filed as an exhibit are not necessarily complete and, in each instance, we refer you to the copy of the document filed as an exhibit to the registration statement.

INCORPORATION BY REFERENCE

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

- Our Annual Report on Form 10-K for the year ended December 31, 2000 filed with the SEC on March 23, 2001;
- Our Quarterly Report on Form 10-Q for the quarter ended March 31, 2001 filed with the SEC on May 14, 2001;
- Our Quarterly Report on Form 10-Q for the quarter ended June 30, 2001 filed with the SEC on August 14, 2001;
- Our Quarterly Report on Form 10-Q for the quarter ended September 30, 2001 filed with the SEC on November 13, 2001;
- Our Current Report on Form 8-K filed with the SEC on August 6, 2001;
- Our Current Report on Form 8-K filed with the SEC on September 28, 2001;
- Our Current Report on Form 8-K filed with the SEC on November 27, 2001; and
- The description of our Common Stock contained in the registration statement on form 8-A filed with the SEC on December 4, 1995.

You may request a copy of any of these filings at no cost, by writing or telephoning us at the following address:

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