

REGISTRATION NO. 333-

SECURITIES AND EXCHANGE COMMISSION  
WASHINGTON, D.C. 20549

FORM S-3

REGISTRATION STATEMENT  
UNDER THE SECURITIES ACT OF 1933

BIOCRYST PHARMACEUTICALS, INC.

(Exact name of Registrant as specified in its Charter)

DELAWARE  
(State or other jurisdiction of  
incorporation or organization)

62-1413174  
(I.R.S. Employer  
Identification Number)

2190 PARKWAY LAKE DRIVE, BIRMINGHAM, ALABAMA 35244  
(205) 444-4600  
(Address, including zip code, and telephone number,  
including area code, of Registrant's principal executive offices)

CHARLES E. BUGG, PH.D.  
CHAIRMAN AND CHIEF EXECUTIVE OFFICER  
BIOCRYST PHARMACEUTICALS, INC.  
2190 PARKWAY LAKE DRIVE  
BIRMINGHAM, ALABAMA 35244  
(205) 444-4600  
(Name, address, including zip code, and telephone number,  
including area code, of agent for service of process)

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APPROXIMATE DATE OF COMMENCEMENT OF PROPOSED SALE TO THE PUBLIC: As soon as practicable on or after this Registration Statement is declared effective.

If the only securities being registered on this Form are being offered pursuant to dividend or interest reinvestment plans, please check the following box. / /

If any of the securities being registered on this Form are to be offered on a delayed or continuous basis pursuant to Rule 415 under the Securities Act of 1933, other than securities offered only in connection with dividend or interest reinvestment plans, check the following box. / /

If this Form is filed to register additional securities for an offering pursuant to Rule 462(b) under the Securities Act, please check the following box and list the Securities Act registration statement number of the earlier effective registration statement for the same offering. / /

If this Form is a post-effective amendment filed pursuant to Rule 462(c) under the Securities Act, check the following box and list the Securities Act registration statement number of the earlier effective registration statement for the same offering. / /

If delivery of the prospectus is expected to be made pursuant to Rule 434, please check the following box. / /

CALCULATION OF REGISTRATION FEE

| TITLE OF SHARES TO BE REGISTERED             | AMOUNT TO BE REGISTERED (1) | PROPOSED MAXIMUM OFFERING PRICE PER SHARE (2) | PROPOSED MAXIMUM AGGREGATE OFFERING PRICE (2) | AMOUNT OF REGISTRATION FEE (2) |
|--|-----------------------------|---|---|--------------------------------|
| Common Stock, par value \$.01 per share..... | 2,300,000                   | \$25.00                                       | \$57,500,000                                  | \$15,985                       |

(1) Includes 300,000 shares of common stock subject to cover the over-allotment

option granted by the company to the underwriters.

- (2) Estimated pursuant to Rule 457(c) solely for the purpose of computing the registration fee, based on the average high and low trading prices of the common stock, as reported on the Nasdaq National Market, on September 20, 1999.

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THE REGISTRANT HEREBY AMENDS THIS REGISTRATION STATEMENT ON SUCH DATE OR DATES AS MAY BE NECESSARY TO DELAY OUR EFFECTIVE DATE UNTIL THE REGISTRANT SHALL FILE A FURTHER AMENDMENT WHICH SPECIFICALLY STATES THAT THIS REGISTRATION STATEMENT SHALL THEREAFTER BECOME EFFECTIVE IN ACCORDANCE WITH SECTION 8(A) OF THE SECURITIES ACT OF 1933 OR UNTIL THE REGISTRATION STATEMENT SHALL BECOME EFFECTIVE ON SUCH DATE AS THE SECURITIES AND EXCHANGE COMMISSION, ACTING PURSUANT TO SECTION 8(A), MAY DETERMINE.

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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. THIS 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 OR SALE IS NOT PERMITTED.

P R O S P E C T U S

2,000,000 SHARES

[LOGO]

COMMON STOCK  
\$ PER SHARE  
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We are selling 2,000,000 shares of our common stock. The underwriters named in this prospectus may purchase up to 300,000 additional shares of common stock from us under certain circumstances.

Our common stock is quoted on the Nasdaq National Market under the symbol "BCRX." The last reported sale price of our common stock on the Nasdaq National Market on September 20, 1999 was \$24.75 per share.

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INVESTING IN OUR COMMON STOCK INVOLVES CERTAIN RISKS. SEE "RISK FACTORS" BEGINNING ON PAGE 7.

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.

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|  | PER SHARE | TOTAL |
|--|-----------|-------|
|  | -----     | ----- |
| Public Offering Price                  | \$        | \$    |
| Underwriting Discount                  | \$        | \$    |
| Proceeds to BioCryst (before expenses) | \$        | \$    |

The underwriters are offering the shares subject to various conditions. The underwriters expect to deliver the shares to purchasers on or about \_\_\_\_\_, 1999.

-----  
SALOMON SMITH BARNEY

HAMBRECHT & QUIST

RAYMOND JAMES & ASSOCIATES, INC.

, 1999

YOU SHOULD RELY ONLY ON THE INFORMATION CONTAINED IN THIS PROSPECTUS. WE HAVE NOT AUTHORIZED ANYONE TO PROVIDE YOU WITH DIFFERENT INFORMATION. WE ARE NOT MAKING AN OFFER OF THESE SECURITIES IN ANY STATE WHERE THE OFFER IS NOT PERMITTED. YOU SHOULD NOT ASSUME THAT THE INFORMATION PROVIDED BY THIS PROSPECTUS IS ACCURATE AS OF ANY DATE OTHER THAN THE DATE ON THE FRONT OF THIS PROSPECTUS.

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WHERE YOU CAN FIND MORE INFORMATION

We file annual, quarterly and special reports, proxy statements and other information with the Securities and Exchange Commission, or the SEC. You may read and copy any document we file at the public reference facilities of the SEC located at 450 Fifth Street, N.W., Washington D.C. 20549. You may obtain information on the operation of the SEC's public reference facilities by calling the SEC at 1-800-SEC-0330. You can also access copies of such material electronically on the SEC's home page on the World Wide Web at <http://www.sec.gov>.

This prospectus is part of a registration statement (Registration No. 333- ) we filed with the SEC. The SEC permits us to "incorporate by reference" the information that we file with them, 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 with the SEC after the date of this prospectus will automatically update and supercede this information. We incorporate by reference the following documents filed by us with the SEC (File No. 0-27066). We also incorporate by reference any future filings made with the SEC under Sections 13(a), 13(c), 14 or 15(d) of the Securities Exchange Act of 1934, as amended, after the date of this prospectus until the termination of this offering:

1. Our Annual Report on Form 10-K for the fiscal year ended December 31, 1998.
2. Our Quarterly Reports on Form 10-Q for the quarters ended March 31, 1999 and June 30, 1999.
3. Our Proxy Statement dated April 2, 1999 filed in connection with our 1999 Annual Meeting of Stockholders.
4. The description of our common stock which is contained in our registration statement on Form 8-A filed under the Exchange Act on January 8, 1994, including any amendment or reports filed for the purpose of updating such description.

If you request a copy of any or all of the documents incorporated by reference, we will send to you the copies requested at no charge. However, we will not send exhibits to such documents, unless such exhibits are specifically incorporated by reference in such documents. You should direct requests for such copies to: Mr. Ronald E. Gray, Chief Financial Officer, BioCryst Pharmaceuticals, Inc., 2190 Parkway Lake Drive, Birmingham, Alabama 35244, (205) 444-4600.

## PROSPECTUS SUMMARY

THIS SUMMARY HIGHLIGHTS INFORMATION CONTAINED ELSEWHERE IN THIS PROSPECTUS. YOU SHOULD READ THIS ENTIRE PROSPECTUS CAREFULLY, INCLUDING THE "RISK FACTORS" SECTION. IN ADDITION, WE INCORPORATE BY REFERENCE IMPORTANT BUSINESS AND FINANCIAL INFORMATION IN THIS PROSPECTUS.

### OUR COMPANY

BioCryst Pharmaceuticals, Inc. is a biotechnology company focused on the development of small-molecule pharmaceuticals for the treatment of infectious, T-cell mediated and cardiovascular diseases and disorders. We utilize our structure-based drug design technologies to develop potent, selective inhibitors directed at the active sites of target enzymes. Our lead product candidate, BCX-1812, is a neuraminidase inhibitor designed to treat and prevent viral influenza. In September 1998, we entered into an exclusive worldwide license agreement with The R.W. Johnson Pharmaceutical Research Institute, or PRI, and Ortho-McNeil Pharmaceutical, Inc., both Johnson & Johnson companies. Pursuant to this agreement, these Johnson & Johnson companies now have sole responsibility for the development, manufacture and commercialization of BCX-1812. We have been informed by PRI that the planning of Phase III trials for the 1999/2000 flu season is underway.

An important element of our business strategy is to control costs and overhead through outsourcing and partnering. Our strategy of focusing on discovery and early-stage development of drug candidates and leveraging pharmaceutical partners' rapid and effective development and commercialization expertise is designed to control our expenses, minimize risks and allow us to have a larger number of attractive drug candidates progress to advanced-stage clinical trials.

### OUR INFLUENZA NEURAMINIDASE INHIBITOR

Influenza, commonly known as the flu, is perceived by many people as a transient, inconvenient viral infection that leaves its sufferers bed-ridden for a few days. In truth, however, it is a virulent, acute respiratory disease that is sometimes deadly. In North America, Western Europe and Japan, an estimated 70 million to 150 million individuals suffer from influenza annually. The flu is particularly dangerous to the elderly, young children and debilitated patients and accounts for approximately 20,000 deaths in the United States each year. The flu and associated complications are the sixth leading cause of death in the United States. The annual cost to the U.S. economy associated with influenza epidemics was estimated to be in excess of \$12 billion, according to a 1994 article in THE NEW ENGLAND JOURNAL OF MEDICINE.

In collaboration with scientists from The University of Alabama at Birmingham, we used structure-based drug design to develop several novel inhibitors of influenza neuraminidase. The structure of the active site of influenza neuraminidase is similar among most strains of influenza. Consequently, we believe our lead compound, BCX-1812, may be effective in the treatment and prevention of the flu, regardless of viral mutations.

Our preclinical studies demonstrated that BCX-1812 has the following benefits:

- excellent safety profile;
- broad spectrum inhibition of influenza A and B;
- good oral efficacy;
- probable once-a-day dosage indicated by a positive pharmacokinetic profile; and
- stability in liquid, making a liquid formulation possible for pediatric and elderly applications.

We have entered into an exclusive worldwide license agreement with PRI and Ortho-McNeil to develop and market our proprietary influenza neuraminidase inhibitors, including our lead product candidate, BCX-1812. We received an initial \$6.0 million payment from Ortho-McNeil and an additional \$6.0 million common stock equity investment from Johnson & Johnson Development Corporation. In June 1999, we received a \$2.0 million milestone payment from Ortho-McNeil in connection with the initiation of Phase II clinical testing in the United States. In addition, we may receive cash

payments upon achievement of specified developmental and regulatory milestones and royalties on product sales, if any.

Since the collaboration was established, BCX-1812 moved through Phase I clinical trials and a Phase II clinical study by August 1999. We recently announced preliminary results from a Phase II placebo-controlled, randomized study conducted by PRI for the treatment of healthy volunteers infected with a strain of influenza A. The primary efficacy endpoint was the reduction in viral titers in infected subjects. PRI advised us that the data from this Phase II study indicated a statistically significant result for the primary endpoint, and evaluation of safety showed that the drug was well tolerated at all dosage levels. We have been informed by PRI that the planning of the Phase III clinical trials for the 1999/2000 influenza season is underway.

#### OTHER DRUG DEVELOPMENT PROGRAMS

We are also seeking to develop potent, selective inhibitors for the treatment of a variety of other diseases and disorders. Two important drug development programs currently underway include our purine nucleoside phosphorylase, or PNP, inhibitor program and our complement inhibitor program. Our lead PNP inhibitor drug candidate, BCX-34, is a novel mechanism for suppressing T-cell replication. Although T-cells are an essential part of the body's immune system, there are diseases in which T-cells multiply uncontrollably or attack normal cells. PNP is believed to play an important role in T-cell proliferation by facilitating DNA synthesis. Inhibiting PNP suppresses T-cell replication without significantly affecting other cells. We believe this could have an impact on several diseases such as psoriasis, cutaneous T-cell lymphoma and T-cell leukemia.

Complement proteins circulate in the blood in a non-activated form. Upon activation, these proteins can result in adverse biological effects including tissue damage. Based on research done in our complement inhibitor program, we have identified a class of compounds that may have therapeutic applications for several disorders by limiting the rapid and aggressive damage caused by complement activation.

#### OUR BUSINESS STRATEGY

Our business strategy is to use structure-based drug design technologies to develop innovative, small-molecule pharmaceuticals to treat a variety of diseases and disorders. The principal elements of our strategy are:

- SELECT AND IN-LICENSE ATTRACTIVE ENZYME TARGETS FOR THE DEVELOPMENT OF SMALL-MOLECULE PHARMACEUTICALS. We use our technical expertise and network of academic and industry contacts to evaluate and select promising enzyme targets to in-license for drug development.
- FOCUS ON HIGH VALUE-ADDED, STRUCTURE-BASED DRUG DESIGN TECHNOLOGIES. We believe structure-based drug design is a powerful tool for the rapid and efficient development of small-molecule drug candidates that have the potential to be safe, effective and relatively inexpensive to manufacture. We focus on the use of these technologies to design and develop our drug candidates.
- DEVELOP INHIBITORS THAT ARE PROMISING CANDIDATES FOR COMMERCIALIZATION. Drug candidates are selected, in part, on the basis of their potential for relatively efficient Phase I and Phase II clinical trials. We may consider more complex drug candidates if we believe they offer promising commercial opportunities in large markets.
- LEVERAGE RELATIONSHIPS WITH ACADEMIC INSTITUTIONS AND BIOTECHNOLOGY COMPANIES. By leveraging our relationships with academic institutions and biotechnology companies, we believe we can significantly reduce the time, cost and risk involved in drug development.
- PARTNER DEVELOPMENT CANDIDATES. Our goal is to advance drug candidates through preclinical development and early-stage clinical trials, then license these drug candidates to pharmaceutical partners for final development and marketing. This strategy should allow us to remain focused on our core competencies and leverage our pharmaceutical partners' development and commercialization expertise.

THE OFFERING

Common stock offered..... 2,000,000 shares

Common stock to be outstanding after the offering..... 17,229,707 shares

Use of proceeds..... For in-licensing drug development candidates, research and development activities, preclinical studies and clinical trials, expanding facilities, hiring additional personnel, working capital and general corporate purposes.

Nasdaq National Market symbol..... "BCRX"

Unless we specifically state otherwise, the information in this prospectus does not take into account the issuance of up to 300,000 shares of common stock which the underwriters have the option to purchase solely to cover over-allotments. If the underwriters exercise their over-allotment option in full, 17,529,707 shares of common stock will be outstanding after the offering.

The number of shares of common stock to be outstanding immediately after the offering is based upon shares outstanding as of September 20, 1999 and does not take into account 2,258,301 shares of common stock issuable upon exercise of options outstanding at a weighted average exercise price of \$7.50 per share and 602,107 shares reserved under our existing stock option plan and employee stock purchase plan.

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Our principal offices are located at 2190 Parkway Lake Drive, Birmingham, Alabama 35244, and our telephone number is (205) 444-4600.

This prospectus contains a description of our exclusive worldwide license agreement with The R.W. Johnson Pharmaceutical Research Institute, or PRI, and Ortho-McNeil Pharmaceutical, Inc. Both PRI and Ortho-McNeil are Johnson & Johnson companies. We have been informed that PRI will be responsible for research and development of the compounds, including expenses, Ortho-McNeil will market products approved by the FDA in the United States, if any, and other Johnson & Johnson companies, including Janssen-Cilag, will market products cleared for marketing outside the United States.

SUMMARY FINANCIAL DATA

|   | YEARS ENDED DECEMBER 31,              |            |            |             |            | SIX MONTHS ENDED<br>JUNE 30, |            |
|---|---------------------------------------|------------|------------|-------------|------------|------------------------------|------------|
|   | 1994                                  | 1995       | 1996       | 1997        | 1998       | 1998                         | 1999       |
|   | (IN THOUSANDS, EXCEPT PER SHARE DATA) |            |            |             |            |                              |            |
| STATEMENT OF OPERATIONS DATA:                         |                                       |            |            |             |            |                              |            |
| Revenues:   |                                       |            |            |             |            |                              |            |
| Collaborative and other research and development..... | \$ 269                                | \$ 223     | \$ 1,558   | \$ 1,000    | \$ 6,371   | \$ --                        | \$ 2,408   |
| Interest and other.....                               | 465                                   | 662        | 1,094      | 1,692       | 1,255      | 671                          | 633        |
| Total revenues.....                                   | 734                                   | 885        | 2,652      | 2,692       | 7,626      | 671                          | 3,041      |
| Expenses:   |                                       |            |            |             |            |                              |            |
| Research and development.....                         | 5,552                                 | 7,107      | 7,586      | 10,577      | 9,291      | 5,353                        | 4,006      |
| General and administrative.....                       | 1,904                                 | 2,210      | 2,664      | 2,682       | 3,105      | 1,295                        | 1,683      |
| Interest.....   | 216                                   | 144        | 100        | 52          | 15         | 10                           | 3          |
| Total expenses.....                                   | 7,672                                 | 9,461      | 10,350     | 13,311      | 12,411     | 6,658                        | 5,692      |
| Net loss.....   | \$ (6,938)                            | \$ (8,576) | \$ (7,698) | \$ (10,619) | \$ (4,785) | \$ (5,987)                   | \$ (2,651) |
| Net loss per share.....                               | \$ (1.02)                             | \$ (0.96)  | \$ (0.69)  | \$ (0.77)   | \$ (0.34)  | \$ (0.43)                    | \$ (0.18)  |
| Weighted average shares outstanding....               | 6,787                                 | 8,905      | 11,171     | 13,780      | 14,120     | 13,926                       | 14,981     |

The as-adjusted information that follows gives effect to this offering and assumes no exercise of the underwriters' over-allotment option.

|   | JUNE 30, 1999  |             |
|---|----------------|-------------|
|   | ACTUAL         | AS ADJUSTED |
|   | (IN THOUSANDS) |             |
| BALANCE SHEET DATA:   |                |             |
| Cash, cash equivalents and securities held-to-maturity..... | \$ 24,317      | \$ 70,097   |
| Total assets.....   | 26,546         | 72,326      |
| Accumulated deficit.....                                    | (55,821)       | (55,821)    |
| Total stockholders' equity.....                             | 25,199         | 70,979      |

## RISK FACTORS

AN INVESTMENT IN OUR COMMON STOCK INVOLVES SIGNIFICANT RISKS. YOU SHOULD CAREFULLY CONSIDER THE FOLLOWING RISKS BEFORE YOU DECIDE TO BUY OUR COMMON STOCK.

WE HAVE INCURRED SUBSTANTIAL LOSSES SINCE OUR INCEPTION, EXPECT TO CONTINUE TO INCUR SUCH LOSSES AND MAY NEVER BE PROFITABLE

We have incurred operating losses since our inception in 1986. As of June 30, 1999, our accumulated deficit was approximately \$55.8 million. We expect to incur additional losses for the foreseeable future, and we expect our losses to increase as our research and development efforts progress. To become profitable, we must successfully develop drug candidates, enter into profitable agreements with collaborative partners and our drug candidates must obtain regulatory approval. The drug candidates must then be successfully manufactured and marketed by our collaborative partners. It will be several years, if ever, before we will recognize significant revenues from royalties pursuant to our existing license agreements and future license agreements, if any. In addition, we do not expect to ever generate revenue directly from product sales. We may never generate significant revenue or become profitable.

OUR DEVELOPMENT EFFORTS MAY NOT RESULT IN COMMERCIALY SUCCESSFUL PRODUCTS

The development of our drug candidates is highly uncertain, costly and depends on many factors that are beyond our control. There are many reasons that we may fail in our efforts to develop commercially successful products, including:

- our drug candidates may be ineffective or toxic;
- our drug candidates may fail to receive necessary regulatory approvals;
- our drug candidates may be too expensive to develop, manufacture or market effectively;
- our drug candidates may not be accepted by physicians and patients;
- our collaborative partners may not pursue or successfully develop our drug candidates;
- others may hold or acquire proprietary rights that could prevent us from developing our products; and
- others may develop equivalent or superior products.

All of our drug candidates are in early stages of development. The uncertainties inherent in the development of our drug candidates are especially significant in view of their early-stage nature. Failure to develop our drug candidates would have a material adverse effect on our business, financial condition and results of operations.

WE ARE HIGHLY DEPENDENT ON PRI AND ORTHO-MCNEIL FOR SUBSTANTIALLY ALL OF OUR REVENUE

Approximately 79.2% of our revenues for the six months ended June 30, 1999 and approximately 83.5% of our revenues for the year ended December 31, 1998 resulted from our exclusive worldwide license agreement with PRI and Ortho-McNeil. These revenues represent approximately 45.0% of our total revenues since our inception in 1986. The termination of the license agreement with PRI and Ortho-McNeil, any changes to the existing agreement that are less favorable to us or the failure of PRI and Ortho-McNeil to fulfill their obligations under the license agreement would materially and adversely affect our business.

THE DEVELOPMENT, MANUFACTURING AND COMMERCIALIZATION OF OUR INFLUENZA NEURAMINIDASE INHIBITORS IS HIGHLY DEPENDENT ON PRI AND ORTHO-MCNEIL

We rely on the exclusive license agreement we entered into with PRI and Ortho-McNeil and PRI in September 1998 for the development, manufacture and commercialization of our influenza neuraminidase inhibitors, including BCX-1812. Under this agreement, PRI and Ortho-McNeil have the following rights that could adversely affect the development of our influenza neuraminidase inhibitors:

- sole discretion on all elements of research and development of BCX-1812, including timing and design of further clinical trials;
- sole responsibility to initiate and complete clinical trials, interpret data, prepare and file a new drug application, or NDA, obtain the approval of the U.S. Food and Drug Administration, or FDA, or foreign regulatory agencies and commercialize BCX-1812;
- sole control over the amount of resources devoted to the research and development of BCX-1812;
- the right to terminate or cancel the agreement, which may be done at any time on four months notice; and
- the right to subject us to penalties, including reducing their royalty payments or forcing us to assign all of our interest in joint inventions and patents to be done Ortho-McNeil, if we breach the agreement.

Any revenue we may receive in connection with BCX-1812 is dependent upon PRI and Ortho-McNeil successfully attaining specified development milestones or successfully commercializing BCX-1812 and paying us royalties on sales of the product. We do not know when, if ever, PRI and Ortho-McNeil will receive FDA or foreign regulatory approval for, or commence commercialization of BCX-1812. We cannot be certain that our relationship with PRI and Ortho-McNeil will continue or be successful. If PRI and Ortho-McNeil terminate the license agreement or fails to aggressively develop or commercialize BCX-1812, our business would be materially and adversely affected.

WE ARE HIGHLY DEPENDENT UPON THIRD PARTIES FOR MANY OF THE STEPS REQUIRED FOR DRUG DEVELOPMENT, INCLUDING IDENTIFYING TARGETS, CONDUCTING CLINICAL TRIALS, OBTAINING REGULATORY APPROVALS, MANUFACTURING AND COMMERCIALIZATION

We generally rely on in-licensing drug targets from academic institutions and biotechnology companies from which we develop inhibitors that are then advanced in-house through early stage clinical trials. Our goal is to then license the inhibitors to pharmaceutical and biotechnology companies for further clinical development, manufacturing and commercialization. Consequently, our business is highly dependent upon third parties.

THE SUCCESSFUL IMPLEMENTATION OF OUR BUSINESS STRATEGY DEPENDS UPON OUR ABILITY TO IN-LICENSE ENZYME TARGETS FROM RESEARCH PARTNERS

Our drug development strategy depends on our ability to in-license enzyme targets from academic institutions and other biotechnology companies. Initially, we rely on preliminary research conducted by the scientists at these organizations to discover attractive enzyme targets for us to in-license. Once we have entered into an agreement with the organization, we then rely on their scientists' ability to collaborate with our staff and to further the development of the drug candidate. To date, we have entered into such collaborative agreements with only three parties, and the only enzyme target from these agreements that has successfully been out-licensed for further development is our influenza neuraminidase inhibitor. We cannot assure you that we will be able to successfully identify research partners, enter into license agreements on acceptable terms with any we do identify, or develop any

drug candidates from any in-licensed enzyme targets. If we cannot in-license enzyme targets to support our drug development strategy, our business will be materially adversely affected.

#### WE ARE LARGELY DEPENDENT ON COLLABORATIVE PARTNERS FOR THE DEVELOPMENT OF OUR COMPOUNDS

A key part of our strategy is to out-license our drug candidates to third parties for further clinical development and to obtain regulatory approval. We have entered into only a limited number of such out-licensing arrangements. We cannot assure you that we will be able to negotiate additional collaborative arrangements on acceptable terms, maintain the collaborative arrangements we currently have or that any of our collaborative arrangements will prove successful. Our reliance on third parties for the continued development of our compounds, if any, presents several risks, including:

- a contract with a third party may expire or be unilaterally terminated, as was the case with our contract with Torii Pharmaceutical Co., Ltd.;
- business combinations or significant changes in a collaborative partner's business strategy may adversely affect a partner's willingness or ability to complete its obligations under the arrangement;
- our collaborative partners may choose to pursue alternative technologies, including those of our competitors;
- we may have disputes with a partner, such as disputes regarding ownership rights of the drug candidate, that could delay research and development of a compound or require us to devote resources to litigation or arbitration;
- a partner involved in the development of our drug candidates may not commit sufficient capital or resources to successfully develop our compounds; or
- we may be contractually bound to terms that, in the future, are not commercially favorable to us.

If we are not able to establish further collaborative arrangements or any of our existing collaborative arrangements are terminated, we would be required to seek new collaborative arrangements or to undertake further product development at our own expense. Such an undertaking might:

- limit the number of drug candidates that we will be able to develop and commercialize;
- reduce the likelihood of successful product introduction;
- significantly increase our capital requirements; and
- place additional strain on management's time.

#### WE ARE DEPENDENT ON THIRD-PARTY CONTRACT RESEARCH ORGANIZATIONS

We rely heavily on contract research organizations, or CROs, to execute our initial clinical trials. The failure by the CROs to execute our initial clinical trials satisfactorily or any breach of their obligations to us could delay or prevent the commercialization of our drug candidates. Delays by CROs would be particularly harmful to us, because we typically commence negotiations with potential collaborative partners for further development and commercialization of our drug candidates only after receiving the results of the trials conducted by the CRO. Any such failures by our contract research partners would have a material adverse effect on our business.

WE ARE DEPENDENT UPON THIRD PARTIES TO MANUFACTURE OUR PRODUCT CANDIDATES; IF THEY ARE UNWILLING OR UNABLE TO PRODUCE OUR PRODUCT CANDIDATES OR IF THEY FAIL TO COMPLY WITH GOVERNMENTAL REGULATIONS, OUR BUSINESS WILL SUFFER

We have no manufacturing facilities for any of our product candidates. We have no experience in commercial manufacturing and intend to rely on our collaborative partners for the commercial manufacture of our product candidates. For example, we are relying solely on Ortho-McNeil for the manufacture of our influenza neuraminidase inhibitor. We cannot assure you that we will be able to make arrangements with third parties to manufacture our potential products on acceptable terms, or at all. Our inability to efficiently manufacture or provide for the manufacture of any of our product candidates would materially and adversely affect our business.

We cannot assure you that our present or future suppliers will be able to comply with applicable good manufacturing practice regulations and other FDA regulatory requirements. Failure of our third-party manufacturers to comply with the applicable governmental requirements may result in restrictions on the marketing of a product, withdrawal of the product from the market, seizures, injunctions, or criminal sanctions, any of which could materially and adversely affect our business.

WE INTEND TO RELY ON THE SALES, MARKETING OR DISTRIBUTION CAPABILITIES OF THIRD PARTIES

We have no experience in sales, marketing or distribution of pharmaceuticals and currently do not intend to employ personnel in any of these capacities. We intend to rely on collaborative partners with established distribution systems and direct sales forces for the sales, marketing and distribution of potential products. We cannot assure you that we will be able to establish marketing relationships with others on acceptable terms, if at all. Even if we establish sales, marketing or distribution arrangements with other parties, they may have substantial control over the commercialization of our product candidates. We will be unable to control the resources that any third party may devote to our product candidates, and our revenues, if any, will largely depend on their efforts. If we fail to enter into successful third-party sales, marketing or distribution arrangements, our business will be materially adversely affected.

CLINICAL TRIALS ARE INHERENTLY UNPREDICTABLE AND OUR FAILURE TO SUCCESSFULLY IMPLEMENT AND COMPLETE THEM WOULD HARM OUR BUSINESS

To obtain the regulatory approvals necessary for the sale of our drug candidates, it must be demonstrated through preclinical studies and clinical trials that each drug candidate is safe and effective. The clinical trial process is complex and uncertain. Positive results from preclinical studies and early clinical trials do not ensure positive results in pivotal clinical trials. Many companies in our industry, including us, have suffered significant setbacks in pivotal clinical trials, even after promising results in earlier clinical trials. Any of our drug candidates may produce undesirable side effects in humans. These side effects could cause us or regulatory authorities to interrupt, delay or halt clinical trials of a drug candidate. These side effects could also result in the FDA or foreign regulatory authorities refusing to approve the drug candidate for any targeted indications. We, the FDA or foreign regulatory authorities may suspend or terminate clinical trials at any time if we or they believe the trial participants face unacceptable health risks. Clinical trials may fail to demonstrate that our drug candidates are safe or effective.

Clinical trials are lengthy and expensive. We incur substantial expense for, and devote significant time to, preclinical testing and clinical trials, yet cannot be certain that the tests and trials will ever result in the commercial sale of a product. For example, clinical trials require adequate supplies of drug and sufficient patient enrollment. Delays in patient enrollment can result in increased costs and longer development times. Even if clinical trials are successfully completed for our product candidates, our

third-party licensees might not file the required regulatory submissions in a timely manner and may not receive regulatory approval for the drug candidate.

In 1995 and 1996, the FDA inspected us and certain of our clinical sites relating to certain clinical trials for the topical version of BCX-34. The FDA issued to us two Lists of Inspectional Observations on Form FDA 483. These matters may have a negative impact on our future relationships with the FDA, which could delay clinical trials or any potential product approvals.

PRI has completed a Phase II trial of BCX-1812, and we have been informed by PRI that the planning of the Phase III clinical trials of BCX-1812 is underway. We cannot assure you that the FDA will accept PRI's clinical protocols, that PRI will commence the Phase III clinical trials in 1999 or at all, or that the Phase III clinical trials, if initiated, will be successful. Even if PRI does complete the Phase III trials, we do not know when, if ever, PRI will receive FDA or foreign regulatory agency approvals for, or Ortho-McNeil will commence commercialization of, BCX-1812. If we or PRI are unable to commence clinical trials as planned, complete the clinical trials or demonstrate the safety and efficacy of our compounds, our business will be harmed. Even if the results of PRI's trials are positive, products, if any, are not likely to be commercially available for several years, if at all.

IF OUR DRUG CANDIDATES, INCLUDING OUR INFLUENZA NEURAMINIDASE INHIBITORS, DO NOT ACHIEVE BROAD MARKET ACCEPTANCE, OUR BUSINESS MAY NEVER BECOME PROFITABLE

Our drug candidates, even if approved for sale by the FDA or foreign regulatory agencies, may not gain the market acceptance required for us to be profitable. The degree of market acceptance of any drug candidates that we or our partners develop will depend on a number of factors, including:

- establishment and demonstration of the clinical efficacy and safety of our drug candidates;
- cost-effectiveness of our drug candidates;
- their effectiveness relative to alternative treatment methods, such as the efficacy and ease of use of our influenza neuraminidase inhibitor over other products, including vaccines, existing drugs such as amantadine and rimantadine, Hoffmann-La Roche's and Glaxo Wellcome's influenza neuraminidase inhibitors and over-the-counter products;
- reimbursement policies of government and third-party payors which, for example, may not cover the costs of treatments that provide symptom relief; and
- marketing and distribution support for our drug candidates.

Physicians, patients, payors or the medical community in general may not accept or use our drug candidates, including our influenza neuraminidase inhibitor, even after regulatory approval has been obtained. If our drug candidates do not achieve significant market acceptance, our business and financial condition will be materially adversely affected.

IF WE OR OUR COLLABORATIVE PARTNERS DO NOT OBTAIN AND MAINTAIN GOVERNMENTAL APPROVALS FOR OUR PRODUCTS UNDER DEVELOPMENT, WE WILL NOT BE ABLE TO SELL THESE POTENTIAL PRODUCTS, WHICH WOULD SIGNIFICANTLY HARM OUR BUSINESS

All of our products under development will require regulatory approval by the FDA before we or our collaborative partners are permitted to sell them in the United States. Clinical trial data can be the subject of differing interpretation. We cannot assure you that the FDA will interpret our clinical data the way we or our partners do, or that the FDA will not require additional clinical data to support approval. The results from earlier-stage studies may not be predictive of results obtained in later-stage trials.

After we or our partners complete the clinical trials for a potential product, we or our partners will be required to file an NDA. The requirements for submission of NDAs and the approval processes

on the part of the FDA require substantial time, expense and effort, and we cannot assure you that any approval will be granted on a timely basis, if at all. The FDA can take years to review NDAs and may take longer if significant questions are raised during the review process. In addition, delays or rejections may be encountered during FDA review. Moreover, it is possible that the current regulatory framework could change or additional regulations could arise at any stage during our product development, which may affect our ability to obtain approval of our compounds. We cannot assure you that even after such time and expenditures, regulatory approval will be obtained. Delays in obtaining regulatory approvals may:

- adversely affect the successful commercialization of any drug candidates that we and our collaborative partners develop;
- impose costly procedures on our collaborative partners;
- diminish any competitive advantages that we or our collaborative partners may attain; and
- adversely affect our receipt of revenues or royalties.

Even if regulatory approval of a potential product is granted, the approval may limit the indicated uses for which the potential product may be marketed and/or may require post-marketing studies.

The FDA regulates, among other things, the record-keeping and storage of data pertaining to potential pharmaceutical products. We currently store all of our preclinical research data at our facilities and do not store duplicate copies off-site. We cannot assure you that we would not lose important preclinical data if our facilities were damaged.

In order to market our potential products in countries outside of the United States, we and our partners are required to obtain similar approvals from foreign regulatory bodies. The process of obtaining these approvals is time consuming and requires the expenditure of substantial resources, and we and our collaborative partners may encounter similar delays, rejections, requests for additional data, and other setbacks with regulatory authorities in other countries as we face in the United States.

If we get approval to market our potential products, whether in the United States or internationally, we will continue to be subject to extensive regulatory requirements. These requirements are wide ranging and govern, among other things:

- adverse drug experience reporting regulations;
- product promotion;
- product manufacturing, including good manufacturing practice requirements; and
- product changes or modifications.

Loss of or changes to previously obtained approvals or our failure to comply with existing or future regulatory requirements could have a material adverse effect on our business.

In June 1995, we notified the FDA that we submitted incorrect efficacy data for our Phase II dose-ranging studies of topical BCX-34 for CTCL and psoriasis. The FDA inspected us in November 1995 and issued to us a List of Inspectional Observations, Form FDA 483, that cited our failure to follow good clinical practices. In June 1996, the FDA inspected us and two of our 1995 Phase II dose-ranging studies of topical BCX-34 for the treatment of CTCL and psoriasis. As a result of the investigation, the FDA issued us a Form FDA 483, which cited our failure to follow good clinical practices. As a consequence, our ongoing and future clinical studies may receive increased scrutiny, which may delay the regulatory review process. Also in June 1996, the FDA investigated one of the clinical trial sites that participated in our 1995 Phase II dose-ranging studies of topical BCX-34 for the treatment of CTCL and psoriasis. As a result, the FDA issued a Form FDA 483 to the principal investigator at the clinical site. In November 1997, the FDA notified us that they would not accept work performed by this investigator without further validation. The majority of the work performed by this investigator was for a topical formulation of BCX-34, which work was discontinued in 1997. Work performed by this investigator for oral BCX-34, however, will not be accepted by the FDA in any NDA to support efficacy.

WE HAVE RECENTLY CHANGED OUR BUSINESS MODEL WHICH, TO DATE, HAS NOT BEEN TESTED

Prior to 1998, our strategy was to discover, develop and commercialize small-molecule pharmaceutical products using structure-based drug design with the intention to be a fully-integrated pharmaceutical company. In 1998, we substantially changed our business model to focus exclusively on drug discovery, initial product candidate development and the out-licensing of late-stage products to collaborative partners for clinical testing, regulatory approval and global commercialization. We cannot assure you that our new out-licensing strategy will be successful.

IF WE NEED ADDITIONAL FUNDS AND ARE UNABLE TO RAISE THEM, WE WOULD HAVE TO CURTAIL OR CEASE OUR DEVELOPMENT EFFORTS

We have expended and will continue to expend substantial funds to complete the research, development and clinical testing of our compounds. Our future capital requirements will depend on many factors, including:

- the progress of our research, drug discovery and development programs;
- changes in existing collaborative relationships;
- our ability to establish additional collaborative relationships;
- the magnitude of our research and development programs;
- the scope and results of preclinical studies and clinical trials to identify drug candidates;
- competitive and technological advances;
- the time and costs involved in obtaining regulatory approvals;
- the costs involved in preparing, filing, prosecuting, maintaining and enforcing patent claims;
- our dependence on others, including PRI and Ortho-McNeil, for development and commercialization of our product candidates, in particular, our neuraminidase inhibitors; and
- successful commercialization of our products consistent with our out-licensing strategy.

We believe that our cash and anticipated sources of funding, including the net proceeds of this offering, will be adequate to satisfy our anticipated capital needs through 2001. If our plans change, we may need to raise additional funds through new or existing collaborations or through private or public equity or debt financings. However, additional financing may not be available on acceptable terms or at all.

COMPETITIVE PRODUCTS FROM OTHER COMPANIES MAY RENDER SOME OR ALL OF OUR PRODUCT CANDIDATES NONCOMPETITIVE OR OBSOLETE

The biotechnology and pharmaceutical industries are highly competitive and are subject to rapid and substantial technological change. Other products and therapies that either currently exist on the market or are under development could compete directly with some of the compounds that we are seeking to develop and market. These other products may render some or all of our compounds under development noncompetitive or obsolete.

If our influenza neuraminidase inhibitor drug candidate, which is partnered with PRI and Ortho-McNeil, receives FDA or foreign regulatory approval, we expect it to have substantial competition from a number of existing and future therapies. Glaxo Wellcome plc's influenza neuraminidase inhibitor has received approval from the FDA for marketing in the United States and has received approval for marketing in several other countries. Gilead Sciences, Inc., in collaboration with Hoffmann-La Roche, Inc., also has an influenza neuraminidase inhibitor that is under review by the FDA. If approved, our influenza neuraminidase inhibitor, BCX-1812, will likely be the third neuraminidase inhibitor to the

market. We believe that this may provide marketing challenges. In addition, current therapies available for the treatment or prevention of flu include vaccines and the drugs amantadine and rimantadine, as well as over-the-counter products.

There are numerous pharmaceutical and biotechnology companies and academic institutions throughout the world engaged in research and development efforts with respect to therapeutic products targeted at diseases or conditions addressed by us. Many of these competitors may be able to develop products and processes, in addition to those treatments that already exist, that are competitive with, or superior to, our own for many reasons, because competitors may have:

- substantially greater financial, technical and human resources;
- larger production and marketing capabilities;
- greater experience in preclinical testing, clinical trials and other regulatory matters; and
- entered into arrangements with, or acquired, biotechnology companies or technologies to enhance their capabilities.

We cannot assure you that these products will not prove to be more effective than our own or that our products, if any, will offer an economically feasible or preferable alternative to existing modes of therapy.

#### WE MAY FAIL TO ADEQUATELY PROTECT OR ENFORCE OUR INTELLECTUAL PROPERTY RIGHTS OR SECURE RIGHTS TO THIRD PARTY PATENTS

Our success will depend in part on our ability and the abilities of our licensors to obtain patent protection for our products, methods, processes and other technologies to preserve our trade secrets, and to operate without infringing the proprietary rights of third parties. To date, we have been issued nine U.S. patents for our various inventions. Additional patent applications and provisional patent applications have been filed with the U.S. Patent and Trademark Office, or PTO. We have filed certain corresponding foreign patent applications and intend to file additional foreign and U.S. patent applications, as appropriate. We cannot assure you as to:

- the degree and range of protection any patents will afford against competitors with similar products;
- if and when patents will issue;
- whether or not others will obtain patents claiming aspects similar to those covered by our patent applications;
- whether or not others will design around our patents or obtain access to our know-how; or
- the extent to which we will be successful in avoiding any patents granted to others.

If certain patents issued to others are upheld or if certain patent applications filed by others issue and are upheld, we may be:

- required to obtain licenses or redesign our products or processes to avoid infringement;
- prevented from practicing the subject matter claimed in those patents; or
- required to pay damages.

For example, one of our compounds not currently under development may be subject to a patent held by Warner-Lambert, if we market a product containing this compound. We have obtained a right of first refusal to negotiate a license from Warner-Lambert, but cannot assure you that this license would be available on acceptable terms. Moreover, we cannot assure you that any such license, if

required, will be available on acceptable terms, or at all, or that we would be successful in any attempt to redesign our products or processes to avoid infringement.

Litigation or administrative proceedings, including interference proceedings before the PTO, related to intellectual property rights could be brought against us or initiated by us. Any judgement adverse to us in any patent application or patent interference, litigation or other proceeding arising in connection with a patent application could materially and adversely affect our business, financial condition and results of operations. In addition, the costs of any such proceeding may be substantial whether or not we are successful.

Our success is also dependent upon the skills, knowledge and experience, none of which is patentable, of our scientific and technical personnel. To help protect our rights, we require all employees, consultants, advisors and collaborators to enter into confidentiality agreements which prohibit the disclosure of confidential information to anyone outside of our company and require disclosure and assignment to us of their ideas, developments, discoveries and inventions. We cannot assure you, however, that these agreements will provide adequate protection for our trade secrets, know-how or other proprietary information in the event of any unauthorized use or disclosure or the lawful development by others of such information.

WE ARE DEPENDENT ON OUR KEY PERSONNEL AND WILL NEED TO ATTRACT AND RETAIN ADDITIONAL KEY PERSONNEL IN THE FUTURE

We are highly dependent upon our senior management and scientific team, the loss of whose services might impede the achievement of our development and commercial objectives. Although we maintain, and are the beneficiary of, a \$2.0 million key-man insurance policy on the life of Charles E. Bugg, Ph.D., Chairman of the Board of Directors and Chief Executive Officer, we do not believe the proceeds would be adequate to compensate for his loss. We are actively seeking additional members for our senior management team. Competition for key personnel with the experience that we require is intense and is expected to continue to increase. If we are unable to attract and retain the required number of skilled and experienced management, operational and scientific personnel, our business will be harmed.

In addition, we rely on members of our scientific advisory board and consultants to assist us in formulating our research and development strategy. All of the members of the scientific advisory board and all of our consultants are otherwise employed and each such member or consultant may have commitments to other entities that may limit their availability to us.

THE UNAVAILABILITY OF THIRD-PARTY REIMBURSEMENT MAY LIMIT THE USE OF OUR PRODUCT CANDIDATES, WHICH WOULD CAUSE OUR REVENUES TO DECLINE

If third-party reimbursement is unavailable for the use of our product candidates by hospitals, clinics, patients and doctors, our business will be harmed. We cannot be certain that Medicare, Medicaid, health maintenance organizations and other third-party payors will authorize or otherwise budget for the reimbursement of our products. Governmental and third-party payors are increasingly challenging the prices charged for medical products and services. We cannot be certain that our product candidates will be viewed as cost-effective, that reimbursement will be available to consumers or that such reimbursement will be sufficient to allow our product candidates to be marketed on a competitive basis. To the extent that changes in reimbursement policies or health care cost containment initiatives limit or restrict reimbursement for our product candidates, our business would be materially and adversely affected.

**WE MAY FACE CLINICAL TRIAL LIABILITY CLAIMS RELATED TO THE USE OR MISUSE OF OUR COMPOUNDS IN CLINICAL TRIALS**

We face an inherent business risk of liability claims in the event that the use or misuse of our compounds results in personal injury or death. We have not experienced any clinical trial liability claims to date, but we cannot be certain that we will not in the future or that after commercial introduction of our products we will not experience losses due to product liability claims. We currently maintain clinical trial liability insurance coverage in the amount of \$1.0 million per occurrence and in the aggregate, with an additional \$5.0 million potentially available under our umbrella policy. We cannot assure you that the insurance policy will be sufficient to cover claims that may be made against us. Clinical trial liability insurance is expensive, difficult to obtain and may not be available in the future on acceptable terms, if at all. Any claims against us, regardless of their merit, could materially and adversely affect our financial condition.

**WE USE HAZARDOUS MATERIALS IN OUR BUSINESS AND ARE SUBJECT TO ENVIRONMENTAL CONTROLS AND REGULATIONS**

Our research and development involves the controlled use of hazardous materials, chemicals and various radioactive compounds. We are subject to federal, state and local laws and regulations governing the use, storage, handling and disposal of such materials and certain waste products. Accidental contamination or injury from these materials could occur. In the event of such an accident, we could be held liable for any damages that result and any such liability could exceed our resources. We could be required to incur substantial costs to comply with environmental laws and regulations, and if that were to happen our business and results of operations could be materially and adversely affected.

**BECAUSE STOCK OWNERSHIP IS CONCENTRATED, YOU AND OTHER INVESTORS WILL HAVE MINIMAL INFLUENCE ON STOCKHOLDER DECISIONS**

Prior to this offering, our directors, executive officers and certain principal stockholders and their affiliates, including Johnson & Johnson Development Corporation, own approximately 40.5% of our outstanding common stock. As a result, these holders, if acting together, are able to significantly influence matters requiring stockholder approval, including the election of directors. Such concentration of ownership may have the effect of delaying, deferring or preventing a change in our control.

**WE DEPEND SIGNIFICANTLY ON OUR COMPUTER AND COMMUNICATIONS SYSTEMS**

Our drug development activities depend on the security, integrity and performance of the computer and communications systems supporting them. We currently store all of our preclinical and clinical data at our facilities, do not store duplicate copies of all data off-site and cannot assure you that we would not lose important data if our systems were impaired. Extraordinary volume or other events could cause our computer systems to operate at an unacceptably low speed or even fail. Any significant degradation or failure of our computer systems could cause our data to be inaccurately calculated or lost. Loss of data could result in delays in our drug development process. We cannot assure you that our network protections will work.

Our systems may also fail as a result of:

- a tornado, fire or any other natural disaster;
- power or telecommunications failure;
- act of God; or
- war.

Any computer or communications system failure or decrease in the performance of our computer systems that causes an interruption in our business or causes us to lose data could have a material and adverse effect on our business.

WE HAVE ANTI-TAKEOVER PROVISIONS IN OUR CORPORATE CHARTER DOCUMENTS THAT MAY RESULT IN OUTCOMES WITH WHICH YOU DO NOT AGREE

Our board of directors has the authority to issue up to 5,000,000 shares of undesignated preferred stock and to determine the rights, preferences, privileges and restrictions of such shares without further vote or action by our stockholders. 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 preferred stock that may be issued in the future. The issuance of preferred stock could have the effect of making it more difficult for third parties to acquire a majority of our outstanding voting stock.

In addition, our certificate of incorporation provides for staggered terms for the members of the board of directors and super majority approval of the removal of any member of the board of directors and prevents our stockholders from acting by written consent. Our certificate also requires supermajority approval of any amendment of these provisions. These provisions and certain provisions of our by-laws and of Delaware law applicable to us could delay or make more difficult a merger, tender offer or proxy contest involving us.

INVESTORS IN THIS OFFERING WILL SUFFER IMMEDIATE AND SUBSTANTIAL DILUTION

You will incur immediate and substantial dilution in the net tangible book value per share of the shares you purchase in this offering. To the extent outstanding options to purchase common stock are exercised, there will be further dilution.

OUR MANAGEMENT HAS BROAD DISCRETION OVER USE OF PROCEEDS AND MAY FAIL TO USE THEM EFFECTIVELY TO GROW OUR BUSINESS

As of the date of this prospectus, we cannot specify the particular uses for the net proceeds we will receive from this offering. If our management does not apply these funds effectively, our revenue could decrease and our stock price could decline.

OUR STOCK PRICE IS LIKELY TO BE HIGHLY VOLATILE

The market prices for securities of biotechnology companies in general have been highly volatile and may continue to be highly volatile in the future. The following factors, in addition to other risk factors described in this section, may have a significant impact on the market price of our common stock:

- announcements of technological innovations or new products by us or our competitors;
- developments or disputes concerning patents or proprietary rights;
- our collaborative partners achieving or failing to achieve development milestones;
- publicity regarding actual or potential medical results relating to products under development by us or our competitors;
- regulatory developments in both the United States and foreign countries;
- public concern as to the safety of pharmaceutical products;
- actual or anticipated fluctuations in our operating results;

- changes in financial estimates or recommendations by securities analysts;
- economic and other external factors or other disasters or crisis; and
- period-to-period fluctuations in our financial results.

WE MAY INCUR SIGNIFICANT COSTS IF YEAR 2000 COMPLIANCE ISSUES ARE NOT PROPERLY ADDRESSED

Some of our older computer software programs and equipment are unable to distinguish between the year 1900 and the year 2000. As a result, time-sensitive functions of those software programs and equipment may misinterpret dates after December 31, 1999 to refer to the 1900s rather than the 2000s. This could cause system equipment shutdowns, failures or miscalculations resulting in inaccuracies in computer output or disruptions of operations, including, among other things, inaccurate processing of financial information and/or temporary inability to process transactions or engage in normal business activities. In addition to risks associated with our own computer systems and equipment, we have relationships with third parties that provide information, goods and services to us. These include financial institutions, suppliers, vendors, utilities, research partners, governmental entities and customers. If significant numbers of these third parties experience failure in their computer systems or equipment due to year 2000 non-compliance, it could affect our ability to process transactions or engage in similar normal business activities.

## INFORMATION REGARDING FORWARD-LOOKING STATEMENTS

This prospectus contains forward-looking statements. The forward-looking statements are principally contained in the sections on "Prospectus Summary," "Business" and "Management's Discussion and Analysis of Financial Condition and Results of Operations." These statements involve known and unknown risks, uncertainties and other factors which may cause our actual results, performance or achievements to be materially different from any future results, performances or achievements expressed or implied by the forward-looking statements. Forward-looking statements include, but are not limited to:

- the progress of our product development programs, including PRI's and Ortho-McNeil's progress with respect to our influenza neuraminidase inhibitors;
- developments with respect to clinical development of drug candidates, clinical trials and the regulatory approval process;
- our estimates regarding our capital requirements and our needs for additional financing;
- developments relating to our selection and in-licensing of targets; and
- our ability to attract development partners with acceptable development, regulatory and commercialization expertise.

In some cases, you can identify forward-looking statements by terms such as "may," "will," "should," "could," "would," "expects," "plans," "anticipates," "believes," "estimates," "projects," "predicts," "potential" and similar expressions intended to identify forward-looking statements. These statements reflect our current views with respect to future events and are based on assumptions and subject to risks and uncertainties. Given these uncertainties, you should not place undue reliance on these forward-looking statements. We discuss many of these risks in greater detail under the heading "Risk Factors." Also, these forward-looking statements represent our estimates and assumptions only as of the date of this prospectus.

You should read this prospectus and the documents that we incorporate by reference in this prospectus completely and with the understanding that our actual future results may be materially different from what we expect. We may not update these forward-looking statements, even though our situation may change in the future. We qualify all of our forward-looking statements by these cautionary statements.

## USE OF PROCEEDS

We estimate that the net proceeds we will receive from the sale of 2,000,000 shares of common stock will be approximately \$45.8 million, or approximately \$52.8 million if the underwriters fully exercise their over-allotment option, after deducting the estimated underwriting discounts and offering expenses and assuming an offering price of \$24.75 per share. We expect to use the net proceeds of this offering as follows:

- to in-license drug development candidates from academic institutions or from biotechnology companies;
- to fund drug discovery and other research programs;
- to fund preclinical studies and clinical trials of our product candidates;
- to expand our facilities, as needed, and hire additional personnel;
- to provide working capital; and
- for general corporate purposes.

We have not determined the amount of net proceeds to be used for each of the specific purposes listed. Accordingly, we will have broad discretion to use the proceeds as we see fit.

Based upon the current status of our product development programs, we believe that the net proceeds from this offering, together with interest thereon, and our existing capital resources will satisfy our capital requirements through 2001.

Pending such uses, we intend to invest the net proceeds in interest-bearing, investment-grade instruments, certificates of deposit or direct or guaranteed obligations of the United States or its agencies.

## MARKET PRICE OF COMMON STOCK

Our common stock began trading publicly on the Nasdaq National Market under the symbol "BCRX." We completed the initial public offering of our common stock on March 4, 1994. The following table sets forth the range of high and low sale prices per share of our common stock as reported by the Nasdaq National Market for the periods indicated.

|   | COMMON STOCK PRICE |          |
|---|--------------------|----------|
|   | HIGH               | LOW      |
| Year ended December 31, 1997                    |                    |          |
| First Quarter.....                              | \$ 17.00           | \$ 11.50 |
| Second Quarter.....                             | 14.75              | 10.06    |
| Third Quarter.....                              | 13.75              | 4.25     |
| Fourth Quarter.....                             | 8.38               | 6.25     |
| Year ended December 31, 1998                    |                    |          |
| First Quarter.....                              | 9.50               | 6.88     |
| Second Quarter.....                             | 9.13               | 6.00     |
| Third Quarter.....                              | 8.00               | 6.00     |
| Fourth Quarter.....                             | 8.44               | 4.38     |
| Year ended December 31, 1999                    |                    |          |
| First Quarter.....                              | 11.00              | 6.38     |
| Second Quarter.....                             | 9.50               | 6.38     |
| Third Quarter (through September 20, 1999)..... | 35.31              | 8.38     |

On September 20, 1999, the last sale price of our common stock reported by the Nasdaq National Market was \$24.75 per share. As of August 1, 1999, there were 483 holders of record of our common stock.

## DIVIDEND POLICY

We have not declared or paid cash dividends on our common stock in the past and do not intend to pay dividends on our common stock in the foreseeable future.

CAPITALIZATION

The following table sets forth our capitalization as of June 30, 1999 on an actual basis and as adjusted to reflect the sale of 2,000,000 shares of common stock pursuant to this offering, assuming an offering price of \$24.75 per share and after deducting the estimated underwriting discounts and offering expenses. This table should be read in conjunction with the financial statements and related notes incorporated herein by reference and "Management's Discussion and Analysis of Financial Condition and Results of Operations" appearing elsewhere in this prospectus.

|  | JUNE 30, 1999                     |             |
|--|-----------------------------------|-------------|
|  | ACTUAL                            | AS ADJUSTED |
|  | (IN THOUSANDS, EXCEPT SHARE DATA) |             |
| Capital lease obligations, less current portion.....   | \$ 15                             | \$ 15       |
| Stockholders' equity:  |                                   |             |
| Preferred stock, \$0.01 par value; 5,000,000 shares authorized; none issued and outstanding.....   | --                                | --          |
| Common stock, \$0.01 par value; 45,000,000 shares authorized; 14,987,634 issued and outstanding, and 16,987,634 shares issued and outstanding as adjusted for this offering..... | 150                               | 170         |
| Additional paid-in capital.....  | 80,870                            | 126,630     |
| Accumulated deficit.....   | (55,821)                          | (55,821)    |
| Total stockholders' equity.....  | 25,199                            | 70,979      |
| Total capitalization.....  | \$ 25,214                         | \$ 70,994   |

The above data excludes 2,507,501 shares of common stock issuable upon exercise of options outstanding as of June 30, 1999 at a weighted average exercise price of \$7.37 per share.

DILUTION

Our net tangible book value as of June 30, 1999 was approximately \$25.0 million, or \$1.67 per share. Net tangible book value per share represents the amount of our total tangible assets less total liabilities, divided by the total number of shares of common stock outstanding. After giving effect to the sale by us of 2,000,000 shares of common stock offered by this prospectus at an assumed offering price of \$24.75 per share and after deducting estimated underwriting discounts and offering expenses, our net tangible book value at June 30, 1999 would have been approximately \$70.8 million, or \$4.17 per share. This represents an immediate increase in net tangible book value of \$2.50 per share to existing stockholders and an immediate dilution of \$20.58 per share to new investors in this offering, as illustrated by the following table:

|  |         |          |
|--|---------|----------|
| Assumed public offering price per share.....                     |         | \$ 24.75 |
| Net tangible book value per share before the offering.....       | \$ 1.67 |          |
| Increase per share attributable to new investors.....            | 2.50    |          |
|  | -----   |          |
| Net tangible book value per share after the offering.....        |         | 4.17     |
|  |         | -----    |
| Net tangible book value dilution per share to new investors..... |         | \$ 20.58 |
|  |         | -----    |
|  |         | -----    |

SELECTED FINANCIAL DATA

The following selected financial data should be read in conjunction with the financial statements and related notes, incorporated by reference in this prospectus, and "Management's Discussion and Analysis of Financial Condition and Results of Operations" appearing elsewhere in this prospectus. The selected historical financial data below as of and for each of the five years ended December 31, 1998 have been derived from our audited financial statements. Our selected historical financial data as of and for each of the six months ended June 30, 1998 and 1999 were derived from our unaudited condensed financial statements. We believe that the unaudited financial data fairly reflects our results of operations and financial condition for the respective periods.

|   | YEARS ENDED DECEMBER 31, |            |            |             |            | SIX MONTHS ENDED<br>JUNE 30, |            |
|---|--------------------------|------------|------------|-------------|------------|------------------------------|------------|
|   | 1994                     | 1995       | 1996       | 1997        | 1998       | 1998                         | 1999       |
| (IN THOUSANDS, EXCEPT PER SHARE DATA)                 |                          |            |            |             |            |                              |            |
| STATEMENT OF OPERATIONS DATA:                         |                          |            |            |             |            |                              |            |
| Revenues:   |                          |            |            |             |            |                              |            |
| Collaborative and other research and development..... | \$ 269                   | \$ 223     | \$ 1,558   | \$ 1,000    | \$ 6,371   | \$ --                        | \$ 2,408   |
| Interest and other.....                               | 465                      | 662        | 1,094      | 1,692       | 1,255      | 671                          | 633        |
| Total revenues.....                                   | 734                      | 885        | 2,652      | 2,692       | 7,626      | 671                          | 3,041      |
| Expenses:   |                          |            |            |             |            |                              |            |
| Research and development.....                         | 5,552                    | 7,107      | 7,586      | 10,577      | 9,291      | 5,353                        | 4,006      |
| General and administrative.....                       | 1,904                    | 2,210      | 2,664      | 2,682       | 3,105      | 1,295                        | 1,683      |
| Interest.....   | 216                      | 144        | 100        | 52          | 15         | 10                           | 3          |
| Total expenses.....                                   | 7,672                    | 9,461      | 10,350     | 13,311      | 12,411     | 6,658                        | 5,692      |
| Net loss.....   | \$ (6,938)               | \$ (8,576) | \$ (7,698) | \$ (10,619) | \$ (4,785) | \$ (5,987)                   | \$ (2,651) |
| Net loss per share.....                               | \$ (1.02)                | \$ (0.96)  | \$ (0.69)  | \$ (0.77)   | \$ (0.34)  | \$ (0.43)                    | \$ (0.18)  |
| Weighted average shares outstanding....               | 6,787                    | 8,905      | 11,171     | 13,780      | 14,120     | 13,926                       | 14,981     |

|   | DECEMBER 31, |           |           |           |           | JUNE 30,  |  |
|---|--------------|-----------|-----------|-----------|-----------|-----------|--|
|   | 1994         | 1995      | 1996      | 1997      | 1998      | 1999      |  |
| (IN THOUSANDS)  |              |           |           |           |           |           |  |
| BALANCE SHEET DATA:   |              |           |           |           |           |           |  |
| Cash, cash equivalents and securities held-to-maturity..... | \$ 10,873    | \$ 11,414 | \$ 35,785 | \$ 24,643 | \$ 27,012 | \$ 24,317 |  |
| Total assets.....   | 12,803       | 13,056    | 37,149    | 26,485    | 29,100    | 26,546    |  |
| Accumulated deficit.....                                    | (21,491)     | (30,067)  | (37,766)  | (48,384)  | (53,170)  | (55,821)  |  |
| Total stockholders' equity.....                             | 11,176       | 11,326    | 35,403    | 25,285    | 27,682    | 25,199    |  |

MANAGEMENT'S DISCUSSION AND ANALYSIS OF  
FINANCIAL CONDITION AND RESULTS OF OPERATIONS

YOU SHOULD READ THE FOLLOWING DISCUSSION AND ANALYSIS IN CONJUNCTION WITH OUR FINANCIAL STATEMENTS AND RELATED NOTES INCORPORATED HEREIN BY REFERENCE.

OVERVIEW

Since our inception in 1986, we have been engaged in research and development activities and organizational efforts, including:

- identification and in-licensing of drug targets;
- drug discovery;
- structure-based design of drug candidates;
- small-scale synthesis of compounds;
- conducting preclinical studies and clinical trials;
- recruiting our scientific and management personnel;
- establishing laboratory facilities;
- engaging our scientific advisory board; and
- raising capital.

Our revenues have generally been limited to license fees, milestone payments, interest income, collaboration research, development and option fees. Research and development revenue on cost-reimbursing agreements is recognized as expenses are incurred up to contractual limits. Research and development revenues, license fees, milestone payments and option fees are recognized as revenue when irrevocably due. Payments received, which are related to future performance, are deferred and taken into income as earned over a specified future performance period. We have not received any revenue from the sale of pharmaceutical products. It will be several years, if ever, before we will recognize significant revenues from royalties received pursuant to our license agreements, and we do not expect to ever generate revenues directly from product sales. Future revenues, if any, are likely to fluctuate substantially from quarter to quarter.

We have incurred operating losses since our inception. Our accumulated deficit at June 30, 1999 was \$55.8 million. We will require substantial expenditures relating to the development of our current and future drug candidates. During the three years ended December 31, 1998, we spent 44.7% of our research and development expenses on contract research and development, including:

- payments to consultants;
- analytical tests that we are unable to perform;
- funding of research at academic institutions;
- large scale synthesis of compounds;
- preclinical studies;
- engaging investigators to conduct clinical trials;
- hiring CROs to monitor and gather data on clinical trials; and
- using statisticians to evaluate the results of clinical trials.

The above expenditures for contract research and development for our current and future drug candidates will vary from quarter to quarter depending on the status of our research and development projects. Changes in our existing and future research and development and collaborative relationships will also impact the status of our research and development projects. While we may, in some cases, be able to control the timing of development expenses, in part by accelerating or decelerating certain of

these costs, many of these costs will be incurred irrespective of whether or not we are able to discover drug candidates or obtain collaborative partners for commercialization. As a result, we believe that quarter-to-quarter comparisons of our financial results are not necessarily meaningful and should not be relied upon as an indication of future performance. If we fail to meet the clinical and financial expectations of securities analysts and investors, it could have a material adverse effect on the price of our common stock.

## RESULTS OF OPERATIONS

### SIX MONTHS ENDED JUNE 30, 1999 AND 1998

Collaborative and other research and development revenue increased to \$2.4 million in the first six months of 1999. This increase is attributable to the \$2.0 million milestone payment received from Ortho-McNeil in June 1999 and approximately \$0.4 million of research and development work performed for PRI. There was no such revenue in the first six months of 1998. Interest and other income declined 5.7% to \$633,000 in the first six months of 1999 from \$671,000 in the first six months of 1998. The decline in interest and other income is primarily due to a decline in interest rates.

Research and development expenses decreased 25.2% to \$4.0 million in the first six months of 1999 from \$5.4 million in the first six months of 1998. The decrease is primarily attributable to a decrease in costs associated with conducting clinical trials and a reduction in contracted research costs at UAB. These costs tend to fluctuate from period to period depending upon the status of our research projects and collaborative efforts.

General and administrative expenses increased 30.0% to \$1.7 million in the first six months of 1999 from \$1.3 million in the first six months of 1998. The increase is primarily the result of a royalty payment to UAB in connection with the milestone payment received from Ortho-McNeil and increased legal expenses.

Interest expense decreased to \$2,776 in the first six months of 1999 from \$9,914 in the first six months of 1998. The decrease was primarily due to a decline in capitalized lease obligations resulting in lesser interest expense. We obtained most of our leases in connection with the move to our facilities in April 1992.

### YEARS ENDED DECEMBER 31, 1998 AND 1997

Collaborative and other research and development revenue increased to \$6.4 million in 1998 from \$1.0 million in 1997, primarily due to the \$6.0 million in up-front fees received from Ortho-McNeil in 1998 for a license agreement for our influenza neuraminidase inhibitors compared to the \$1.0 million milestone payment received from Torii in 1997. Interest and other income decreased 25.9% to \$1.3 million in 1998 from \$1.7 million in 1997, primarily due to a decline in the weighted average investment for 1998.

Research and development expenses decreased 12.2% to \$9.3 million in 1998 from \$10.6 million in 1997. Such expenses vary from period to period based on the status of our projects. We completed two Phase III clinical trials in 1997. In 1998, we commenced two Phase I clinical trials for our serine protease inhibitor, continued our two Phase I/II clinical trials for an oral formulation of our PNP inhibitor and initiated preclinical studies for our influenza neuraminidase and complement inhibitors. Overall, the decline in costs associated with our PNP inhibitor project were partially offset by the increases in our serine protease and influenza neuraminidase projects. As a result, there was a slight decrease in 1998 in the outside research and development efforts associated with our three primary research and development projects. We reduced some of our other discretionary costs, which were offset by one-time costs associated with signing an exclusive worldwide license agreement for our proprietary influenza neuraminidase inhibitors and certain related agreements in September 1998.

General and administrative expenses increased 15.8% to \$3.1 million in 1998 from \$2.7 million in 1997. The increase was primarily due to the fees and expenses incurred in connection with the license

agreement and related agreements for our influenza neuraminidase inhibitors signed in September 1998.

Interest expense decreased 71.1% to \$14,986 in 1998 from \$51,880 in 1997. The decrease was primarily due to a decline in capitalized lease obligations resulting in lesser interest expense. We obtained most of our leases in connection with the move to our facilities in April 1992.

#### YEARS ENDED DECEMBER 31, 1997 AND 1996

Collaborative and other research and development revenue decreased 35.8% to \$1.0 million in 1997 from \$1.6 million in 1996, primarily due to a \$1.0 million milestone payment received from Torii in 1997 compared to the \$1.5 million license fee received from Torii and a Factor D grant in 1996. Interest and other income increased 54.8% to \$1.7 million in 1997 from \$1.1 million in 1996, primarily due to interest earned on funds invested from our public offering in September 1996.

Research and development expenses increased 39.4% to \$10.6 million in 1997 from \$7.6 million in 1996. The increase was primarily attributable to costs associated with manufacturing compounds, clinical trials and preclinical studies and expenses associated with increased personnel. These costs tend to fluctuate from period to period depending upon the stage of development and the conduct of clinical trials.

General and administrative expenses increased 0.7% to \$2.7 million in 1997 from \$2.7 million in 1996. The increase was primarily attributable to increased personnel costs and the fact that 1996 expenses were reduced by the reversal of a liability recorded in 1995 for use taxes assessed that we successfully contested in 1996, and was partially offset by decreased fees and taxes on the Torii milestone in 1997 as compared to the fees and taxes on the Torii license in 1996 and decreased legal expenses in 1997.

Interest expense decreased 48.1% to \$51,880 in 1997 from \$100,031 in 1996. The decrease was primarily due to a decline in capitalized lease obligations and the current portion of long-term debt, resulting in lesser interest expense. We obtained most of our leases in connection with the move to our facilities in April 1992.

#### LIQUIDITY AND CAPITAL RESOURCES

Cash expenditures have exceeded revenues since our inception. Our operations have principally been funded through public offerings and private placements of equity and debt securities, equipment lease financing, facility leases, collaborative and other research and development agreements, licenses and options for licenses, research grants and interest income. In addition, we have attempted to contain costs and reduce cash flow requirements by renting scientific equipment and facilities, contracting with third parties to conduct certain research and development and using consultants. We expect to incur additional expenses, resulting in significant losses, as we continue and expand our research and development activities and undertake additional preclinical studies and clinical trials of compounds which have been or may be discovered. We also expect to incur substantial expenses related to the filing, prosecution, maintenance, defense and enforcement of patent and other intellectual property claims.

At December 31, 1998, our cash, cash equivalents and securities held-to-maturity were \$27.0 million, an increase of \$2.4 million from December 31, 1997, principally due to the \$6.0 million equity investment in us in connection with the influenza neuraminidase license which offset the cash used in operations. At June 30, 1999, our cash, cash equivalents and securities held-to-maturity were \$24.3 million, a decrease of approximately \$2.7 million from December 31, 1998, principally due to the cash used by operations for the six months ended June 30, 1999.

We have financed some of our equipment purchases with lease lines of credit. We currently have a \$500,000 line of credit with our bank to finance capital equipment. In January 1992, we entered into an operating lease for our current facilities which expires on June 30, 2003. We have an option to renew the lease for an additional three years at current market rates. The operating lease requires us to pay

monthly rent ranging from \$21,405 and escalating annually to a minimum of \$24,814 per month in the final year, and a pro rata share of operating expenses and real estate taxes in excess of base year amounts.

At December 31, 1998, we had long-term capital lease and operating lease obligations which provide for aggregate minimum payments of \$280,254 in 1999, \$288,128 in 2000 and \$285,816 in 2001. In 1999, we increased the amount of office space we lease by approximately 1,700 square feet. This additional space should increase our annual lease obligations by less than \$15,000 annually.

Pursuant to our license agreement with PRI and Ortho-McNeil for the development and commercialization of our influenza neuraminidase inhibitors, we received an initial \$6.0 million payment from Ortho-McNeil and an additional \$6.0 million common stock equity investment from Johnson & Johnson Development Corporation. In June 1999, we received a \$2.0 million milestone payment from Ortho-McNeil in connection with the initiation of Phase II clinical testing in the United States. In addition, we may receive cash payments upon achievement of specified developmental and regulatory milestones and royalties on product sales, if any. We cannot assure you that PRI or Ortho-McNeil will continue to develop the product or, if they do so, that such development will result in receiving milestone payments, obtaining regulatory approval or achieving future sales of licensed products.

We previously entered into an exclusive license agreement with Torii under which Torii paid us \$1.5 million in initial license fees and made a \$1.5 million equity investment in us in 1996. The first milestone payment of \$1.0 million was received in 1997. This exclusive license agreement was terminated by Torii in July 1999.

We plan to finance our needs principally from the following:

- our existing capital resources and interest thereon;
- payments under collaborative and licensing agreements with corporate partners; and
- to the extent available, through lease or loan financing and future public or private financings.

We believe that our available funds, including the net proceeds from this offering, will be sufficient to fund our operations at least through 2001. However, this is a forward-looking statement, and no assurance can be given that there will be no change that would consume available resources significantly before such time. Our long-term capital requirements and the adequacy of our available funds will depend upon many factors, including, but not limited to:

- the progress of our research, drug discovery and development programs;
- changes in existing collaborative relationships;
- our ability to establish additional collaborative relationships;
- the magnitude of our research and development programs;
- the scope and results of preclinical studies and clinical trials to identify drug candidates;
- competitive and technological advances;
- the time and costs involved in obtaining regulatory approvals;
- the costs involved in preparing, filing, prosecuting, maintaining and enforcing patent claims;
- our dependence on others, including PRI and Ortho-McNeil, for development and commercialization of our product candidates, in particular, our neuraminidase inhibitors; and
- successful commercialization of our products consistent with our out-licensing strategy.

Additional funding, whether through additional sales of securities or collaborative or other arrangements with corporate partners or from other sources, may not be available when needed or on terms acceptable to us. The issuance of preferred or common stock or convertible securities, on terms and prices significantly more favorable than those of the currently outstanding common stock, could

have the effect of diluting or adversely affecting the holdings or rights of our existing stockholders. In addition, collaborative arrangements may require us to transfer certain material rights to such corporate partners. Insufficient funds may require us to delay, scale-back or eliminate certain of our research and development programs.

#### RISKS ASSOCIATED WITH THE YEAR 2000

The year 2000 issue is the result of computer programs being written using two digits rather than four digits to represent the year. Thus, computer software may recognize a date using "00" as the year 1900 rather than the year 2000. This could result in system failures or miscalculations causing disruptions of operations, including among others, a temporary inability to process certain data or engage in similar normal business activities.

PLAN AND STATUS. Our plan to resolve the year 2000 issue involves four phases: assessment, remediation, testing and implementation. We have completed our assessment of our systems. In 1997, we installed a computer network, upgraded our desktop computers and upgraded our information technology software to a common standard. As a consequence, most of our information technology systems are identified by the manufacturer as year 2000 compliant. Major vendors and suppliers have been contacted with regard to their year 2000 compliance and we will continue to monitor their compliance. Systems identified as not being year 2000 compliant will be brought into compliance by upgrading either the software or hardware. We have begun remediation and testing and expect to be fully implemented by the end of 1999.

While we have queried our significant suppliers, vendors and other outside parties and will continue to monitor their year 2000 compliance status, we have no means of ensuring that suppliers, vendors and other outside parties will be year 2000 ready. The inability of suppliers, vendors and other outside parties, including the government, to complete their year 2000 compliance process in a timely fashion could materially impact us. The effect of non-compliance by suppliers, vendors and outside parties is not determinable.

COSTS. Our costs incurred to date for year 2000 compliance have not been material and are not expected to be material when completed. We anticipate that we will be able to fund our costs from current funds available for operations. If, however, the costs are higher than anticipated, this could have a material adverse effect on our business, results of operations and financial condition.

RISKS. While we believe we have an effective program in place to resolve the year 2000 issue in a timely manner, as noted above, we have not completed all necessary phases of the year 2000 program for compliance. In the event that we, or third parties we depend upon, are not fully compliant by the year's end, we may not be able to complete the testing of our compounds and advance our projects into clinical trials as required to support the filings with the FDA which are necessary to our business. In addition, disruptions in the economy generally resulting from year 2000 issues could also materially adversely effect us. We are unable to estimate any potential liability or potential lost revenue at this time. We cannot assure you that we will not discover year 2000 compliance issues that will have a material adverse effect on our business, results of operations and financial condition.

CONTINGENCY. We have contingency plans for certain critical applications and are working on such plans for others. These contingency plans involve, among other actions, manual workarounds, increasing inventories and adjusting staffing strategies. We cannot assure you that these contingency plans will be adequate.

## OVERVIEW

BioCryst Pharmaceuticals, Inc. is a biotechnology company focused on the development of small-molecule pharmaceuticals for the treatment of infectious, T-cell mediated and cardiovascular diseases and disorders. We utilize our structure-based drug design technologies to develop potent, selective inhibitors directed at the active sites of target enzymes. Our lead product candidate, BCX-1812, is a neuraminidase inhibitor designed to treat and prevent viral influenza. In September 1998, we entered into an exclusive worldwide license agreement with The R.W. Johnson Pharmaceutical Research Institute, or PRI, and Ortho-McNeil Pharmaceutical, Inc., both Johnson & Johnson companies. Pursuant to this agreement, these Johnson & Johnson companies now have sole responsibility for the development, manufacture and commercialization of BCX-1812. We have been informed by PRI that the planning of Phase III trials for the 1999/2000 flu season is underway.

## OUR BUSINESS STRATEGY

Our business strategy is to use structure-based drug design technologies to develop innovative, small-molecule pharmaceuticals to treat a variety of diseases and disorders. Our drug development efforts are primarily focused on the development of potent, selective enzyme inhibitors for the treatment of infectious, T-cell mediated and cardiovascular diseases and disorders. The principal elements of our strategy are:

- SELECT AND IN-LICENSE ATTRACTIVE ENZYME TARGETS FOR THE DEVELOPMENT OF SMALL-MOLECULE PHARMACEUTICALS. We use our technical expertise and network of academic and industry contacts to evaluate and select promising enzyme targets to in-license for drug development. We choose enzyme targets that meet as many of the following criteria as possible:
  - mediate biochemical processes along disease pathways;
  - have well-defined active sites;
  - have relevant preclinical test models; and
  - have the potential for short duration clinical trials.

We focus on enzyme targets because they are often relatively easy to crystallize and because functional assays of potential inhibitors can be obtained relatively easily. In the case of infectious diseases, one inhibitor of an enzyme can often be effective against multiple strains of the organism. For instance, preclinical data indicates that our inhibitor of influenza neuraminidase is effective against both influenza A and B.

- FOCUS ON HIGH VALUE-ADDED, STRUCTURE-BASED DRUG DESIGN TECHNOLOGIES. We focus our drug-discovery activities and expenditures on applications of structure-based drug design technologies to design, develop and optimize drug candidates. We believe that structure-based drug design is a powerful tool for rapid and efficient development of small-molecule drug candidates that have the potential to be safe, effective and relatively inexpensive to manufacture. Our structure-based drug design technologies typically allow us to design and synthesize multiple compounds that effectively inhibit the enzyme target. We believe this strategy can lead to broad patent protection and enhance the competitive advantages of our compounds.
- DEVELOP INHIBITORS THAT ARE PROMISING CANDIDATES FOR COMMERCIALIZATION. We test our multiple compounds to identify those that are most promising for clinical development. Our selection of promising development candidates is based on product characteristics including bioavailability, formulation, IN VITRO and IN VIVO activity, toxicology and pharmacokinetics. We believe that this

focused strategy allows us to eliminate unpromising candidates from consideration sooner without incurring substantial clinical costs. In addition, drug candidates are selected on the basis of their potential for relatively efficient Phase I and Phase II clinical trials that require fewer patients to initially indicate safety and efficacy. We will consider, however, more complex candidates with longer development cycles if we believe that they offer promising commercial opportunities.

An important element of our business strategy is to control fixed costs and overhead through outsourcing and partnering. With only 56 employees, we maintain a streamlined corporate infrastructure that focuses exclusively on our core areas of expertise. By outsourcing the non-core aspects of our business, we believe that we can control costs, accelerate commercialization of our products and reduce our business risk. Key elements of our outsourcing and partnering strategy include:

- **LEVERAGE RELATIONSHIPS WITH ACADEMIC INSTITUTIONS AND BIOTECHNOLOGY COMPANIES.** Many academic institutions and biotechnology companies perform extensive research on the molecular and structural biology of potential drug development targets. By leveraging our relationships with these institutions, we believe we can significantly reduce the time, cost and risks involved in target development. Our collaborative relationships with such organizations may lead to the in-licensing of one or more drug targets. Upon in-licensing a drug target, the scientists from these institutions typically become working partners as members of our structure-based drug design teams. We believe this makes us a more attractive development partner to these scientists. In addition, we collaborate with outside experts in a number of areas, including crystallography, molecular modeling, combinatorial chemistry, biology, pharmacology, oncology, immunology and infectious diseases. These collaborations enable us to complement our internal capabilities without adding costly overhead. We believe this strategy allows us to save valuable time and expense, complement our technology platform, and further diversify and strengthen our discovery portfolio. An example of such a collaborative relationship is the arrangement that we have with The University of Alabama at Birmingham, or UAB. Our strong relationship with UAB has resulted in the initiation of most of our early programs, including influenza neuraminidase, PNP and Factor D research.
- **PARTNER DEVELOPMENT CANDIDATES.** We plan to advance drug candidates through preclinical development and early-stage clinical trials, then license to pharmaceutical or biotechnology partners for final development and global marketing. This strategy allows us to remain focused internally on our core competencies, leverage the expertise of others and minimize development risks. Partnerships may be a good source of development payments, license fees, milestone payments and royalties. They also reduce the costs and risks of late-stage product development, regulatory approval, manufacturing and marketing. We believe that focusing on discovery and early-stage development while leveraging pharmaceutical partners' proven development and commercialization expertise will reduce our internal expenses and allow us to have a larger number of attractive drug candidates progress to advanced stage clinical trials. For example, following our preclinical development of our influenza neuraminidase inhibitors, we entered into an exclusive worldwide license agreement with PRI and Ortho-McNeil in September 1998 to develop and market our proprietary neuraminidase inhibitors. By August 1999, PRI had successfully completed Phase I clinical trials and a Phase II clinical study, and they recently informed us that the planning of Phase III clinical trials is underway for the 1999/2000 flu season.

#### STRUCTURE-BASED DRUG DESIGN

Structure-based drug design is a drug discovery approach by which synthetic compounds are designed from detailed structural knowledge of the active sites of enzyme targets associated with particular diseases. Enzymes are proteins that act as catalysts for many vital biological reactions. Our goal generally is to design a compound that will fit in the active site of an enzyme (the active site of an

enzyme is the area into which a chemical or biological molecule fits to initiate a biochemical reaction) and thereby interfere with the progression of disease.

Our structure-based drug design involves the integrated application of traditional biology and medicinal chemistry along with an array of advanced technologies. We use X-ray crystallography, combinatorial chemistry, computer modeling of molecular structures and protein biophysical chemistry to focus on the three-dimensional molecular structure and active site characterization of the enzymes that control cellular biology. The following diagram outlines the structure-based drug design process:

[DESCRIPTION OF FLOWCHART]

[Diagram showing steps of the structure-based drug design process, from selection of the enzyme target through commercialization of the drug.]

The initial enzyme targets for structure-based drug design are selected based on their involvement in the biological pathways integral to the course of a disease. Once an enzyme target is selected, its structure is determined by X-ray crystallography, a method used in determining the precise three-dimensional molecular structures of enzymes. This structure is then used as a blueprint for the drug design of a lead compound. The compounds are modeled for their fit in the active sites of the enzyme target, considering both steric aspects (geometric shape) and functional group interactions, such as hydrogen bonding and hydrophobic interactions.

The initial design phase is followed by the synthesis of a lead compound, quantitative measurements of its ability to interact with the enzyme target and X-ray crystallographic analysis of the compound-target complex. This analysis reveals important, empirical information on how the compound actually binds to the enzyme target and the nature and extent of changes induced in the enzyme target by the binding. These data, in turn, suggest ways to refine the lead compound in order to improve its binding to the enzyme target. The refined lead compound is then synthesized and bound to the enzyme target, and further refined in an iterative process.

Once a sufficiently potent compound has been designed and optimized, its activity is evaluated in a biological system to establish the compound's ability to function in a physiological environment. If the compound fails at any stage of the biological evaluation, the design team reviews the structural model and uses crystallographic data to guide adjustments to the structural features of the compound. This process continues until a designed compound exhibits the desired properties.

The compound is then evaluated in an experimental disease model. If the compound fails, the reasons for failure (E.G., adverse metabolism, plasma binding, distribution, etc.) are determined and new modified compounds are designed to overcome the deficiencies without interfering with their ability to interact with the active site of the target enzyme. The experimental drug is then ready for conventional drug development (E.G., studies in safety assessment, formulation, clinical trials, etc.).

We believe that structure-based drug design is superior to drug screening techniques. By identifying the target enzyme in advance and by discovering the chemical and molecular structure of the enzyme, we believe it is possible to design a more optimal drug to interact with the enzyme. In addition, the structural data obtained by X-ray crystallographic analysis allows iterative analysis and compound modification at each stage of the biological evaluation. This capability renders structure-based drug design a powerful tool for rapid and efficient development of drugs that are highly specific for particular enzyme target sites.

PRODUCTS UNDER DEVELOPMENT

The following table summarizes our development projects as of September 20, 1999:

| PROGRAM AND INDICATION             | DELIVERY FORM | DEVELOPMENT STAGE     | WORLDWIDE RIGHTS        |
|------------------------------------|---------------|-----------------------|-------------------------|
| NEURAMINIDASE INHIBITOR (BCX-1812) |               |                       |                         |
| Influenza                          | Oral          | A Phase II--Completed | PRI/<br>Ortho-McNeil(1) |
| PNP INHIBITOR (BCX-34)             |               |                       |                         |
| Cutaneous T-Cell Lymphoma          | Oral          | Phase I/II--Underway  | BioCryst                |
| Other T-Cell Cancers               | Intravenous   | Phase I/II--Planned   | BioCryst                |
| Psoriasis                          | Oral          | Phase I/II--Completed | BioCryst                |
| HIV                                | Oral          | Phase I--Completed    | BioCryst                |
| COMPLEMENT INHIBITORS              |               |                       |                         |
| Cardiopulmonary Bypass Surgery     | Intravenous   | Preclinical--Ongoing  | BioCryst                |

(1) Our neuraminidase inhibitor, BCX-1812, has been licensed to PRI and Ortho-McNeil, both Johnson & Johnson companies.

NEURAMINIDASE INHIBITOR (BCX-1812)

INFLUENZA BACKGROUND

OVERVIEW. Influenza, commonly known as the flu, is perceived by many people as a transient, inconvenient viral infection that leaves its sufferers bed-ridden for a few days. In truth, however, it is a virulent, acute respiratory disease that is sometimes deadly. In North America, Western Europe and Japan, an estimated 70 million to 150 million individuals suffer from influenza annually. The flu is particularly dangerous to the elderly, young children and debilitated patients accounting for approximately 20,000 deaths in the United States each year. The flu and associated complications are the sixth leading cause of death in the United States. The annual cost to the U.S. economy associated with influenza epidemics was estimated to be in excess of \$12 billion, according to a 1994 article in THE NEW ENGLAND JOURNAL OF MEDICINE.

Flu epidemics are regional outbreaks that cause an average of 40,000 flu-related deaths. Flu pandemics, however, are much more severe. Pandemics are worldwide outbreaks of a particular strain of the virus that occur relatively infrequently but can be disastrous, with deaths ranging from 9 million to 70 million in a single such pandemic. The Spanish flu pandemic of 1918-19 killed more than 20 million people worldwide. In the United States alone, the Asian flu of 1957-58 resulted in 70,000 deaths, and the Hong Kong flu of 1968-69 caused 34,000 deaths. The worldwide deaths caused by the Asian and Hong Kong pandemics topped 1.5 million, with an estimated impact to the world economy of \$32 billion. Due to increases in the world population and international air travel, a particularly virulent mutation of the flu virus could spread rapidly, resulting in widespread morbidity and mortality. The Center for Disease Control and Prevention estimates that, in the United States alone, an influenza pandemic would cause between 88,000 and 227,000 deaths, and the economic impact would range between \$71 billion and \$166 billion.

**SYMPTOMS AND TREATMENT OF INFLUENZA.** Although influenza is considered a respiratory disease, flu sufferers usually become acutely ill with high fever, chills, headache, weakness, loss of appetite and aching joints. The flu sufferer may also have a sore throat, dry cough and burning eyes.

For most healthy children and adults, influenza is typically a moderately severe illness. However, for people with pre-existing medical conditions, influenza can be very severe and, in many cases, fatal. In these patients, bacterial infections may occur because the body's immune system is so weakened by influenza that its defenses against bacteria are low. Bacterial pneumonia is the most common complication of influenza.

The development of effective therapeutics has challenged medical researchers due to the seasonal variation in viral strains and the highly infectious nature of influenza. Patients, therefore, have limited treatment options. Amantadine and rimantadine, which are both ion channel blockers, are used for treatment of influenza A but are ineffective against influenza B, cause some adverse side effects and are subject to rapid development of viral resistance.

Vaccines are available against the disease but have limitations: people require advance vaccination; vaccines are limited by their specificity to particular strains of the virus; and also offer little protection if the antigen matching of the vaccine is inaccurate. In addition, many people decline the required injections because of fear and/or discomfort. The ability of the virus to change its antigenic structure is a serious obstacle to developing an effective vaccine against influenza. Different strains can arise when surface antigens on the virus (the portion of the virus that causes an immune reaction in humans) undergo minor genetic mutations each year as the virus replicates. Because of this mutation ability, the immunity acquired in response to infection by a particular strain does not provide adequate protection against viruses that subsequently arise. The production of a new vaccine each year is not only complex and expensive, but also an inefficient method of global disease control.

**INHIBITING INFLUENZA NEURAMINIDASE.** Research during the past two decades has seen dramatic advances in understanding the molecular structure and function of the influenza virus. There are two major surface glycoproteins, hemagglutinin (HA) and neuraminidase (NA), that are involved in the spread of influenza. Considerable attention has been focused on the enzyme neuraminidase, located on the viral surface. Neuraminidase assists in the release and spread of the flu virus by cleaving the sticky sialic acid strands that hold the new virions to the cell surface, allowing the replicated virus to spread and infect other cells. This process progresses until the host's immune response can produce enough antibodies to bring the infection under control. The following diagram illustrates this process:

[DESCRIPTION OF CELL STRUCTURE/VIRUS GRAPHICS]

[Graphic showing the process by which the influenza virus replicates in a host cell and the role of neuraminidase in the process.]

Research suggests that if the neuraminidase enzyme were inhibited, the new virions would adhere to the cell surface, thereby preventing further infection of other cells. Subsequent viral load in the bloodstream would not be enough to cause disease but would be sufficient to induce the body to mount an immune response.

Neuraminidase inhibitors present a promising alternative to patients suffering from the flu. In addition to our neuraminidase inhibitor, both Hoffmann-La Roche, in collaboration with Gilead Sciences, and Glaxo Wellcome are developing neuraminidase inhibitors. Hoffmann-La Roche has developed an orally active neuraminidase inhibitor. Hoffmann-La Roche has filed a new drug application, or NDA, with the FDA for this twice-a-day treatment. Similarly, Glaxo Wellcome's neuraminidase inhibitor, which is administered by dry powder inhaler, received FDA approval and has recently been launched in the United States and other countries.

#### OUR INFLUENZA NEURAMINIDASE INHIBITOR

**BACKGROUND.** In 1987, scientists at UAB, in collaboration with our scientists, began determining the molecular structure of influenza neuraminidase from several different strains of influenza, using X-ray crystallography. Subsequently, our scientists and UAB scientists developed numerous novel inhibitors of these enzymes using structure-based drug design. We licensed the influenza neuraminidase program from UAB in 1994 and proceeded to complete the crystallographic structural studies needed to advance the development of neuraminidase inhibitors. The structure of the active site of influenza neuraminidase is similar among different viral strains. Consequently, we believe that our neuraminidase inhibitors may be effective in the treatment and prevention of influenza, regardless of viral mutations.

Four of the patented compounds from our development efforts emerged as viable product development candidates. We called them BCX-1812, 1827, 1898 and 1923. Preclinical studies demonstrated that our drug candidates have the following benefits:

- excellent safety profile;
- broad spectrum inhibition of influenza A and B;
- good oral efficacy;
- probable once-a-day dosage indicated by a positive pharmacokinetic profile; and
- stability in liquid, making a liquid formulation possible for pediatric and elderly applications.

**CLINICAL DEVELOPMENT.** In September 1998, we entered into an exclusive worldwide license agreement with PRI and Ortho-McNeil to develop and market our proprietary influenza neuraminidase inhibitors to treat and prevent viral influenza. We received an initial \$6.0 million payment from Ortho-McNeil and an additional \$6.0 million common stock equity investment from Johnson & Johnson Development Corporation. In June 1999, we received a \$2.0 million milestone payment from Ortho-McNeil in connection with the initiation of Phase II clinical testing in the United States. In addition, we may receive cash payments upon achievement of specified developmental and regulatory milestones and royalties on product sales, if any. Since the collaboration was established, PRI selected BCX-1812 for clinical development and moved through Phase I clinical trials and a Phase II clinical study by August 1999.

We recently announced preliminary results from a Phase II placebo-controlled, randomized study conducted by PRI for the treatment of healthy volunteers infected with a strain of influenza A. The primary efficacy endpoint was the reduction in viral titers in infected subjects. PRI advised us that the data from this Phase II study indicated a statistically significant result for the primary endpoint, and evaluation of safety showed that the drug was well tolerated at all dosage levels. We have been informed by PRI that the planning of the Phase III clinical trials for the 1999/2000 influenza season is underway. We cannot assure you that the FDA will accept the Phase III clinical protocols, that PRI will

commence the Phase III clinical trials in 1999 or at all, or that the Phase III clinical trials, if initiated, will be successful.

#### PNP INHIBITOR (BCX-34)

##### T-CELL MEDIATED DISEASES

OVERVIEW. The human immune system employs specialized cells, including T-cells and B-cells, to control infection by recognizing and attacking disease-causing viruses, bacteria and parasites. T-cells are an essential part of the body's immune system that serve a dual purpose--orchestrate the body's immune response and participate in host defense response. For the most part, this system works flawlessly to protect the body. However, there are diseases in which T-cells multiply uncontrollably (T-cell proliferative diseases) or attack normal cells (autoimmune diseases). Proliferating T-cells have been implicated in cutaneous T-cell lymphoma, or CTCL, and in T-cell leukemias. Autoimmune diseases such as psoriasis, rheumatoid arthritis and Crohn's disease are also T-cell mediated. Under these circumstances, pharmacologic control of the immune system is desirable.

Purine nucleoside phosphorylase, or PNP, is an enzyme that is believed to play an important role in T-cell proliferation by facilitating synthesis of DNA. PNP is necessary to maintain normal DNA synthesis in T-cells. The link between T-cell proliferative disorders and the PNP enzyme was first discovered approximately 20 years ago when a patient, who was genetically deficient in PNP, exhibited limited T-cell activity but reasonably normal activity of other immune functions. These findings suggested that inhibition of PNP might produce selective suppression of T-cell function without significantly impairing B-cell function.

PNP INHIBITION. In the absence of PNP activity, deoxyguanosine, or dGuo, accumulates in T-cells. T-cells have an unusually high capacity to add phosphate groups to dGuo; therefore, dGuo is ultimately converted by other enzymes to form deoxyguanosine triphosphate, or dGTP. This nucleotide accumulates in T-cells because the T-cells have a limited ability to remove or metabolize it.

High concentrations of intracellular dGTP inhibit the enzyme ribonucleotide reductase, an enzyme necessary for DNA synthesis. The unique accumulation of dGTP in human T-cells prevents their proliferation. Hence, inhibiting PNP is a novel mechanism for suppressing T-cell replication without significantly affecting other cells, and we believe this may prove to have an impact on several diseases.

##### OUR PNP INHIBITOR CANDIDATE (BCX-34)

BACKGROUND. Our lead PNP inhibitor drug candidate, BCX-34, is designed to suppress T-cell replication without significantly affecting other cells. BCX-34 has been in clinical trials since 1992. Our initial approach was to develop a topical cream formulation of BCX-34, which if effective could have led to a rapid, cost-effective regulatory approval. We conducted two Phase III, double-blinded placebo controlled clinical trials in 1996 and 1997 to determine the effects of topical BCX-34 on two diseases: psoriasis and CTCL. These trials, however, did not show statistically significant results between the treated and placebo groups. Therefore, we discontinued the topical program.

CURRENT DEVELOPMENT STRATEGY. We believe that in order for BCX-34 to demonstrate sufficient activity against certain diseases, such as psoriasis, CTCL and HIV infections, we must obtain adequate blood levels of BCX-34 to elevate plasma dGuo. In the clinical trials we have completed, the dosage levels of BCX-34 were insufficient to generate adequate levels of dGuo. In several clinical trials with an oral formulation of BCX-34, however, we have established:

- safety of BCX-34 at various dose levels;
- the pharmacokinetic parameters of drug administration;
- the optimal oral dose for maximum bioavailability; and

- the correlation between BCX-34 and dGuo levels in plasma.

These studies have enabled us to design two new Phase I/II clinical trials. The first trial is for treatment of CTCL at the maximum bioabsorbable oral dose of BCX-34 for 12 weeks. We expect that this trial will allow us to determine the maximum attainable levels of plasma dGuo with the currently available oral formulation and to evaluate its long-term clinical effect. This trial is expected to be completed in early 2000. The second trial is for treatment of T-cell cancers such as T-lymphoblastic leukemias and lymphomas. This trial is designed to evaluate higher blood levels of BCX-34, which can only be obtained with intravenous therapy. Continuous intravenous infusion for 72 hours will be done at increasing dose levels to measure safety and efficacy.

These two Phase I/II clinical trials should provide us with the baseline information to begin other studies in T-cell mediated diseases. Hence, our future clinical evaluation of BCX-34 will be determined by the outcome of these two studies in T-cell malignant diseases. If we are unable to demonstrate the clinical efficacy of BCX-34 at these higher dose levels, we will likely discontinue the PNP inhibitor program.

**CUTANEOUS T-CELL LYMPHOMA.** CTCL is a severe chronic form of cancer that primarily involves the skin, but can invade other organs as well and affects an estimated 1,000 new patients annually. Several clinical trials in this disease have been completed and have served as our model for developing our current clinical development strategy.

**OTHER T-CELL CANCERS.** Assessing an intravenous formulation of BCX-34 in patients with T-cell cancers, such as T-lymphoblastic leukemias and lymphomas, is an opportunity to address a patient population that is suffering from a serious unmet medical need. Most of these patients have failed numerous standard forms of therapy and have a generally unfavorable clinical outlook. We expect to initiate a Phase I/II clinical trial, described above, using increasing intravenous doses of BCX-34. We expect this trial to be complete next year and may outline the optimal regimen for inhibition of T-cell proliferation.

**HUMAN IMMUNODEFICIENCY VIRUS.** Current evidence suggests that HIV replication in CD4 T-cells occurs only during T-cell proliferation. Because PNP inhibition can shut down T-cell activation and proliferation, it could be possible to slow HIV replication by treating patients with BCX-34. Because one of the major drawbacks in the current therapy for HIV disease is the tendency for development of drug resistance, and since the development of drug resistance is caused by rapid turnover of virus, any drug that slows down the virus proliferation should help prevent development of resistant mutants.

We have completed a Phase I feasibility study with BCX-34 in HIV patients. Future clinical development plans in this area will be made after the oral and intravenous Phase I/II trials in T-cell cancer patients are complete.

**PSORIASIS.** Psoriasis is a chronic skin disorder that affects approximately 6.4 million people in the United States. Psoriasis is an autoimmune disease in which T-cells attack the body's own tissues and most commonly appears on the scalp, knees, hands, feet and elbows. The most common forms of psoriasis are characterized by lesions, scaling and inflammation of the skin.

We have completed two Phase I/II studies using low dosages of oral BCX-34 for treatment of patients with psoriasis. Further development of BCX-34 for psoriasis will depend on the outcomes of the Phase I/II clinical trials in CTCL and other T-cell cancers.

**OTHER POTENTIAL APPLICATIONS.** Effective inhibition of PNP increases blood levels of dGuo and, therefore, we believe provides the desired biological effect on proliferation of activated T-cells. Assuming our current approach is favorable, then BCX-34 can be tested in clinical trials of T-cell mediated diseases, including rheumatoid arthritis, Crohn's disease and multiple sclerosis.

## COMPLEMENT INHIBITORS

### COMPLEMENT CASCADE

OVERVIEW. The human body is equipped with defense mechanisms that respond aggressively to infection or injury. The immune system is a complex array in which all of the components act in concert to protect us. This response is uniquely designed for each challenge whether caused by viruses, bacteria, or other foreign pathogens or materials. Once the immune system recognizes a "foreign invader," complement is activated to destroy or remove it. One part of this system, the complement cascade, is a system of functionally linked proteins that assists in the removal of bacteria or destruction of cells which the body does not recognize as its own.

Complement proteins circulate in the blood in a non-activated form. Upon activation, complement can result in adverse biological effects including tissue damage. This occurs in an unregulated way in certain medical situations such as cardiopulmonary bypass surgery, reperfusion injury following heart attacks and hemodialysis.

## OUR COMPLEMENT INHIBITOR

**BACKGROUND.** Working closely with UAB scientists, we characterized the three-dimensional structure of Factor D, a component of the complement cascade. In 1997, we made progress using X-ray crystallographic and molecular modeling techniques to design and synthesize a class of small molecule compounds that are highly potent inhibitors of both complement and certain other blood enzymes. These compounds may have therapeutic applications for several acute immunological disorders by limiting the rapid and aggressive damage caused by the complement cascade. In addition, preclinical studies to examine the safety, efficacy and bioavailability of several of these compounds are currently in progress.

Initially, BCX-1470 was selected as the lead compound in our complement program based on its ability to inhibit the enzymes Factor D, C1s, kallikrein and plasmin. This broad reactivity made BCX-1470 a candidate for intervention in acute inflammatory disorders that require control of both coagulation and complement activation.

**CLINICAL DEVELOPMENT.** Developed as an intravenous formulation, BCX-1470 was the subject of an Investigational New Drug, or IND, application approved by the FDA in February 1998 for evaluation in patients during cardiopulmonary bypass surgery. We completed two Phase I studies of the safety and pharmacokinetics of BCX-1470 in healthy volunteers. These studies showed that the effective dose for blocking complement activation was too close to toxicologic limits to be used in the operating room. Hence, other compounds in this series are now being evaluated for clinical development.

**PRECLINICAL DEVELOPMENT.** Through our partnership with 3-Dimensional Pharmaceuticals, Inc., we are also developing orally-active inhibitors of the enzyme C1s of the complement system for treatment of lupus, rheumatoid arthritis and Alzheimer's disease. The pathogenesis of each of these diseases is believed to involve the activation of C1s.

## TISSUE FACTOR/VIIA

Blood coagulation proceeds by a cascade of reactions leading to the formation of a blood clot. The cascade is initiated by the Tissue Factor/VIIa complex. Animal models show that blood clot formation can be treated by inhibiting the Tissue Factor/VIIa complex. Tissue Factor/VIIa inhibitors may potentially be useful in coronary thrombosis, disseminated intravascular coagulation, stroke and ischemia-reperfusion injury. We are at the research stage of development of intravenous and oral formulations for inhibition of Tissue Factor/VIIa. We have an agreement with Sunol Molecular Corp. to expedite the discovery of new drug candidates designed to inhibit Tissue Factor/VIIa for our cardiovascular program. Under the terms of this agreement, Sunol conducts research and supplies us with tissue factor for our drug design program.

## RESEARCH AND DEVELOPMENT

We initiated our research and development program in 1986, with drug synthesis beginning in 1987. We have assembled a scientific research staff with expertise in a broad base of advanced research technologies including protein biochemistry, X-ray crystallography, chemistry and pharmacology. Our research facilities include protein biochemistry and organic synthesis laboratories, IN VITRO and IN VIVO testing facilities, X-ray crystallography, computer and graphics equipment and formulation facilities.

During the years ended December 31, 1996, 1997 and 1998, we spent an aggregate of \$27.5 million on research and development. Approximately \$15.2 million of that amount was spent on in-house research and development, and \$12.3 million was spent on contract research and development.

## COLLABORATIVE RELATIONSHIPS

### CORPORATE ALLIANCES

#### 3-DIMENSIONAL PHARMACEUTICALS, INC.

In October 1996, we signed a research collaboration agreement with 3-Dimensional Pharmaceuticals under which we will share resources and technology to develop inhibitors of complement enzymes. The agreement combines our capabilities in structure-based drug design with the selection power of 3-Dimensional Pharmaceuticals' Directed Diversity-Registered Trademark-technology, a proprietary method of directing combinatorial chemistry and high throughput screening toward specific molecular targets. In June 1999, we updated and renewed our original agreement to concentrate on selected complement enzymes as targets for the design of inhibitors. Under the terms of the agreement, the companies are responsible for their own research costs. If a drug candidate emerges as a result of the joint research, the companies will negotiate the product development and commercialization rights and responsibilities.

#### THE R.W. JOHNSON PHARMACEUTICAL RESEARCH INSTITUTE AND ORTHO-MCNEIL PHARMACEUTICAL, INC.

We have entered into an exclusive worldwide license agreement with PRI and Ortho-McNeil to develop and market our proprietary influenza neuraminidase inhibitors to treat and prevent viral influenza. We received an initial \$6.0 million payment from Ortho-McNeil and an additional \$6.0 million common stock equity investment from Johnson & Johnson Development Corporation. In June 1999, we received a \$2.0 million milestone payment from Ortho-McNeil in connection with the initiation of Phase II clinical testing in the United States. In addition, we may receive cash payments upon achievement of specified developmental and regulatory milestones and royalties on product sales, if any.

PRI will be responsible for research and development of the compounds, including expenses. Ortho-McNeil will market products approved by the FDA for marketing in the United States. Other Johnson & Johnson companies, including Janssen-Cilag, will market products approved for marketing outside the United States.

#### NOVARTIS AG

In 1990, we entered into an exclusive worldwide license agreement with Novartis AG, formerly Ciba-Geigy, for use of certain of our PNP inhibitors, not including BCX-34. We received an initial \$500,000 payment from Novartis, up to \$300,000 of which is refundable in circumstances specified in the agreement. The agreement also provides for Novartis to pay us royalties on sales, if any, of the PNP inhibitors. We cannot assure you that we will receive any additional revenue pursuant to this license agreement or that the initial payment will not be refunded.

#### SUNOL MOLECULAR CORP.

In April 1999, we entered into an agreement with Sunol. This agreement requires Sunol to conduct research and supply us with protein targets for drug design to expedite the discovery of new drug candidates designed to inhibit Tissue Factor/VIIa for our cardiovascular program.

The initial focus of the agreement will be on identifying compounds that work to inhibit the coagulation cascade of Tissue Factor/VIIa. Tissue Factor/VIIa is a promising target for the development of anticoagulants for cardiopulmonary bypass surgery, angioplasty and other cardiovascular disorders. Sunol will produce Tissue Factor and provide us with quantities of the protein to assist in the identification of inhibitors specific to the activity of Tissue Factor/VIIa.

#### TORII PHARMACEUTICAL CO., LTD.

In 1996, we granted Torii an exclusive license, with the right to sublicense, develop, manufacture and commercialize BCX-34 and certain other PNP inhibitor compounds in Japan for the treatment of

rheumatoid arthritis, T-cell cancers and atopic dermatitis. The exclusive license agreement was terminated by Torii and the rights to develop, manufacture and commercialize BCX-34 and certain other PNP inhibitor compounds in Japan reverted to us. Torii paid us an aggregate of \$4.0 million for license fees, milestone payments and an equity investment.

#### ACADEMIC ALLIANCES

##### THE UNIVERSITY OF ALABAMA AT BIRMINGHAM

We have had a close relationship with UAB since our formation. Our Chairman and Chief Executive Officer, Dr. Bugg, was the previous Director of the UAB Center for Macromolecular Crystallography, and our President and Chief Operating Officer, Dr. Bennett, was the former President of UAB, the former Chairman of the Department of Medicine at UAB and a former Chairman of the Department of Microbiology at UAB. Several of our consultants are employed by UAB. UAB has one of the largest X-ray crystallography centers in the world with approximately 124 full-time staff members and approximately \$20.7 million in research grants and contract funding in 1998. Three of our early programs, PNP, influenza and Factor D, originated at UAB. When we were founded in 1986, we entered into an agreement with UAB which granted us exclusive rights to discoveries resulting from research relating to PNP. We also entered into an agreement with UAB that gives us the first option to obtain a non-exclusive license to patents and copyrights of UAB not developed in collaboration with us or an exclusive license, in some cases worldwide, to patents, copyrights or intellectual property arising from research of UAB collaborators or investigators under contract to us.

Subsequently, we entered into agreements with UAB for influenza neuraminidase and Factor D. Under the influenza neuraminidase and Factor D agreements, UAB performs specific research for us in return for research payments and license fees. The Factor D agreement was later expanded to include other enzyme targets of the complement system. UAB has granted us certain rights to any discoveries in these areas resulting from research developed by UAB or jointly developed with us. We have agreed to pay certain royalties on sales of any resulting product and to share in future payments received from other third-party collaborators. UAB has received and will continue to receive a portion of any license fees, milestone payments and royalties we receive from PRI and Ortho-McNeil for the influenza collaboration. We have completed the research under the UAB influenza agreement. We are continuing to fund the research program under the Factor D agreement, which entitles us to an assignment of, or a right to an exclusive license for, any inhibitors of specified complement enzymes developed by UAB scientists during the period of support or for a one-year period thereafter. These two agreements have initial 25-year terms, are automatically renewable for five-year terms throughout the life of the last patent or any extension thereof and are terminable by us upon three-month's notice and by UAB under certain circumstances.

#### PATENTS AND PROPRIETARY INFORMATION

Our success will depend in part on our ability to obtain and enforce patent protection for our products, methods, processes and other proprietary technologies, preserve our trade secrets, and operate without infringing on the proprietary rights of third parties, both in the United States and in other countries. We own or have rights to certain proprietary information, proprietary technology, issued and allowed patents and patent applications which relate to compounds we are developing. We actively seek, when appropriate, protection for our products, proprietary technology and proprietary information by means of U.S. and foreign patents, trademarks and contractual arrangements. In addition, we rely upon trade secrets and contractual arrangements to protect certain of our proprietary information, proprietary technology and products.

To date, we have been issued seven U.S. patents which expire between 2009 and 2015 and relate to our PNP inhibitor compounds. We have also been issued a U.S. patent covering a manufacturing process for our PNP inhibitors, which expires in 2015, and have filed a patent application for new

processes to prepare BCX-34 and other PNP inhibitors. The U.S. Patent and Trademark Office, or PTO, has also issued to us a U.S. patent relating to inhibitors of influenza neuraminidase, which expires in 2015. We have also sought to protect our technology through the following patent applications which are still pending: three U.S. patent applications, two of which are provisional applications and one of which is a Patent Cooperation Treaty, or PCT, application, related to the preparation of certain neuraminidase inhibitors; two provisional applications related to compounds and methods for detecting influenza virus; a PCT application related to complement inhibitors; and a provisional application relating to inhibiting T-cell proliferation. We cannot assure you, however, that any of our pending applications will result in issued patents, nor that any of our patents will provide us with sufficient protection against competitive products or otherwise be commercially available.

Our success is also dependent upon the skills, knowledge and experience of our scientific and technical personnel, none of which is patentable. To help protect our rights, we require all employees, consultants, advisors and collaborators to enter into confidentiality agreements which prohibit the disclosure of confidential information to anyone outside of our company and requires disclosure and assignment to us of their ideas, developments, discoveries and inventions. We cannot assure you, however, that these agreements will provide adequate protection for our trade secrets, know-how or other proprietary information in the event of any unauthorized use or disclosure or the lawful development by others of such information.

#### MARKETING AND SALES

We lack experience in marketing, distributing or selling pharmaceutical products. Our strategy is to rely on collaborators, licensees or arrangements with others to provide for the marketing, distribution and sales of any products we may develop. We cannot assure that we will be able to establish and maintain acceptable commercial arrangements with collaborators, licensees or others to perform such activities.

If approved, BCX-1812 will likely be the third influenza neuraminidase inhibitor to the market behind the influenza neuraminidase inhibitors currently marketed by Glaxo Wellcome and in development by Hoffmann-LaRoche, in collaboration with Gilead Sciences. We believe this may provide marketing challenges. However, we believe that there may be some advantages to not being first to market. We expect that both Glaxo Wellcome and Hoffmann-La Roche will play a major role in establishing the influenza treatment market and creating a demand for neuraminidase inhibitors on which Ortho-McNeil will be able to capitalize if our neuraminidase inhibitor is approved for marketing. Because neuraminidase inhibitors represent a new class of drugs that could impact a large number of people, a major education effort will be required to promote acceptance by both the treating physicians and the target patient population.

#### COMPETITION

The pharmaceutical and biotechnology industries are intensely competitive. Many companies, including biotechnology, chemical and pharmaceutical companies, are actively engaged in activities similar to ours, including research and development of drugs for the treatment of infectious, T-cell mediated and cardiovascular diseases and disorders. Many of these companies have substantially greater financial and other resources, larger research and development staffs, and more extensive marketing and manufacturing organizations than we do. In addition, some of them have considerable experience in preclinical testing, clinical trials and other regulatory approval procedures. There are also academic institutions, governmental agencies and other research organizations which are conducting research in areas in which we are working. They may also market commercial products, either on their own or through collaborative efforts.

We expect to encounter significant competition for any of the pharmaceutical products we plan to develop. Companies that complete clinical trials, obtain required regulatory approvals and commence

commercial sales of their products before their competitors may achieve a significant competitive advantage. In addition, certain pharmaceutical and biotechnology firms, including major pharmaceutical companies and specialized structure-based drug design companies have announced efforts in the field of structure-based drug design and in the fields of PNP and complement inhibitors. In addition, we are aware that other companies or institutions are pursuing development of new drugs and technologies directly targeted at applications for which we are developing our drug compounds. For example, Glaxo Wellcome's influenza neuraminidase inhibitor has received approval from the FDA, and they recently received approval to market their inhibitor in the United States and other countries. This product is administered in the form of a dry-powder inhaler, which could be difficult to use and may cause patient discomfort. Hoffmann-La Roche, in collaboration with Gilead Sciences, also has an influenza neuraminidase inhibitor which is under review by the FDA. If approved, our influenza neuraminidase inhibitor, BCX-1812, will likely be the third neuraminidase inhibitor to the market. We believe this may provide marketing challenges. In addition, other therapies for the treatment or prevention of flu include vaccines and the drugs amantadine and rimantadine, as well as over-the-counter products.

We expect structure-based drug design to attract significant additional competitors over time. In order to compete successfully, we must develop proprietary positions in patented drugs for therapeutic markets that have not been satisfactorily addressed by conventional research strategies and, in the process, expand our expertise in structure-based drug design. We cannot assure you that our products, even if successfully tested and developed, will be adopted by physicians over such other products, or that our products will offer economically feasible alternatives to other therapies.

#### GOVERNMENT REGULATION

The FDA regulates the pharmaceutical and biotechnology industries in the United States, and our drug candidates are subject to extensive and rigorous domestic government regulations prior to commercialization. The FDA regulates, among other things, the development, testing, manufacture, safety, efficacy, record-keeping, labeling, storage, approval, advertising, promotion, sale and distribution of pharmaceutical products. In foreign countries, our products are also subject to extensive regulation by foreign governments. These government regulations will be a significant factor in the production and marketing of any pharmaceutical products that we develop. Failure to comply with applicable FDA and other regulatory requirements at any stage during the regulatory process may subject us to sanctions, including:

- delays;
- warning letters;
- fines;
- product recalls or seizures;
- injunctions;
- penalties;
- refusal of the FDA to review pending market approval applications or supplements to approval applications;
- total or partial suspension of production;
- civil penalties;
- withdrawals of previously approved marketing applications; and
- criminal prosecutions.

The regulatory review and approval process is lengthy, expensive and uncertain. Before obtaining regulatory approvals for the commercial sale of any products, our product candidates must be demonstrated to be safe and effective for use in humans. The approval process takes many years, substantial expenses may be incurred and significant time may be devoted to clinical development.

Before testing potential candidates in humans, laboratory and animal studies are carried out to determine safety and biological activity. After completing preclinical trials, an IND, including a proposal to begin clinical trials, must be filed with the FDA. We have filed eight IND's to date and plan to file additional IND's, or rely on certain collaborative partners to file IND's, in the future. Thirty days after filing an IND, a Phase I human clinical trial can start unless the FDA places a hold on the study.

Phase I trials to determine safety are conducted in a small group of patients or healthy volunteers. Tolerances and the metabolic and pharmacologic actions of our drug candidates at different doses are also assessed. After completion of the initial trial, a Phase II trial is conducted to assess safety and efficacy and establish the optimal dose in patients. If Phase II is successful, a Phase III trial is conducted to verify the results in a larger patient population. A Phase III trial is required for FDA approval to market a drug. A Phase III trial may require hundreds or even thousands of patients and is the most expensive to conduct. The goal in Phase III is to collect enough safety and efficacy data to obtain FDA approval for treatment of a particular disease.

Initiation and completion of the clinical trial phases is dependent on several factors including things that are beyond our control. For example, the clinical trials are dependent on patient enrollment, but the rate at which patients enroll in the study depends on:

- size of the patient population we intend to treat;
- the availability and proximity of patients to clinical sites where the trial is underway;
- the willingness and formal consent of patients to participate in our clinical trials; and
- the patient meeting the eligibility criteria.

Delays in planned patient enrollment may result in increased expense.

After completion of the clinical trials of a product, a new drug application, or NDA, is submitted to the FDA for marketing approval before commercialization of the product. We cannot assure you that any approval will be granted on a timely basis, if at all. The FDA, as a result of the Food and Drug Administration Modernization Act of 1997, has six months to review and act upon license applications for priority therapeutics that are for a life-threatening or unmet medical need. Standard reviews can take between one and two years, and can even take longer if significant questions arise during the review process. Any required approvals, once obtained, may be withdrawn.

In addition to clinical development regulations, we and our contract manufacturers and collaborators also are required to comply with the applicable FDA current good manufacturing practice regulations. Good manufacturing practice regulations include requirements relating to quality control and quality assurance as well as the corresponding maintenance of records and documentation. Manufacturing facilities are subject to inspection by the FDA. Such facilities must be approved before we can use them in commercial manufacturing of our potential products. We or our contract manufacturers may not be able to comply with the applicable good manufacturing practice requirements and other FDA regulatory requirements. If we or our contract manufacturers fail to comply, our business, financial condition and results of operations will be materially adversely affected.

In June 1995, we notified the FDA that we submitted incorrect efficacy data for our Phase II dose-ranging studies of topical BCX-34 for CTCL and psoriasis. The FDA inspected us in November 1995 and issued us a List of Inspectional Observations, Form FDA 483, that cited our failure to follow good clinical practices. The FDA also inspected us in June 1996, the focus was on the two 1995 Phase II dose-ranging studies of topical BCX-34 for the treatment of CTCL and psoriasis. As a result

of the investigation, the FDA issued us a Form FDA 483, which cited our failure to follow good clinical practices. As a consequence, our ongoing and future clinical studies may receive increased scrutiny, which may delay the regulatory review process.

Also in June 1996, the FDA investigated one of the clinical trial sites that participated in our 1995 Phase II dose-ranging studies of topical BCX-34 for the treatment of CTCL and psoriasis. As a result, the FDA issued a Form FDA 483 to the principal investigator at a clinical site which cited a number of deficiencies, including:

- improper delegations of authority by the principal investigator;
- failures to follow the protocols;
- institutional review board deviations; and
- discrepancies or deficiencies in documentation and reporting.

Following the failure of topical BCX-34 in 1997, we discontinued the development of the topical formulations of BCX-34. In November 1997, the FDA notified us that they would not accept work performed by the deficient investigator without further validation. The majority of the work performed by this investigator was for a topical formulation of BCX-34, which was discontinued in 1997. However, work performed by this investigator for oral BCX-34 will not be accepted by the FDA to support efficacy in any NDA.

#### SCIENTIFIC ADVISORY BOARD AND CONSULTANTS

We have assembled a scientific advisory board comprised of five scientific advisors who are leaders in certain of our core disciplines or who otherwise have specific expertise in our therapeutic focus areas. We also have consulting agreements with a number of other scientists with expertise in our core disciplines or in our therapeutic focus areas who are consulted from time to time by us. The scientific advisory board meets as a group at scheduled meetings and the consultants meet more frequently, on an individual basis, with our scientific personnel and management to discuss our ongoing research and drug discovery and development projects.

The scientific advisory board consists of the following individuals:

| NAME                                     | POSITION   |
|--|--|
| Albert F. LoBuglio, M.D. (Chairman)..... | Professor of Medicine and the Director of The University of Alabama at Birmingham Comprehensive Cancer Center.   |
| Gordon N. Gill, M.D. ....                | Professor of Medicine and Chair of the Faculty of Basic Biomedical Sciences at the University of California, San Diego School of Medicine.   |
| Herbert A. Hauptman, Ph.D. ....          | President of the Hauptman-Woodward Medical Research Institute, Inc. (formerly the Medical Foundation (Buffalo), Inc.), and Research Professor in Biophysical Sciences at the State University of New York (Buffalo), recipient of the Nobel Prize in Chemistry (1985). |
| Yuichi Iwaki, M.D., Ph.D. ....           | Professor of Urology and Pathology, University of Southern California School of Medicine.  |
| Hamilton O. Smith, M.D. ....             | Professor, Molecular Biology and Genetics Department at The Johns Hopkins University School of Medicine, retired, Director of DNA Resources at Celera Genomics Corporation, recipient of the Nobel Prize in Medicine (1978).   |

The scientific advisors and the consultants are reimbursed for their expenses and receive nominal cash compensation in connection with their service and have been issued options and/or shares of common stock. The scientific advisors and the consultants are all employed by or have consulting agreements with entities other than us, some of which may compete with us in the future. The scientific advisors and the consultants are expected to devote only a small portion of their time to our business, although no specific time commitment has been established. They are not expected to participate actively in our affairs or in the development of our technology. Certain of the institutions with which the scientific advisors and the consultants are affiliated may adopt new regulations or policies that limit the ability of the scientific advisors and the consultants to consult with us. The loss of the services of certain of the scientific advisors and the consultants could adversely affect us to the extent that we are pursuing research or development in areas relevant to the scientific advisors' and consultants' expertise. To the extent members of our scientific advisory board or the consultants have consulting arrangements with or become employed by any of our competitors, we could be materially adversely affected. One member of the scientific advisory board, Dr. Gordon N. Gill, is a member of the Board of Directors of the Agouron Institute. The Agouron Institute is a shareholder in, and has had contractual relationships with, Agouron Pharmaceuticals, Inc., a subsidiary of Warner-Lambert, that uses a core technology which is similar to the core technology employed by us.

Any inventions or processes independently discovered by the scientific advisors or the consultants may not become our property and will probably remain the property of such persons or of such persons' employers. In addition, the institutions with which the scientific advisors and the consultants are affiliated may make available the research services of their personnel, including the scientific advisors and the consultants, to our competitors pursuant to sponsored research agreements. We require the scientific advisors and the consultants to enter into confidentiality agreements which prohibit the disclosure of confidential information to anyone outside of our company and require disclosure and assignment to us of their ideas, developments, discoveries or inventions. However, no assurance can be

given that our competitors will not gain access to trade secrets and other proprietary information developed by us and disclosed to the scientific advisors and the consultants.

#### HUMAN RESOURCES

As of September 20, 1999, we had 56 employees, of whom 43 were engaged in research and development and 13 were in general and administrative functions. Our scientific staff, 19 of whom hold Ph.D. or M.D. degrees, has diversified experience in biochemistry, pharmacology, X-ray crystallography, synthetic organic chemistry, computational chemistry, medicinal chemistry and pharmacology. We consider our relations with our employees to be satisfactory.

#### PROPERTIES

Our administrative offices and principal research facility are located in 42,950 square feet of leased office space in Riverchase Industrial/Research Park in Birmingham, Alabama. The lease runs through June 30, 2003 with an option to lease for an additional three years at current market rates. We believe that our facilities are adequate for our current operations.

#### LEGAL PROCEEDINGS

We are not currently a party in any material legal proceedings.

MANAGEMENT

EXECUTIVE OFFICERS AND DIRECTORS

The following table sets forth information about our executive officers and directors as of June 30, 1999:

| NAME                               | AGE | POSITION  |
|------------------------------------|-----|---|
| Charles E. Bugg, Ph.D.....         | 58  | Chairman, Chief Executive Officer and Director                          |
| J. Claude Bennett, M.D.....        | 65  | President, Chief Operating Officer, Medical Director and Director       |
| John A. Montgomery, Ph.D. ....     | 75  | Senior Vice President, Secretary, Chief Scientific Officer and Director |
| Ronald E. Gray.....                | 58  | Chief Financial Officer, Assistant Secretary and Treasurer              |
| John R. Uhrin.....                 | 46  | Vice President, Corporate Development                                   |
| William W. Featheringill.....      | 56  | Director  |
| Edwin A. Gee, Ph.D.....            | 79  | Director  |
| Zola P. Horovitz, Ph.D.....        | 64  | Director  |
| Joseph H. Sherrill, Jr.....        | 58  | Director  |
| William M. Spencer, III.....       | 78  | Director  |
| Randolph C. Steer, M.D., Ph.D..... | 49  | Director  |

Messrs. Featheringill and Spencer and Dr. Gee are members of our Compensation and Audit Committees.

CHARLES E. BUGG, PH.D. was named Chairman of the Board, Chief Executive Officer and Director in November 1993 and President in January 1995. Dr. Bugg relinquished the position of President in December 1996 when Dr. Bennett joined BioCryst in that position. Prior to joining BioCryst, Dr. Bugg had served as the Director of the Center for Macromolecular Crystallography, Associate Director of the Comprehensive Cancer Center and Professor of Biochemistry at UAB since 1975. He was a Founder of BioCryst and served as BioCryst's first Chief Executive Officer from 1987 to 1988 while on a sabbatical from UAB. Dr. Bugg also served as Chairman of our scientific advisory board from January 1986 to November 1993. He continues to hold the position of Professor Emeritus in Biochemistry and Molecular Genetics at UAB, a position he has held since January 1994.

J. CLAUDE BENNETT, M.D. was named President and Chief Operating Officer in December 1996 and elected a Director in January 1997. He was appointed our Medical Director in August 1999. Prior to joining BioCryst, Dr. Bennett was President of UAB from October 1993 to December 1996, Professor and Chairman of the Department of Medicine of UAB from January 1982 to October 1993, and Professor and Chairman of the Department of Microbiology from January 1970 to December 1982. Dr. Bennett served on BioCryst's scientific advisory board from 1989 to 1996. He continues to hold the position of Distinguished University Professor Emeritus at UAB, a position he has held since January 1997.

JOHN A. MONTGOMERY, PH.D. has been a Director since November 1989 and has been Secretary and Chief Scientific Officer since joining BioCryst in February 1990. He was Executive Vice President from February 1990 until May 1997, at which time he was named Senior Vice President. Dr. Montgomery was a Founder of BioCryst. Prior to joining BioCryst, Dr. Montgomery served as Senior Vice President of Southern Research Institute of Birmingham from January 1981 to February 1990. He continues to hold the position of Distinguished Scientist at Southern Research Institute, a position he has held since February 1990.

RONALD E. GRAY joined BioCryst in January 1993 as Chief Financial Officer. In 1994, Mr. Gray received the additional title of Treasurer and Assistant Secretary. Prior to joining BioCryst, from

June 1992 to September 1992, Mr. Gray was Chief Financial Officer of The ACB Companies, a collection agency. From July 1988 to March 1992, Mr. Gray was Chief Financial Officer and Secretary of Image Data Corporation, a medical imaging company. He was previously Vice President of Finance, Secretary and Treasurer of CyCare Systems, Inc., a health care information processing company.

JOHN R. UHRIN joined BioCryst in March 1998 as Vice President, Corporate Development with 21 years of sales and marketing experience in the pharmaceutical, biotechnology, medical and managed care industries. He joined BioCryst following 11 years at Genentech, Inc. From 1987 to 1998, he held various management positions at Genentech, most recently as Director of Special Markets/Managed Care. Prior to working for Genentech, he held various sales and management positions with Eli Lilly from 1977 to 1987.

WILLIAM W. FEATHERINGILL was elected a Director in May 1995. Since June 1995, Mr. Featheringill has been Chairman and Chief Executive Officer of Electronic Healthcare Systems, a software company, and President, Chief Executive Officer and director, since 1973, of Private Capital Corporation, a venture capital management company. From 1988 to 1995, Mr. Featheringill was Chairman and Chief Executive Officer of MACESS Corporation, which designs and installs paperless data management systems for the managed care industry. MACESS Corporation merged with Sungard Data Systems in late 1995. From 1985 to December 1994, Mr. Featheringill was the developer, Chairman and President of Complete Health Services, Inc., a health maintenance organization. Complete Health Services, Inc. was acquired by United HealthCare Corporation in June 1994. Mr. Featheringill is a director of Citation Corporation.

EDWIN A. GEE, PH.D. was elected a Director in August 1993. Dr. Gee, who retired in 1985 as Chairman of the Board and Chief Executive Officer of International Paper Company, has been active as an executive in biotechnology, pharmaceutical and specialty chemical companies since 1970. He is Chairman Emeritus and a director of OSI Pharmaceuticals, Inc., one of the leading biotechnology companies for the diagnosis and treatment of cancer.

ZOLA P. HOROVITZ, PH.D. was elected a Director in August 1994. Dr. Horovitz was Vice President of Business Development and Planning at Bristol-Myers Squibb from 1991 until his retirement in April 1994 and previously was Vice President of Licensing at the same company from 1990 to 1991. Prior to 1990, he spent over 30 years with The Squibb Institute for Medical Research, most recently as Vice President Research, Planning, & Scientific Liaison. He has been an independent consultant in pharmaceutical sciences and business development since his retirement from Bristol-Myers Squibb in April 1994. He serves on the Board of Directors of Avigen, Inc., Clinacor Inc., Diacrin, Inc., Magainin Pharmaceuticals, Inc., Procept Corporation, Roberts Pharmaceutical Corporation and Synaptic Pharmaceutical Corp. Dr. Horovitz is also Chairman of Magainin Pharmaceuticals, Inc.

JOSEPH H. SHERRILL, JR. was elected a Director in May 1995. Mr. Sherrill served as President of R.J. Reynolds Asia Pacific, based in Hong Kong, where he oversaw R.J. Reynolds' operations across Asia, including licensing, joint ventures and a full line of operating companies from August 1989 to his retirement in October 1994. Prior management positions with R.J. Reynolds include Senior Vice President of Marketing for R.J. Reynolds International, President and Chief Executive Officer of R.J. Reynolds Tabacos de Brazil, and President and General Manager of R.J. Reynolds Puerto Rico.

WILLIAM M. SPENCER, III was a Founder and has been a Director of BioCryst since its inception. Mr. Spencer, who is retired, is also a private investor in Birmingham, Alabama. He served as Chairman of the Board of BioCryst from its founding in 1986 until April 1992. He co-founded and operated Motion Industries from 1946 through its merger into Genuine Parts Company in 1976. He has founded several businesses and has served on the Board of Directors of numerous private corporations.

RANDOLPH C. STEER, M.D., PH.D. was elected a Director in February 1993. Dr. Steer has been active as a consultant to biotechnology and pharmaceutical companies since 1989. Dr. Steer serves on the Board of Directors of Techne Corporation.

PRINCIPAL STOCKHOLDERS

The following table sets forth information regarding beneficial ownership of our common stock as of September 20, 1999 by:

- each of our directors and executive officers;
- all directors and executive officers as a group; and
- each person known by us to be the beneficial owner of more than five percent of our common stock.

| NAME OF BENEFICIAL OWNER   | NUMBER OF<br>SHARES<br>BENEFICIALLY<br>OWNED(1) | PERCENT OF<br>COMMON STOCK<br>BENEFICIALLY OWNED |                   |
|--|---|--|-------------------|
|  |   | BEFORE<br>OFFERING                               | AFTER<br>OFFERING |
| William W. Featheringill.....<br>100 Brookwood Place #410<br>Birmingham, Alabama 35209                           | 2,699,872(2)                                    | 17.7%  | 15.6%             |
| Johnson & Johnson Development Corporation.....<br>One Johnson & Johnson Plaza<br>New Brunswick, New Jersey 08933 | 918,836(3)                                      | 6.0  | 5.3               |
| Max Cooper.....<br>121 Summit Parkway<br>Birmingham, Alabama 35209   | 780,100(4)                                      | 5.1  | 4.5               |
| Charles E. Bugg, Ph.D.....   | 609,127(5)                                      | 3.9  | 3.4               |
| William M. Spencer, III.....   | 539,858(6)                                      | 3.5  | 3.1               |
| Joseph H. Sherrill, Jr.....  | 421,500(7)                                      | 2.8  | 2.4               |
| John A. Montgomery, Ph.D. ....   | 160,620(8)                                      | 1.0  | 0.9               |
| J. Claude Bennett, M.D. ....   | 107,460(9)                                      | *  | *                 |
| Ronald E. Gray.....  | 88,672 10)                                      | *  | *                 |
| Randolph C. Steer, M.D., Ph.D. ....  | 74,999 11)                                      | *  | *                 |
| Zola P. Horovitz, Ph.D.....  | 43,749 11)                                      | *  | *                 |
| Edwin A. Gee, Ph.D. ....   | 39,999 11)                                      | *  | *                 |
| John R. Uhrin.....   | 26,246 12)                                      | *  | *                 |
| All executive officers and directors as a group (11 persons).....  | 4,812,102 13)                                   | 29.4   | 26.2              |

\* Less than one percent.

(1) Gives effect to the shares of common stock issuable within 60 days after September 20, 1999 upon the exercise of all options and other rights beneficially held by the indicated stockholder on that date.

(2) Includes 364,900 shares of common stock held by the Featheringill Family Trust of which he is a beneficial owner and 32,500 shares of common stock issuable upon exercise of stock options.

(3) Johnson & Johnson Development Corporation is a wholly owned subsidiary of Johnson & Johnson and shares investment and voting power with Johnson & Johnson.

(4) Based on filings made by Mr. Cooper with the SEC.

- (5) Includes 539,084 shares of common stock issuable upon exercise of stock options.
- (6) Includes 43,749 shares of common stock issuable upon exercise of stock options and 10,000 shares of common stock held by Mr. Spencer's spouse. Mr. Spencer disclaims beneficial ownership of the 10,000 shares of common stock held by his spouse.
- (7) Includes 32,500 shares of common stock issuable upon exercise of stock options, 10,000 shares of common stock which Mr. Sherrill holds jointly with his spouse, 1,000 shares of common stock held by Mr. Sherrill's son and 10,000 shares of common stock held by Mr. Sherrill's spouse. Mr. Sherrill disclaims beneficial ownership of the 11,000 shares of common stock held by his spouse and son.
- (8) Includes 127,498 shares of common stock issuable upon exercise of stock options and 12,600 shares of common stock held by Dr. Montgomery's spouse. Dr. Montgomery disclaims beneficial ownership of the 12,600 shares of common stock held by his spouse.
- (9) Includes 102,725 shares of common stock issuable upon exercise of stock options.
- (10) Includes 1,500 shares of common stock held by the retirement accounts of Mr. Gray and his spouse and 78,394 shares of common stock issuable upon exercise of stock options.
- (11) Represents shares of common stock issuable upon exercise of stock options.
- (12) Includes 21,666 shares of common stock issuable upon exercise of stock options.
- (13) See Notes (2) through (11).

## RELATIONSHIPS AND RELATED PARTY TRANSACTIONS

Dr. Bugg, an executive officer and Director of BioCryst, is a Professor Emeritus of UAB and is paid an annual stipend of \$9,040 by UAB. Dr. Bennett, an executive officer and Director of BioCryst, is a consultant to and a Distinguished University Professor of UAB and is paid an annual stipend of \$12,500 by the UAB Education Foundation. We paid approximately \$877,000 to UAB in 1998 and approximately \$281,000 to UAB in 1999 through August 31 for conducting certain clinical trials, research and data analysis.

Dr. Montgomery, an executive officer and Director of BioCryst, is a former executive officer of Southern Research Institute. He is currently a Distinguished Scientist at Southern Research Institute and was paid approximately \$6,482 by Southern Research Institute in 1998 for various consulting services unrelated to the services performed by Southern Research Institute for us. We paid approximately \$209,000 to Southern Research Institute in 1998 and approximately \$28,000 to Southern Research Institute in 1999 through August 31 for certain research, library use and supplies.

In September 1998, we entered into an exclusive worldwide license agreement with PRI and Ortho-McNeil to develop and market our proprietary influenza neuraminidase inhibitors. We received an initial \$6.0 million payment from Ortho-McNeil and an additional \$6.0 million common stock equity investment from Johnson & Johnson Development Corporation. In June 1999, we received a \$2.0 million milestone payment from Ortho-McNeil in connection with the initiation of Phase II clinical testing in the United States. In addition, we may receive cash payments upon achievement of specified developmental and regulatory milestones and royalties on product sales, if any. PRI and Ortho-McNeil are responsible for all development, regulatory and commercialization expenses. The agreement is subject to termination by PRI and Ortho-McNeil at any time and by us in certain circumstances.

UNDERWRITING

Subject to the terms and conditions stated in the underwriting agreement dated the date hereof, each underwriter named below has severally agreed to purchase, and BioCryst has agreed to sell to such underwriter, the number of shares set forth opposite the name of such underwriter.

| NAME                                 | NUMBER<br>OF SHARES |
|--------------------------------------|---------------------|
| Salomon Smith Barney Inc. ....       |                     |
| Hambrecht & Quist LLC.....           |                     |
| Raymond James & Associates, Inc..... |                     |
| Total.....                           | 2,000,000           |
|                                      | -----               |

The underwriting agreement provides that the obligations of the several underwriters to purchase the shares included in this offering are subject to approval of certain legal matters by counsel and to certain other conditions. The underwriters are obligated to purchase all the shares (other than those covered by the over-allotment option described below) if they purchase any of the shares.

The underwriters propose to offer some of the shares directly to the public at the public offering price set forth on the cover page of this prospectus and some of the shares to certain dealers at the public offering price less a concession not in excess of \$ \_\_\_\_\_ per share. The underwriters may allow, and such dealers may reallow, a concession not in excess of \$ \_\_\_\_\_ per share on sales to certain other dealers. If all of the shares are not sold at the initial offering price, the representatives may change the public offering price and the other selling terms.

BioCryst has granted to the underwriters an option, exercisable for 30 days from the date of this prospectus, to purchase up to 300,000 additional shares of common stock at the public stock at the public offering price less the underwriting discount. The underwriters may exercise such option solely for the purpose of covering over-allotments, if any, in connection with this offering. To the extent such option is exercised, each underwriter will be obligated, subject to certain conditions, to purchase a number of additional shares approximately proportionate to such underwriter's initial purchase commitment.

BioCryst, its officers and directors, and certain other stockholders of BioCryst have agreed that, for a period of 90 days from the date of this prospectus, they will not, without the prior written consent of Salomon Smith Barney Inc., dispose of or hedge any shares of common stock of BioCryst or any securities convertible into or exchangeable for common stock. Salomon Smith Barney Inc. in its sole discretion may release any of the securities subject to these lock-up agreements at any time without notice.

The common stock is quoted on the Nasdaq National Market under the symbol "BCRX."

The following table shows the underwriting discounts and commissions to be paid to the underwriters by BioCryst and the selling stockholders in connection with this offering. These amounts are shown assuming both no exercise and full exercise of the underwriters' option to purchase additional shares of common stock.

|                | PAID TO BIOCRYST |                  |
|----------------|------------------|------------------|
|                | NO EXERCISE      | FULL<br>EXERCISE |
| Per share..... | \$               | \$               |
| Total.....     | \$               | \$               |

In connection with the offering, Salomon Smith Barney Inc., on behalf of the underwriters, may purchase and sell shares of common stock in the open market. These transactions may include

over-allotment, syndicate covering transactions and stabilizing transactions. Over-allotment involves syndicate sales of common stock in excess of the number of shares to be purchased by the underwriters in the offering, which creates a syndicate short position. Syndicate covering transactions involve purchases of the common stock in the open market after the distribution has been completed in order to cover syndicate short positions. Stabilizing transactions consist of certain bids or purchases of common stock made for the purpose of preventing or retarding a decline in the market price of the common stock while the offering is in progress.

The underwriters also may impose a penalty bid. Penalty bids permit the underwriters to reclaim a selling concession from a syndicate member when Salomon Smith Barney Inc., in covering syndicate short positions or making stabilizing purchases, repurchases shares originally sold by that syndicate member.

Any of these activities may cause the price of the common stock to be higher than the price that otherwise would exist in the open market in the absence of such transactions. These transactions may be effected on the Nasdaq National Market or in the over-the-counter market, or otherwise and, if commenced, may be discontinued at any time.

In addition, in connection with this offering, certain of the underwriters (and selling group members) may engage in passive market making transactions in the common stock on the Nasdaq National Market, prior to the pricing and completion of the offering. Passive market making consists of displaying bids on the Nasdaq National Market no higher than the bid prices of independent market makers and making purchases at prices no higher than those independent bids and effected in response to order flow. Net purchases by a passive market maker on each day are limited to a specified percentage of the passive market maker's average daily trading volume in the common stock during a specified period and must be discontinued when such limit is reached. Passive market making may cause the price of the common stock to be higher than the price that otherwise would exist in the open market in the absence of such transactions. If passive market making is commenced, it may be discontinued at any time.

BioCryst estimates that the total expenses of this offering will be \$750,000.

BioCryst has agreed to indemnify the underwriters against certain liabilities, including liabilities under the Securities Act of 1933, or to contribute to payments the underwriters may be required to make in respect of any of those liabilities.

#### LEGAL MATTERS

The validity of the common stock offered in this prospectus will be passed upon for BioCryst by Brobeck, Phleger & Harrison LLP, Broomfield, Colorado. As of September 20, 1999, a member of Brobeck, Phleger and Harrison LLP beneficially owned a total of 5,000 shares of our common stock. Other legal matters in connection with this offering will be passed upon for the underwriters by Cravath, Swaine & Moore, 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, 1998, as set forth in their report, which is incorporated by reference in this prospectus and elsewhere in this 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.

The statements in this prospectus under the sections "Risk Factors--We may fail to adequately protect or enforce our intellectual property rights or secure rights to third-party patents" and "Business--Patents and Proprietary Information" and other references in this prospectus to U.S. patent matters have been reviewed and approved by Pollock, Vande Sande & Amernick, R.L.L.P., our patent counsel, as experts on such matters and are included in this prospectus in reliance upon that review and approval.

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-----  
2,000,000 SHARES

[LOGO]

COMMON STOCK

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P R O S P E C T U S

, 1999

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SALOMON SMITH BARNEY  
HAMBRECHT & QUIST  
RAYMOND JAMES & ASSOCIATES, INC.

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PART II  
INFORMATION NOT REQUIRED IN PROSPECTUS

ITEM 14. OTHER EXPENSES OF ISSUANCE AND DISTRIBUTION

The following table sets forth all costs and expenses, other than the underwriting discounts and commissions, payable by the company in connection with the sale of common stock being registered hereby. All of the amounts shown are estimates except the SEC registration fee and the Nasdaq National Market additional listing fee.

|  | AMOUNT<br>TO BE PAID<br>----- |
|--|-------------------------------|
| SEC registration fee.....                    | \$ 15,985                     |
| NASD filing fee.....                         | 6,250                         |
| Nasdaq additional listing of shares fee..... | 17,500                        |
| Accounting fees and expenses.....            | 40,000                        |
| Legal fees and expenses.....                 | 500,000                       |
| Printing and engraving expenses.....         | 150,000                       |
| Transfer Agent and registrar fees.....       | 5,000                         |
| Miscellaneous.....                           | 15,265                        |
|  | -----                         |
| Total.....                                   | \$ 750,000<br>-----<br>-----  |

ITEM 15. INDEMNIFICATION OF DIRECTORS AND OFFICERS

Section 145 of the Delaware General Corporation Law authorizes a court to award, or a corporation's Board of Directors to grant, indemnification to directors and officers in terms sufficiently broad to permit such indemnification under certain circumstances for liabilities (including reimbursement for expenses incurred) arising under the Securities Act of 1933, as amended (the "Act"). Article Eight of the Registrant's Composite Certificate of Incorporation provides for indemnification of its directors and officers and permissible indemnification of employees and other agents to the maximum extent permitted by the Delaware General Corporation Law. The Registrant has liability insurance for its Directors and Officers.

ITEM 16. EXHIBITS

The following is a list of Exhibits filed as part of the Registration Statement:

- 1.1 Form of Underwriting Agreement\*
- 4.1 Specimen certificate for shares of the Registrant's Common Stock, incorporated herein by reference to Exhibit 4.1 the Registrant's Registration Statement No. 33-73868.
- 4.2 Provisions of the Composite Certificate of Incorporation and By-Laws of the Registrant defining rights of holders of Common Stock of the Registrant, incorporated herein by reference to Exhibits 3.1 and 3.2 to the Company's Form 10-Q for the second quarter ending June 30, 1995 dated August 11, 1995
- 5.1 Opinion of Brobeck, Phleger & Harrison LLP\*
- 23.1 Consent of Brobeck, Phleger & Harrison LLP (included in the opinion filed as Exhibit 5.1).
- 23.2 Consent of Ernst & Young LLP, independent accountants
- 24.1 Power of Attorney (included with signature page)
- 27.1 Financial Data Schedule

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\* To be filed by amendment.

ITEM 17. UNDERTAKINGS

Insofar as indemnification for liabilities arising under the Securities Act of 1933 may be permitted to directors, officers and controlling persons of the Registrant pursuant to the provisions described in Item 14 above, or otherwise, the Registrant has been advised that in the opinion of the Securities and Exchange Commission such indemnification is against public policy as expressed in the Act, and is, therefore, unenforceable. In the event that a claim for indemnification against such liabilities (other than payment by the Registrant of expenses incurred or paid by a director, officer or controlling person of the Registrant in the successful defense of any action, suit or proceeding) is asserted by such director, officer or controlling person in connection with the securities being registered, the Registrant will, unless in the opinion of our counsel the matter has been settled by controlling precedent, submit to a court of appropriate jurisdiction the question whether such indemnification by it is against public policy as expressed in the Act and will be governed by the final adjudication of such issue.

The undersigned Registrant hereby undertakes:

- (1) To file, during any period in which offers or sales are being made of the securities offered hereby, a post-effective amendment to this Registration Statement;
- (i) To include any prospectus required by Section 10(a)(3) of the Securities Act of 1933;
- (ii) To reflect in the prospectus any facts or events arising after the effective date of the registration statement (or the most recent post-effective amendment thereof) which, individually or in the aggregate, represent a fundamental change in the information set forth in the registration statement. Notwithstanding the foregoing, any increase or decrease in volume of securities offered (if the total dollar value of securities offered would not exceed that which was registered) and any deviation from the low or high end of the estimated maximum offering range may be reflected in the form of prospectus filed with the Commission pursuant to Rule 424(b) if, in the aggregate, the changes in volume and price represent no more than a 20 percent change in the maximum aggregate offering

price set forth in the "Calculation of Registration Fee" table in the effective registration statement;

- (iii) To include any material information with respect to the plan of distribution not previously disclosed in the registration statement or any material change to such information in the registration statement;

provided, however, that the undertakings set forth in paragraphs (i) and (ii) above do not apply if the information required to be included in a post-effective amendment by those paragraphs is contained in periodic reports filed by the registrant pursuant to Section 13 or Section 15(d) of the Securities Exchange Act of 1934 that are incorporated by reference in this registration statement.

(2) That, for the purpose of determining any liability under the Securities Act of 1933, each such post-effective amendment shall be deemed to be a new registration statement relating to the securities offered therein, and the offering of such securities at that time shall be deemed to be the initial bona fide offering thereof.

(3) To remove from registration by means of a post-effective amendment any of the securities being registered which remain unsold at the termination of the offering.

The undersigned Registrant hereby undertakes that, for purposes of determining any liability under the Securities Act of 1933, each filing of the Registrant's annual report pursuant to Section 13(a) or Section 15(d) of the Securities Exchange Act of 1934 that is incorporated by reference in the registration statement shall be deemed to be a new registration statement relating to the securities offered therein, and the offering of such securities at that time shall be deemed to be the initial bona fide offering thereof.

The undersigned Registrant hereby undertakes that:

(1) For purposes of determining any liability under the Securities Act of 1933, the information omitted from the form of prospectus filed as part of this Registration Statement in reliance upon Rule 430A and contained in a form of prospectus filed by the registrant pursuant to Rule 424(b)(1) or (4) or 497(h) under the Securities Act shall be deemed to be part of this Registration Statement as of the time it was declared effective.

(2) For the purpose of determining any liability under the Securities Act, each post-effective amendment that contains a form of prospectus shall be deemed to be a new registration statement relating to the securities offered therein, and the offering of such securities at that time shall be deemed to be the initial bona fide offering thereof.

SIGNATURES

Pursuant to the requirements of the Securities Act of 1933, as amended, the Registrant certifies that it has reasonable grounds to believe that it meets all of the requirements for filing on Form S-3 and has duly caused this Registration Statement to be signed on our behalf by the undersigned, thereunto duly authorized, in the City of Birmingham, State of Alabama, on September 23, 1999.

BIOCRYST PHARMACEUTICALS, INC.

By: /s/ CHARLES E. BUGG

-----  
Charles E. Bugg, Ph.D. Chairman and Chief  
Executive Officer

KNOW ALL MEN BY THESE PRESENTS, that each person or entity whose signature appears below constitutes and appoints Charles E. Bugg, Ph.D. and Ronald E. Gray, and each of them, our true and lawful attorneys-in-fact and agents, with full power of substitution and resubstitution, for it and in our name, place and stead, in any and all capacities, to sign any and all amendments, including any post-effective amendments, to this Registration Statement on Form S-3, or any registration statement relating to the offering to be effective upon filing pursuant to Rule 462(b) under the Securities Act of 1933, and to file the same, with all exhibits thereto, and other documents in connection therewith, with the Securities and Exchange Commission, granting unto said attorneys-in-fact and agents, and each of them, full power and authority to do and perform each and every act and thing requisite and necessary to be done, as fully to all intents and purposes as it might or could do in person, hereby ratifying and confirming all that said attorneys-in-fact and agents or any of them, or their or his substitute or substitutes may lawfully do or cause to be done by virtue hereof.

Pursuant to the requirements of the Securities Act of 1933, as amended, this Registration Statement has been signed by the following persons in the capacities indicated on September 23, 1999.

| SIGNATURE  | TITLE   |
|--|---|
| -----<br>/s/ CHARLES E. BUGG<br>-----<br>Charles E. Bugg, Ph.D.            | Chairman, Chief Executive Officer and Director<br>(principal executive officer) |
| -----<br>/s/ J. CLAUDE BENNETT<br>-----<br>Claude Bennett, M.D.            | President, Chief Operating Officer and Director                                 |
| -----<br>/s/ JOHN A. MONTGOMERY<br>-----<br>John A. Montgomery, Ph.D.      | Senior Vice President, Secretary, Chief Scientific<br>Officer and Director      |
| -----<br>/s/ RONALD E. GRAY<br>-----<br>Ronald E. Gray                     | Chief Financial Officer (principal financial and<br>accounting officer)         |
| -----<br>/s/ WILLIAM W. FEATHERINGILL<br>-----<br>William W. Featheringill | Director  |
| -----<br>/s/ EDWIN A. GEE<br>-----<br>Edwin A. Gee, Ph.D.                  | Director  |
| -----<br>/s/ ZOLA P. HOROVITZ<br>-----<br>Zola P. Horovitz, Ph.D.          | Director  |
| -----<br>/s/ WILLIAM M. SPENCER, III<br>-----<br>William M. Spencer, III   | Director  |
| -----<br>/s/ JOSEPH H. SHERRILL, JR.<br>-----<br>Joseph H. Sherrill, Jr.   | Director  |
| -----<br>/s/ RANDOLPH C. STEER<br>-----<br>Randolph C. Steer, M.D., Ph.D.  | Director  |

EXHIBIT INDEX

- 1.1 Form of Underwriting Agreement\*
- 4.1 Specimen certificate for shares of the Registrant's Common Stock, incorporated herein by reference to Exhibit 4.1 the Registrants Registration Statement No. 33-73868.
- 4.2 Provisions of the Composite Certificate of Incorporation and By-Laws of the Registrant defining rights of holders of Common Stock of the Registrant, incorporated herein by reference to Exhibits 3.1 and 3.2 to the Company's Form 10-Q for the second quarter ending June 30, 1995 dated August 11, 1995
- 5.1 Opinion of Brobeck, Phleger & Harrison LLP.\*
- 23.1 Consent of Brobeck, Phleger & Harrison LLP (included in the opinion filed as Exhibit 5.1).
- 23.2 Consent of Ernst & Young LLP, independent accountants.
- 24.1 Power of Attorney (included with signature page).
- 27.1 Financial Data Schedule

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\* To be filed by amendment.

CONSENT OF ERNST & YOUNG LLP  
INDEPENDENT AUDITORS

We consent to the reference to our firm under the caption "Experts" in the Registration Statement (Form S-3, No. 333- ) and the related Prospectus of BioCryst Pharmaceuticals, Inc. for the registration of 2,300,000 shares of its common stock and to the incorporation by reference therein of our report dated January 15, 1999, with respect to the financial statements of BioCryst Pharmaceuticals, Inc. included in its Annual Report (Form 10-K) for the year ended December 31, 1998, filed with the Securities and Exchange Commission.

Birmingham, Alabama  
September 20, 1999



This schedule contains summary financial information extracted from the BioCryst Pharmaceuticals, Inc. Financial Statements, and is qualified in its entirety by reference to such financial statements.

|            |             |             |
|------------|-------------|-------------|
| 6-MOS      |             |             |
|            | DEC-31-1999 |             |
|            | JUN-30-1999 |             |
|            |             | 5,335,967   |
|            |             | 18,980,886  |
|            |             | 0           |
|            |             | 0           |
|            |             | 0           |
|            | 18,167,183  |             |
|            |             | 3,476,033   |
|            |             | 1,963,008   |
|            |             | 26,545,685  |
|            | 1,032,175   |             |
|            |             | 0           |
|            | 0           |             |
|            |             | 0           |
|            |             | 149,876     |
|            |             | 25,048,930  |
| 26,545,685 |             |             |
|            |             | 0           |
|            | 3,040,597   |             |
|            |             | 0           |
|            |             | 5,688,837   |
|            |             | 0           |
|            |             | 0           |
|            |             | 2,777       |
|            |             | (2,651,017) |
|            |             | 0           |
|            |             | 0           |
|            |             | 0           |
|            |             | 0           |
|            |             | 0           |
|            |             | 0           |
|            |             | (2,651,017) |
|            |             | (.18)       |
|            |             | (.18)       |