CYTOGEN CORP
Form 10-K
March 15, 2004
Table of Contents

UNITED STATES

SECURITIES AND EXCHANGE COMMISSION

Washington, DC 20549

FORM 10-K

FOR ANNUAL AND TRANSITION REPORTS

PURSUANT TO SECTIONS 13 OR 15(d) OF THE

SECURITIES EXCHANGE ACT OF 1934

(Mark One)

x ANNUAL REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934

For the fiscal year ended December 31, 2003

OR

¨ TRANSITION REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934

For the transition period from _____ to _____

Commission File Number 000-14879

CYTOGEN CORPORATION

(Exact Name of Registrant as Specified in Its Charter)

Delaware	22-2322400
(State or Other Jurisdiction of Incorporation or Organization)	(I.R.S. Employer Identification No.)
650 College Road East, Suite 3100 Princeton, New Jersey	08540
(Address of Principal Executive Offices)	(Zip Code)

Registrant s telephone number, including area code: (609) 750-8200

Securities registered pursuant to Section 12(b) of the Act: None

Securities registered pursuant to Section 12(g) of the Act:

Common Stock, $0.01 par value per share

(Title of Class)

Preferred Stock Purchase Rights, $0.01 par value per share

(Title of Class)

Indicate by check mark whether the registrant: (1) has filed all reports required to be filed by Section 13 or 15(d) of the Securities Exchange Act of 1934 during the preceding 12 months (or for such shorter period that the registrant was required to file such reports), and (2) has been subject to such filing requirements for the past 90 days. Yes x No ¨

Indicate by check mark if disclosure of delinquent filers pursuant to Item 405 of Regulation S-K is not contained herein, and will not be contained, to the best of registrant s knowledge, in definitive proxy or information statements incorporated by reference in Part III of this Form 10-K or any amendment to this Form 10-K. ¨

Indicate by check mark whether the registrant is an accelerated filer (as defined in Exchange Act Rule 12b-2). Yes x No ¨

The aggregate market value of the registrant s voting shares of Common Stock held by non-affiliates of the registrant on June 30, 2003, based on $8.33 per share, the last reported sale price on the NASDAQ National Market on that date, was $61,787,175.

The number of shares of Common Stock, $.01 par value, of the registrant outstanding as of March 1, 2004 was 12,935,910 shares.

The following documents are incorporated by reference into the Annual Report on Form 10-K: Portions of the registrant s definitive Proxy Statement for its 2004 Annual Meeting of Stockholders are incorporated by reference into Part III of this Report.

Table of Contents

TABLE OF CONTENTS

	Item	Page
PART I	1. Business	1
	2. Properties	44
	3. Legal Proceedings	44
	4. Submission of Matters to a Vote of Security Holders	45
PART II	5. Market for the Company s Common Equity, Related Stockholder Matters and Company Purchases of Equity Securities	46
	6. Selected Financial Data	47
	7. Management s Discussion and Analysis of Financial Condition and Results of Operations	49
	7A. Quantitative and Qualitative Disclosures About Market Risk	63
	8. Financial Statements and Supplementary Data	63
	9. Changes in and Disagreements with Accountants on Accounting and Financial Disclosure	63
	9A. Controls and Procedures	64
PART III	10. Directors and Executive Officers of the Company	65
	11. Executive Compensation	65
	12. Security Ownership of Certain Beneficial Owners and Management and Related Stockholder Matters	65
	13. Certain Relationships and Related Transactions	65
	14. Principal Accountant s Fees and Services	65
PART IV	15. Exhibits, Financial Statement Schedules, and Reports on Form 8-K	66
EXHIBIT INDEX		66
SIGNATURES		73
INDEX TO CONSOLIDATED FINANCIAL STATEMENTS		F-1

Table of Contents

PART I

Item 1. Business

OVERVIEW

Founded in 1980, Cytogen Corporation of Princeton, NJ is a product-driven, oncology-focused biopharmaceutical company that licenses, develops and commercializes both therapeutic and molecular imaging/diagnostic products that address the unmet medical needs of physicians and the patients they serve. We directly market QUADRAMET (samarium Sm-153 lexidronam injection), PROSTASCINT® (capromab pendetide) kit for the preparation of Indium In-111 capromab pendetide, and NMP22® BLADDERCHEK® (nuclear matrix protein-22) in the United States. We also have exclusive United States marketing rights to COMBIDEX® (ferumoxtran-10), which is under review by the U.S. Food and Drug Administration. We are also developing therapeutics targeting prostate-specific membrane antigen (PSMA), a protein highly expressed on the surface of prostate cancer cells and the neovasculature of solid tumors.

Our proprietary and licensed products, product candidates and technologies are as follows:

Therapeutics:

Product	Description	Status
QUADRAMET (samarium Sm-153 lexidronam injection)	Third-generation skeletal targeting therapeutic radiopharmaceutical for the relief of pain in patients with confirmed osteoblastic metastatic bone lesions	Developed by Cytogen based upon technology licensed from the Dow Chemical Company Marketed in the United States by Cytogen as of August 1, 2003, and previously by Berlex Laboratories from May 1999 until July 2003
PSMA rs protein vaccine	A vaccine consisting of recombinant soluble PSMA combined with an immune stimulant to induce an immune response	Phase I Jointly developed with Progenics Pharmaceuticals, Inc.
PSMA viral vector vaccine	A vaccine that utilizes viral vectors designed to deliver the PSMA gene to immune system cells in order to generate potent and specific immune response	Preclinical Jointly developed with Progenics Pharmaceuticals, Inc.
PSMA monoclonal antibodies	Novel fully-human monoclonal antibodies that bind to the three-dimensional structure of PSMA as presented on cancer cells, including naked, toxin-linked and radio-labeled approaches	Preclinical Jointly developed with Progenics Pharmaceuticals, Inc.

Molecular Imaging/Diagnostic:

Product	Description	Status
PROSTASCINT® (capromab pendetide)	Monoclonal antibody-based imaging agent targeting PSMA used to image the extent and spread of prostate cancer in previously diagnosed patients	Developed and marketed by Cytogen in the United States

Table of Contents

Molecular Imaging/Diagnostic:

Product	Description	Status
NMP22® BLADDERCHEK® (nuclear matrix protein-22)	A point-of-care *in vitro* diagnostic test for bladder cancer	Developed by Matritech, Inc., marketed to oncologists by Cytogen in the United States
COMBIDEX® (ferumoxtran-10)	Investigational molecular imaging agent consisting of lymphotropic superparamagnetic nanoparticles used in conjunction with magnetic resonance imaging to detect metastatic tumor in local and distant lymph nodes	Developed by Advanced Magnetics, Inc. and exclusively licensed by Cytogen for marketing in the United States
		Under review by the United States Food and Drug Administration
		Received an approvable letter in June 2000

As of March 1, 2004, we market QUADRAMET, PROSTASCINT and NMP22 BLADDERCHEK in the United States through our in-house specialty sales organization, consisting of approximately 36 employees, directly to medical oncologists, radiation oncologists, nuclear medicine professionals, radiologists and urologists.

The Company was incorporated in Delaware on March 3, 1980 under the name Hybridex, Inc. and changed its name to Cytogen Corporation on April 1, 1980. Our executive offices are located at 650 College Road East, Suite 3100, Princeton, New Jersey 08540 and our telephone number is 609-750-8200.

PROSTASCINT and ONCOSCINT® are registered United States trademarks of Cytogen Corporation. We are the owner of a pending United States trademark application, Serial No. 78374967, relating to QUADRAMET. All other trade names, trademarks or servicemarks appearing in this Annual Report on Form 10-K are the property of their respective owners, and not the property of Cytogen Corporation or any of our subsidiaries.

We also maintain a website at www.cytogen.com, which is not a part of this Annual Report on Form 10-K. We provide an internet link on our website to the Securities and Exchange Commission s website where you can find documents that we file with the SEC, including our Annual Report on Form 10-K, Quarterly Reports on Form 10-Q, Current Reports on Form 8-K and amendments to such reports filed pursuant to Section 13(a) or 15(d) of the Exchange Act. These documents are posted as soon as reasonably practicable after we electronically file such material with, or furnish it to, the SEC. Alternatively, we will provide electronic or paper copies of our filings free of charge upon request.

MARKETED PRODUCTS AND PRODUCT CANDIDATES PENDING APPROVAL

THERAPEUTIC PRODUCT

QUADRAMET

Overview

QUADRAMET is a third-generation skeletal targeting therapeutic radiopharmaceutical for relief of pain due to bone metastases arising from prostate, breast, multiple myeloma and other cancers. QUADRAMET is indicated for relief of pain in patients with confirmed osteoblastic metastatic bone lesions that enhance on a radionuclide bone scan. QUADRAMET consists of a radioactive isotope, Samarium-153, which emits both beta and gamma radiation, and a chelating agent, ethylenediaminetetramethylenephosphonic acid (EDTMP), which selectively targets and delivers the drug to sites of new bone formation associated with tumor invasion.

Table of Contents

Once tumors have metastasized to the skeleton, they continue to grow and cause destruction of the adjacent bone. This erosion of bone stimulates new bone formation which encircles the metastatic tumor. By targeting these areas of bone formation, QUADRAMET delivers site-specific radiation, which may result in significant pain reduction. According to American Cancer Society and National Cancer Institute statistics, about half of all people with cancer (other than skin cancer) will have bone metastasis at some point in the course of their disease. Bone metastasis is one of the most frequent causes of cancer related pain.

QUADRAMET has many characteristics which we believe are advantageous for the treatment of cancer bone pain, including early onset of pain relief; predictable and reversible bone marrow toxicity or myelosuppression; ease of administration; and length of pain relief, lasting up to four months with a single injection. QUADRAMET is administered as an intravenous injection on an outpatient basis, and exhibits selective uptake in bone with little or no detectable accumulation in soft tissue.

Further Clinical Development Related to QUADRAMET

We believe the unique combination of nuclear, chemical and biologic properties possessed by QUADRAMET make it an attractive candidate for addition of a skeletal targeted therapeutic component to a number of systemic therapies currently utilized in the treatment of patients with cancers originating in or metastasizing to bone. We believe that future QUADRAMET growth is, in part, dependent upon:

- publishing new clinical data supporting the expanded and earlier use of QUADRAMET in various cancers;
- conducting novel research supporting combination uses of QUADRAMET with other therapies, such as chemotherapy and bisphophonates;
- establishing the use of QUADRAMET at higher doses and earlier in the course of the disease to target and treat primary bone cancers;
- obtaining FDA marketing approval for a desired indication; and
- increasing marketing and sales penetration to radiation and medical oncologists.

Our products, including QUADRAMET, are subject to significant regulation by governmental agencies, including the United States Food and Drug Administration, as is more fully described under the section entitled Government Regulation herein. We cannot assure you that we will be able to complete any of our market expansion strategies set forth above.

QUADRAMET is currently being evaluated both at higher doses and in a series of combination therapy trials in order to assess potential synergies with anti-tumor drugs and other bone seeking agents such as bisphosphonates. Currently active clinical studies sponsored or supported by us in this regard include:

- A Phase I/II study is ongoing at Northwestern University in Illinois using QUADRAMET, paclitaxel (Taxol®), and estramustine phosphate sodium (Emcyt®) in hormone refractory prostate cancer patients. The initial Phase I component of the study will utilize escalating single doses of QUADRAMET in combination with paclitaxel and estramustine phosphate sodium in order to evaluate the

dose level at which dose limiting toxicity is obtained. The Phase II portion of the study will expand the number of patients treated at the maximum tolerated dose obtained in the Phase I portion in order to assess the clinical response to treatment.

A Phase I study is ongoing at Thomas Jefferson University in Pennsylvania using escalating single doses of QUADRAMET combined with ongoing hormonal therapy prior to external beam radiation therapy in men with high risk clinically localized prostate cancer. The objectives of the current study are to assess the safety and determine the maximum tolerated dose of QUADRAMET in this clinical setting. The goal of this type of therapy is to prevent or delay the progression of bone metastases.

Table of Contents

Two Phase I studies are ongoing at the University of Maryland evaluating the potential benefits of combination treatments including QUADRAMET and zoledronic acid (Zometa®) in patients with advanced prostate cancer. One study involves patients who are chemotherapy naïve while the other is for patients who have previously received chemotherapy.

During 2003, we reported that independent investigators from cancer research centers around the world presented new clinical data as follows:

Clinical investigators from the Department of Radiation Sciences at University Umea in Sweden reported data from a pilot study of QUADRAMET in combination with docetaxel (Taxotere®) in hormone refractory prostate cancer patients. The purpose of the study was to evaluate the optimal time frame for co-administration of docetaxel with QUADRAMET. Additional details regarding the conduct and results of this study are available in the *Proc. Am. Soc. Clin. Oncol.,* vol. 22, page 433, 2003 (abstract # 1739).

Clinical investigators from Cantanzaro and Rome in Italy studied the toxicity, clinical impact, and quality of life from sequential doses of QUADRAMET and zoledronic acid (Zometa®) in symptomatic chemorefractory multiple myeloma patients. The purpose of the study was to evaluate the effect of this combination of treatments on pain scores and markers of disease in this patient population. Additional details regarding the conduct and results of this study are available in the *Proc. Am. Soc. Clin. Oncol.,* vol. 22, page 603, 2003 (abstract # 2425) and in the journal *Blood*, vol. 102, no. 11, page 446a, 2003 (abstract # 1630).

Clinical investigators from The Mayo Clinic in Minneapolis reported data on the use of high dose QUADRAMET in combination with high dose melphalan (Alkeran®) as part of a preparative regimen prior to stem cell transplant for the treatment of multiple myeloma. The study consisted of a Phase I component in which the safety of escalating single doses of QUADRAMET was evaluated and a Phase II component in which the response rate of the procedure was evaluated. Additional details regarding the conduct and results of this study are available in the journal *Blood*, vol. 102, no. 11, page 928a, 2003 (abstract # 3656) and *J. Nucl. Med.,* 44j Suppl. 174p, (2003) (abstract # 569).

Clinical investigators from Hadassah University Hospital in Israel reported data on the use of high dose QUADRAMET in combination with chemotherapy followed by non-myeloablative allogeneic stem cell transplantation in patients with a variety of resistant hematologic malignancies including acute leukemia, myelodysplastic syndrome and multiple myeloma. Additional details regarding the conduct and results of this study are available in the *Proc. Am. Soc. Clin. Oncol.,* vol. 22, page 839, 2003 (abstract # 3372).

QUADRAMET is indicated for the relief of pain in patients with confirmed osteoblastic metastatic bone lesions that enhance on a radionuclide bone scan. The foregoing discussion may describe investigational clinical applications that differ from that reported in the QUADRAMET package insert, and that have not been reviewed or approved by FDA. A copy of the full prescribing information for QUADRAMET may be obtained in the United States from us by calling us toll free at 800-833-3533 or by visiting our web site at http://www.cytogen.com, which is not part of this Annual Report on Form 10-K.

Intellectual Property Position Related to QUADRAMET

In May 1993, we obtained an exclusive license from The Dow Chemical Company to North American rights to use QUADRAMET as a therapeutic radiopharmaceutical for metabolic bone disease or tumor regression for cancer caused by metastatic or primary cancer in bone in humans, and for the treatment of disease characterized by osteoblastic response in humans. Our license was expanded to include Latin America in 1995. Our license agreement with Dow with respect to QUADRAMET shall remain in effect, unless earlier terminated pursuant to the terms thereof, for a term of twenty (20) years from May 30, 1993 or until the last to expire of the related patents. We currently anticipate such termination date to be May 30, 2013.

4

Table of Contents

Under our agreement with Dow, we are the licensee of five issued United States patents and certain corresponding foreign patents. Dow is responsible, at its own cost and expense, for prosecuting and maintaining any patents or patent applications included in our agreement. One of these, U.S. Pat. No. 4,898,724, includes claims directed to the QUADRAMET product and methods for its use in the treatment of calcific tumors and bone pain. We have obtained an extension of the term of this U.S. patent, which will now expire March 28, 2011. Other patents licensed to us under this agreement are: (i) U.S. Pat. No. 4,897,254, which expires on January 30, 2007; (ii) U.S. Pat. No. 4,937,333, which expires August 4, 2009; (iii) U.S. Pat. No. 5,300,279, which expires on November 19, 2008; and (iv) U.S. Pat. No. 5,066,478 which expires on November 19, 2008. Additional patents have been issued, U.S. Pat. No. 5,714,604, which expires on February 3, 2015, and U.S. Pat. No. 5,762,907, which expires November 21, 2006, which include claims directed to the QUADRAMET product, methods for its manufacture, and methods for its preparation and administration. We are the owner of a pending United States trademark application, Serial No. 78374967, relating to QUADRAMET.

Upon execution of this agreement with Dow, we issued warrants to purchase shares of our common stock, which have since expired. As of December 31, 2003, we have paid an aggregate of $5.2 million to Dow in milestone payments. We remain obligated to pay Dow additional milestone payments as, and if, our sales of QUADRAMET increase and royalties, which are subject to certain minimum amounts, based on future sales of QUADRAMET.

Manufacturing, Supply and Distribution of QUADRAMET

QUADRAMET is manufactured by Bristol-Myers Squibb Medical Imaging, Inc. (BMSMI), pursuant to the terms of a manufacturing and supply agreement with us effective as of January 1, 2004. Under the manufacturing and supply agreement, BMSMI has agreed to manufacture, supply and distribute QUADRAMET for us in exchange for a minimum payment of at least $4.2 million annually through 2008. The agreement shall thereafter renew for five successive one year periods. The agreement is terminable by either party, at any time, upon two years notice to the other. We also pay BMSMI a variable amount per month for each order placed to cover the costs of customer service and distribution. Upon our reacquisition of marketing rights to QUADRAMET from Berlex Laboratories, Inc., on August 1, 2003, we assumed certain obligations under a previous exclusive manufacturing and supply agreement among Cytogen, Berlex and BMSMI, which were met through December 31, 2003. This agreement was replaced by the manufacturing and supply agreement with BMSMI as of January 1, 2004.

The two primary components of QUADRAMET, particularly Samarium-153 and EDTMP, are provided to BMSMI by outside suppliers. BMSMI obtains its supply of Samarium-153 from a sole supplier, and EDTMP from another sole supplier. Alternative sources for these components may not be readily available, and any alternate suppliers would have to be identified and qualified, subject to all applicable regulatory guidelines. If BMSMI cannot obtain sufficient quantities of these components on commercially reasonable terms, or in a timely manner, it would be unable to manufacture QUADRAMET on a timely and cost-effective basis. Additionally, QUADRAMET must be manufactured in compliance with regulatory requirements. Any inability on the part of BMSMI to manufacture QUADRAMET, or any failure by BMSMI to comply with all applicable regulatory guidelines, including FDA requirements, and those of the U.S. Nuclear Regulatory Commission, could have a material adverse effect on our business, financial condition and results of operations.

Marketing of QUADRAMET

We currently market QUADRAMET through our in-house specialty sales force.

In October 1998, we entered into an exclusive agreement with Berlex pursuant to which Berlex would market QUADRAMET for us in the United States. Berlex re-launched QUADRAMET in March 1999, and maintained a sales force that targeted its sales efforts on the oncological

community. Pursuant to our agreement with Berlex, we were entitled to royalty payments based on net sales of QUADRAMET and milestone payments based upon sales levels that were achieved.

Table of Contents

In June 2003, we entered into an agreement with Berlex to reacquire marketing rights to QUADRAMET in North America and Latin America in exchange for an upfront payment of $8.0 million and royalties based on future sales of QUADRAMET, subject to our receipt of necessary financing for the reacquisition. On August 1, 2003, we reacquired these marketing rights and we began recording product revenue from the sales of QUADRAMET. We no longer receive royalty revenue from Berlex.

Dow is the owner of the technology upon which we developed QUADRAMET. As such, under our license agreement with Dow, we are required to pay royalties or guaranteed contractual minimum payments, whichever is greater, and certain future payments upon the achievement of certain milestones, to Dow.

Competition Related to Quadramet

Current competitive treatments for bone cancer pain include narcotic analgesics, external beam radiation therapy, bisphosphonates, and other skeletal targeting therapeutic radiopharmaceuticals such as Strontium-89 chloride and Phosphorus-32.

QUADRAMET primarily competes with Strontium-89 chloride in the radiopharmaceutical pain palliation market. Strontium-89 chloride is manufactured and marketed either as Metastron®, by Amersham Health, or in a generic form by Bio-Nucleonics Pharma, Inc. Amersham manufactures Metastron and sells the product through its wholly owned network of radiopharmacies, direct to end-users and through other radiopharmacy distributors. The generic version is distributed directly by the manufacturer, or is sold through radiopharmacy distributors such as Cardinal Health and Custom Care Pharmacy. The first radiopharmaceutical introduced as a metastatic bone cancer pain palliation agent, Phosphorus-32 (P-32), is no longer routinely utilized clinically in the United States.

To meet future competitive challenges to QUADRAMET, we continue to focus our efforts on managing radiopharmacy distributor relationships. We also plan to continue to focus on research supporting additional applications and by documenting the safe and effective use of QUADRAMET when used in conjunction with metastatic disease therapies such as bisphosphonates, chemotherapeutics and hormonal therapy.

MOLECULAR IMAGING/DIAGNOSTIC PRODUCTS AND PRODUCT CANDIDATES

PROSTASCINT

Overview

Our PROSTASCINT molecular imaging agent is the first and currently the only commercial product targeting PSMA, a transmembrane protein that is expressed on prostate cancer cells at all stages of disease, including advanced or metastatic disease. PROSTASCINT consists of a murine monoclonal antibody (7E11-C5) directed against PSMA that is linked to the radioisotope Indium-111. A radioisotope is an element, which, because of nuclear instability, undergoes radioactive decay and emits radiation. Due to the selective expression of PSMA by prostate cancer cells, PROSTASCINT can image the extent and spread of prostate cancer using a common gamma camera.

PROSTASCINT is approved for marketing in the United States in two clinical settings: (i) as a diagnostic imaging agent in newly diagnosed patients with biopsy-proven prostate cancer thought to be clinically localized after standard diagnostic evaluation and who are at high risk for spread of their disease to pelvic lymph nodes; and (ii) for use in post-prostatectomy patients with a rising PSA and a negative or equivocal standard metastatic evaluation in whom there is a high clinical suspicion of occult metastatic disease.

During the molecular imaging procedure, PROSTASCINT is administered intravenously into the patient. The 7E11 antibody in PROSTASCINT travels through the bloodstream and binds to PSMA. The radioactivity from the isotope that has been attached to the antibody can be detected from outside the body by a gamma

Table of Contents

camera. Gamma cameras are found in the nuclear medicine departments of most hospitals. The image captured by the camera assists in the identification of the location of the radiolabeled pharmaceutical thus identifying the sites of tumors.

When deciding on a course of therapy for newly diagnosed prostate cancer, physicians must determine the extent of disease in the patient. Patients are most likely to benefit from local treatment options, such as surgical removal of the prostate gland, when disease has not spread beyond the prostate gland. Patients diagnosed with distant disease (not confined to the prostate gland), have a poorer chance of five-year survival than those with disease confined to the gland.

Prior to the availability of PROSTASCINT, determining whether newly diagnosed disease was limited to the prostate or had spread beyond the gland, for instance to lymph nodes, was based upon statistical inference from the biopsy appearance of the tumor, the patient s level of serum PSA, and the stage of other primary tumors. Conventional imaging methods such as computed tomography (CT) or magnetic resonance (MR) are all relatively insensitive because they rely on identifying significant changes to normal anatomic structure to indicate the presence of disease. PROSTASCINT images are based upon expression of the PSMA molecule and, therefore, may identify disease not readily detectable with conventional procedures, such as CT or MR imaging alone. Clinical studies conducted to date by physicians on our behalf indicate that PROSTASCINT may provide new and useful information not available from other conventional diagnostic modalities regarding the existence, location and extent of a specific disease throughout the body.

In addition, in the United States, following initial therapy, prostate cancer patients are monitored to ascertain changes in the level of serum PSA. In this setting, a consistent rise in PSA is evidence of recurrence of the patient s prostate cancer. Knowledge of the extent and location of disease recurrence is important in choosing the most appropriate form of treatment.

Partners In Excellence Sites

PROSTASCINT is a technique-dependent product that requires a high degree of proficiency in nuclear imaging technology in order to correctly obtain and interpret the scan. We have established a network of accredited nuclear medicine imaging centers through our Partners In Excellence, or PIE, program. Since PROSTASCINT images are traditionally difficult to interpret, each PIE site receives initial training and proficiency evaluations. We only sell PROSTASCINT to qualified PIE sites. As of December 31, 2003, there were approximately 400 PIE sites qualified to perform PROSTASCINT imaging. We plan to add PIE sites on a selective basis and, at the present time, we bear part of the expense of qualifying new sites.

Market Expansion Strategies for PROSTASCINT

We believe that future growth and market penetration of PROSTASCINT is largely dependent upon the implementation and continued research of:

- using PROSTASCINT in conjunction with fusion imaging procedures;
- image enhancement technologies; and

image guided applications, such as therapy, biopsy and combinations of the foregoing.

Fusion imaging. Fusion imaging is an *in vivo* diagnostic technique that combines anatomic and functional information directly from patient studies to provide information that cannot be obtained with separate imaging modalities. Fusion imaging can combine CT or MR with radionuclide imaging using single-photon emission computed tomography (SPECT) to image a radio-labeled agent, such as PROSTASCINT. Approximately 74 of our current PIE sites are proficient in performing fusion imaging with PROSTASCINT, which can be accomplished through either software or hardware solutions. Through alliances discussed in the Strategic

Table of Contents

Relationships and Collaborations Related to PROSTASCINT section that follows, we believe that we may increase the use of fusion imaging with PROSTASCINT.

Image Enhancement Technologies. Gamma cameras used in nuclear medicine have advanced in recent years. Some manufacturers now sell cameras with wider segmented crystals, providing advantages in medium and high energy imaging of isotopes (e.g., Indium-labeled agents, such as PROSTASCINT); thus providing enhanced system sensitivity. System enhancements allow improved image quality or reduced scan time, thereby reducing potential risk of patient motion. Equipment vendors have also recently introduced advanced single-photon emission computed tomography (SPECT) reconstruction algorithms, as well as three dimensional iterative reconstruction techniques which potentially increase image contrast with inherent system gains in image quality. These prominent new nuclear medicine imaging algorithms enable advances in image quality as compared to conventional Filtered Back Projection techniques. In addition, nuclear medicine SPECT images of agents such as PROSTASCINT may now be co-registered with an anatomic image obtained with either CT or MR imaging. Device manufacturers generally offer two methods to achieve co-registration between metabolic and anatomical images. Some manufacturers merge information in a single SPECT/CT system, while others utilize fusion software, which has become more widely available in the past few years, as computer workstations have become powerful enough to achieve co-registration.

Image Guided Therapy. Recent advances in nuclear medicine imaging SPECT equipment, computer workstation power, as well as software enhancements allow researchers to utilize cutting-edge imaging technology to explore novel applications of the enhanced PROSTASCINT image. With fusion of an enhanced SPECT, the PROSTASCINT image is registered with CT and/or MR anatomic images; the resulting images have been applied to clinical research in areas of guided brachytherapy (or radioactive seeds), guided external beam radiation therapy (EBRT), intensity modulated radiation therapy (IMRT) and image guided biopsy. An example of this type of application was described in a 2003 publication reporting four-year biochemical outcome after radioimmunoguided (PROSTASCINT) brachytherapy published in the *International Journal of Radiation Oncology Biology Physics*, Vol. 57, No. 2, pp. 362-370, 2003.

Our products, including PROSTASCINT, are subject to significant regulation by governmental agencies, including the United States Food and Drug Administration, as is more fully described under the section entitled Government Regulation herein. We cannot assure you that we will be able to complete any of our market expansion strategies set forth above.

Clinical Studies Related to PROSTASCINT

To support the foregoing market expansion strategies for PROSTASCINT we currently have active clinical studies sponsored or supported by us which include:

Researchers at Case Western University and University Hospital in Cleveland are comparing uptake of PROSTASCINT within the prostate gland of prostate cancer patients with histopathologic findings of the distribution of cancer in the gland based on whole mount pathology specimens prepared following radical prostatectomy. Some of the patients have also been imaged via positron emission tomography (in addition to PROSTASCINT) to provide for additional comparisons between these two imaging methodologies.

Researchers at The Mayo Clinic in Scottsdale, Arizona are using images of PROSTASCINT distribution within the prostate gland to guide the use of intensity modulated radiation therapy (IMRT) for the treatment of prostate cancer. The purpose of this work is to evaluate whether the use of PROSTASCINT in guiding IMRT allows for delivery of increased doses of radiation specifically to the areas of cancer within the prostate without increasing the level of side effects experienced by the patient.

Researchers at Aultman Hospital, Case Western University and University Hospital in Cleveland are using images of PROSTASCINT distribution within the prostate gland to guide the placement of both I-125 and Pd-103 brachytherapy sources (seeds) for the treatment of prostate cancer. The purpose of this

Table of Contents

work is to evaluate whether the use of PROSTASCINT in guiding brachytherapy implantation allows for delivery of increased doses of radiation specifically to the areas of cancer within the prostate without increasing the level of side effects experienced by the patient.

During 2003, we reported that clinical investigators from cancer research centers throughout the country had presented new clinical data indicating that:

PROSTASCINT-guided prostate brachytherapy results in a high probability of actuarial four-year biochemical disease-free survival for patients with localized prostate cancer. Additional details regarding the conduct and results of this study are available in the *International Journal of Radiation Oncology Biology Physics*, Vol. 57, No. 2, pp. 362-370, 2003.

In a retrospective outcomes study sponsored by us, patients exhibiting a certain pattern of PROSTASCINT distribution, namely uptake in the central abdominal lymph nodes, a finding exhibited in approximately 20% of patients in this study, were significantly more likely to have died in the follow-up period of 4-5 years than patients not exhibiting that pattern of uptake. Additional details regarding the conduct and results of this study are available in the journal *Radiology* 2003; Suppl. 576p (abstract #1076).

In a study supported partially by us, researchers at the University of Chicago Hospitals, Illinois, reported that the use of PROSTASCINT imaging in patients with recurrent prostate cancer undergoing radiation therapy of their disease resulted in significant changes in the regions to which the doses of radiation were planned to be delivered. Additional details regarding the conduct and results of this study are available in the *J. Nucl. Med*., Vol. 45, pages 238-246 (2004).

PROSTASCINT is indicated as a diagnostic imaging agent in newly diagnosed patients with biopsy proven prostate cancer, thought to be clinically localized after standard diagnostic evaluation and who are thought to be at high risk for pelvic lymph node metastases. PROSTASCINT is also indicated in post-prostatectomy patients with a rising PSA and a negative or equivocal standard metastatic evaluation in whom there is a high clinical suspicion of occult metastatic disease.

The foregoing discussion describes clinical applications that differ from that reported in the PROSTASCINT package insert, and that have not been reviewed or approved by FDA. A copy of the full prescribing information for PROSTASCINT may be obtained in the United States from us by calling us toll free at 800-833-3533 or by visiting our web site at www.cytogen.com, which is not part of this Annual Report on Form 10-K.

Intellectual Property Position Related to PROSTASCINT

In 1987, Dr. Julius S. Horoszewicz first identified PSMA in a prostate cancer cell line, known as LNCaP, by generating a monoclonal antibody against the protein. That monoclonal antibody, known as 7E11-C5, is conjugated via a proprietary linker technology to the radioisotope Indium-111 to produce the PROSTASCINT product. Dr. Horoszewicz s original patent claiming the 7E11-C5 antibody, as well as additional patents relating to the PROSTASCINT product and commercialization rights thereto, were assigned to us in 1989. Under our agreement, which we believe will remain in effect until the expiration of the last related patent, we have made, and may continue to make, certain payments to Dr. Horoszewicz.

As of December 31, 2003, we were the owner of several issued United States patents and certain corresponding foreign patents relating to PROSTASCINT. One of these, U.S. Pat. No. 5,162,504, is the original Horoszewicz patent and includes claims directed to the monoclonal

antibody and the cell line that produces it. We have obtained an extension of the term for this U.S. patent, which will now expire October 28, 2010. U.S. Pat. No. 4,671,958 and U.S. Pat. No. 4,741,900, both of which expire June 9, 2004, include claims directed to antibody conjugates such as PROSTASCINT, methods for preparing such conjugates, methods for using such conjugates for *in vivo* imaging, testing and therapeutic treatment, and methods for delivering radioisotopes by linking them to such antibodies. U.S. Pat. No. 4,867,973, which also expires June 9, 2004, includes claims directed to antibody conjugates such as PROSTASCINT, and methods for preparing such conjugates. The

Table of Contents

foregoing patents, which expire in 2004, do not provide the primary patent protection for PROSTASCINT. We also currently own the trademark PROSTASCINT®. We are responsible for the costs of prosecuting and maintaining this intellectual property.

We are defendants in litigation filed against us by Immunomedics, Inc. in the United States Federal Court for the District of New Jersey with respect to claims that PROSTASCINT infringes a third-party patent. Under our agreement with Dr. Horoszewicz, we may offset our litigation expenses against payments we make to Dr. Horoszewicz. We have disclosed certain information regarding this lawsuit under the caption Legal Proceedings , herein.

Manufacturing, Supply and Distribution of PROSTASCINT

In January 2003, we entered into a contract manufacturing and supply agreement with Laureate Pharma L.P., pursuant to which Laureate manufactured and supplied us with PROSTASCINT through December 31, 2003, at which time the agreement expired. Laureate was the sole manufacturer of PROSTASCINT and its primary raw materials, which are antibodies. We currently have no alternative manufacturer or supplier for PROSTASCINT or any of its components. As of December 31, 2003, we had a sufficient level of PROSTASCINT inventory on hand to satisfy our requirements into 2005. We intend to negotiate and engage Laureate or another suitable manufacturer to supply us with PROSTASCINT for subsequent periods. Our failure to procure a sufficient supply of PROSTASCINT, or our failure to procure such a supply on commercially reasonable terms, will have a material adverse effect on our business, financial condition and results of operations.

Additionally, PROSTASCINT must be manufactured in compliance with regulatory requirements and at commercially acceptable costs. Prior to January 2004, PROSTASCINT was manufactured at a current good manufacturing practices, or cGMP, compliant manufacturing facility in Princeton, New Jersey which is operated by Laureate. In July 2000, we entered into a development and manufacturing agreement with DSM Biologics Company B.V., pursuant to which DSM conducted certain development activities with respect to PROSTASCINT for testing and evaluation purposes. Our relationship with DSM was subsequently terminated.

PROSTASCINT is distributed for us by CORD Logistics, Inc., a subsidiary of Cardinal Health Inc. under the terms of a distribution services agreement dated March 1, 1999. Pursuant to the agreement, CORD is the exclusive distribution agent of PROSTASCINT in the United States. The initial term of the agreement was for three years. Upon completion of the initial three year term, the agreement was renewed for a one year period, and pursuant to the terms of a May 2003 amendment thereto, will remain in effect until May 19, 2005.

Any arrangement that we enter into with respect to the manufacture, supply or distribution of PROSTASCINT will be subject to FDA oversight. Any failure on our part, or the part of our business partners, to comply with all applicable regulations and FDA requirements will have a material adverse effect on our business, financial condition and results of operations.

Marketing of PROSTASCINT

We market PROSTASCINT, using our in-house specialty sales force to hospitals, diagnostic imaging centers, radiopharmacies, urologists, radiation oncologists and nuclear medicine physicians. Within this sales force are technical specialists who assist in the training of nuclear medicine technologists and nuclear medicine physicians who administer the PIE site qualification process for nuclear imaging centers to perform PROSTASCINT imaging.

Competition Related to PROSTASCINT

The spread of prostate cancer to lymph nodes may be evaluated by a number of imaging modalities, including computed tomography, magnetic resonance imaging, or positron emission tomography.

Table of Contents

Strategic Relationships and Collaborations Related to PROSTASCINT

In June 2003, we entered into a relationship with Siemens Medical Solutions and the University Hospitals of Cleveland to promote advances in prostate cancer imaging. Through this arrangement, physicians at the University Hospitals of Cleveland are using the Siemens e.cam gamma camera with Flash 3D iterative reconstruction and CT attenuation correction technology in combination with PROSTASCINT. We hope to explore advances in the use and application of imaging software through our relationship with Siemens.

Also, in June 2003, we entered into an alliance with GE Medical Systems, a unit of the General Electric Company, to market a total molecular imaging system to help evaluate the extent and spread of prostate cancer by integrating GE Medical s Infinia Hawkeye® imaging system with our PROSTASCINT imaging agent. GE s Infinia Hawkeye imaging system combines the anatomic detail of computed tomography (CT) with the molecular imaging data provided by nuclear medicine cameras using products such as PROSTASCINT. The Infinia Hawkeye provides CT-based attenuation correction and localization for single-photon emission computed tomography (SPECT) studies that can help address the inherent limitations of SPECT imaging. Our agreement with GE provides that Cytogen and GE will work together to advance patient and physician awareness of fusion imaging. GE Medical Systems will maintain installation and customer service activities, while Cytogen will provide technical support for PROSTASCINT fusion imaging.

NMP22 BLADDERCHEK

Overview

NMP22 BLADDERCHEK is a point-of-care *in vitro* diagnostic test for bladder cancer developed by Matritech, Inc.

In October 2002, we entered into a five-year agreement with Matritech to be the sole distributor for NMP22 BLADDERCHEK to urologists and oncologists in the United States. Matritech has retained rights to market NMP22 BLADDERCHEK directly to physicians other than oncologists, such as primary care physicians. In October 2003, we executed an amendment to our agreement that provides that, as of November 8, 2003, we had the non-exclusive right to market and sell NMP22 BLADDERCHEK to urologists until December 31, 2003 and the exclusive right to continue to sell NMP22 BLADDERCHEK to oncologists until December 31, 2004. The amended agreement is renewable annually upon the mutual consent of the parties. We are not subject to any minimum sales targets or other similar obligations under our agreement with Matritech, as amended.

Polymedco manufactures BTAStat®, a point of care urine-based test approved for monitoring bladder cancer patients. BTAStat, marketed by Mentor, competes with NMP22 BLADDERCHEK. NMP22 BLADDERCHEK is, however, the only point of care urine-based test approved for both monitoring and diagnosis of bladder cancer.

COMBIDEX

Overview

COMBIDEX (ferumoxtran-10), which was developed by Advanced Magnetics, Inc., is currently under review by the United States Food and Drug Administration. We cannot market or sell COMBIDEX until Advanced Magnetics receives the appropriate regulatory approvals, and we cannot assure you that Advanced Magnetics will receive such approvals in a timely basis, or at all.

COMBIDEX is an ultrasmall superparamagnetic iron oxide nanoparticle designed to facilitate the differentiation between malignant and non-malignant lymph nodes using magnetic resonance (MR) imaging. COMBIDEX is administered via a 30 minute infusion and accumulates preferentially in non-cancerous lymph node tissue, thus facilitating the differentiation between malignant and non-malignant lymph nodes.

Table of Contents

Numerous cancers spread via the lymphatic system. Common imaging modalities currently used for imaging lymph nodes are CT and MR imaging. Under these existing modalities, normal nodes are distinguished from cancerous nodes solely on the basis of size. Lymph nodes less than ten millimeters in size are often assumed to be normal and lymph nodes greater than ten millimeters in size are often presumed cancerous. Contrast imaging with COMBIDEX, which is not based on size of the lymph nodes, may prove more effective in distinguishing cancerous from non-cancerous lymph nodes.

The American Cancer Society estimated that there would be 900,800 newly diagnosed patients with cancers that potentially metastasize in this manner in 2003. Many of these patients may require, and benefit from, diagnostic tools such as COMBIDEX-enhanced magnetic resonance imaging, to help differentiate malignant from non-malignant lymph nodes, irrespective of node size.

Clinical Data Related to COMBIDEX

In May 2003, Advanced Magnetics and Cytogen announced the presentation of data showing that MR imaging using COMBIDEX helps in the determination of the spread of testicular cancer to lymph nodes. This data, from a study conducted at Massachusetts General Hospital, showed improved accuracy for lymph node characterization, potentially resulting in better patient management. The data involved 13 lymph nodes from 11 patients with proven testicular cancer, all of whom were scheduled for CT guided nodal biopsy. The researchers performed MR imaging of lymph nodes within 24 to 36 hours after the administration of COMBIDEX. When imaging evaluation results were compared to histopathologic analysis, lymph node staging with COMBIDEX was 92% accurate in identifying malignant disease.

In June 2003, Advanced Magnetics and Cytogen announced the publication of clinical data in the *New England Journal of Medicine* (2003, Vol. 348, No. 25, pages 2491-2499) showing that MR imaging with COMBIDEX may aid in the non-invasive evaluation of lymph nodes in patients with prostate cancer. Researchers at Massachusetts General Hospital and the University Medical Center Nijmegen in the Netherlands, concluded that the use of COMBIDEX-enhanced MR imaging allows for the detection of small and otherwise undetectable lymph node metastases in patients with prostate cancer. The study involved 40 patients from MGH and 40 patients from UMCN with prostate cancer, who were scheduled either for surgical lymph node resection or nodal biopsy. The researchers performed MR imaging before and 24 hours after the administration of COMBIDEX. In one of the evaluations done, the researchers determined whether or not each patient had any metastatic nodes. For these evaluations on a patient-by-patient basis, when the before and after MR scans were compared to pathology, the use of COMBIDEX-enhanced MR imaging improved accuracy from 65% to 98% and improved the positive predictive value from 60% to 94%. Sensitivity, the probability that the diagnosis is positive given the presence of disease, increased from 45% to 100%. Specificity, the likelihood that given the absence of disease the diagnosis is negative, increased from 79% to 96%. Of the 33 patients in whom metastatic disease was found, the researchers noted that 9 of those patients had metastatic lymph nodes outside of the standard area for surgical exploration that would not have been found by current standard diagnostic procedures. Additionally, the researchers analyzed the results based on the diagnosis of each individual node. Results of the node-by-node diagnoses with COMBIDEX showed accuracy of 97%, sensitivity of 91%, specificity of 98% and a positive predictive value of 95%. Of the nodes that were determined malignant by pathology, 71% were 10 millimeters or less in size and therefore did not fulfill the traditional imaging criteria for malignancy. Nodal evaluation using COMBIDEX-enhanced images for nodes between 5 millimeters and 10 millimeters in size resulted in accuracy of 99%, sensitivity of 96%, specificity of 99% and an increase in the positive predictive value compared to unenhanced MR images from 29% to 96%.

In September 2003, Advanced Magnetics and Cytogen announced that data from a Phase III clinical study of COMBIDEX in lymph nodes was published in the journal *Radiology*. The data showed that MR imaging with COMBIDEX may aid in the non-invasive evaluation of metastatic lymph nodes in patients with head and neck, chest, breast, abdominal, and pelvic cancers. This study included 147 patients with primary malignancies who were suspected of having nodal metastases of which 29 had head and neck cancer, 32 had lung or mediastinal

Table of Contents

cancer, 23 had breast cancer, 25 had abdominal cancer, 38 had pelvic cancer, and 2 patients had both abdominal and pelvic cancers. For each patient, MR imaging was performed before the administration of COMBIDEX and 24-36 hours after COMBIDEX administration. The MR imaging results were correlated with pathology. No serious adverse events were reported. Overall the data demonstrated that COMBIDEX-enhanced MR imaging improved diagnostic accuracy from 68% to 85% as compared to MR imaging prior to the administration of COMBIDEX.

In April 2003, Advanced Magnetics and Cytogen announced the presentation of data from two separate studies with results suggesting that imaging with COMBIDEX may be useful in defining the periphery of residual and primary brain, head and neck tumors.

The first study, conducted at the University of Washington, reported MR imaging of 15 patients with primary head and neck cancers 24 hours after the administration of COMBIDEX. In 7 of 15 patients, a dark rim was clearly visible at the tumor margin on the post-COMBIDEX images. When imaging evaluation results were compared to histopathologic analysis, iron deposition within macrophages or other inflammatory cells was found predominantly at the periphery of the tumor, and to a lesser extent within the tumor. Researchers found that COMBIDEX may be valuable not only for detecting lymph node metastatsis but also for defining the margin of primary head and neck tumors.

Another study, conducted at Oregon Health and Sciences University, involved 7 patients in whom researchers investigated the value of both Gadolinium-enhanced and COMBIDEX-enhanced MR imaging in assessing malignant brain tumors pre- and post-operatively. The MR imaging with Gadolinium was done at least 24 hours prior to COMBIDEX administration. MR images were then obtained 24 hours after COMBIDEX administration followed by surgery on the same day. Post-operative MR was performed approximately 18 hours after surgery. All malignant tumors showed COMBIDEX accumulation around the periphery of the tumor, which was shown to be in the inflammatory cells on histological analysis. In 5 of the 7 patients there were tumors enhanced by COMBIDEX, but not by Gadolinium. In 1 case available for follow-up, Gadolinium enhancement did develop and progressed in these areas. In 4 of the 7 cases, comparison of the pre- and post-operative COMBIDEX-enhanced MR imaging revealed residual COMBIDEX enhancement, thus avoiding the need to re-administer contrast during post-operative MR imaging to evaluate residual disease.

Agreement with Advanced Magnetics, Inc.

In August 2000, we entered into a license and marketing agreement and a supply agreement with Advanced Magnetics, Inc. for COMBIDEX, for all applications, and ferumoxytol (formerly referred to as Code 7228), for oncology applications only. At this time Advanced Magnetics does not intend to develop ferumoxytol for oncology imaging. Pursuant to the terms of the license agreement, we obtained the exclusive right in the United States to market, distribute and sell COMBIDEX. Advanced Magnetics is continuing its discussions with the FDA relating to outstanding issues regarding an approvable letter received from the FDA dated June 2000, in an effort to bring COMBIDEX to market. The license agreement will continue until August 25, 2010, and shall thereafter automatically renew for successive five year periods, unless notice of non-renewal or termination is given by us or Advanced Magnetics 90 days prior to the commencement of any renewal period.

Upon execution of our agreements with Advanced Magnetics in 2000, we issued 200,000 shares of common stock to Advanced Magnetics. Of such 200,000 shares, 25,000 are being held in escrow pending the achievement of certain milestones relating to COMBIDEX and 25,000 are being held in escrow pending the achievement of certain milestones relating to ferumoxytol. The remaining 150,000 shares were transferred to Advanced Magnetics, subject to certain restrictions, such restrictions having subsequently expired. We remain obligated to make royalty payments, which are subject to certain minimum amounts, to Advanced Magnetics on sales of COMBIDEX we may make, upon the receipt of all requisite regulatory approvals.

Under the terms of the supply agreement, Advanced Magnetics has agreed to manufacture and supply us with COMBIDEX at fixed prices, subject to certain adjustments. The supply agreement is coterminus with the license agreement.

Table of Contents

There can be no assurance that Advanced Magnetics will receive FDA approval for COMBIDEX or ferumoxytol.

DISCONTINUED PRODUCTS

BRACHYSEED

In December 2000, we entered into a 10-year agreement with Draximage Inc., the radiopharmaceutical subsidiary of Draxis Health, Inc. to market and distribute Draximage s BRACHYSEED® implants in the United States. On January 24, 2003, we provided Draximage with notice of termination for each of our license and distribution agreement and product manufacturing and supply agreement with respect to both of Draximage s BRACHYSEED Iodine-125 and BRACHYSEED Palladium-103 products and, as of January 2003, we no longer accepted or filled new orders for the BRACHYSEED products. On April 8, 2003, we formally terminated these agreements and announced the amicable resolution of all open matters with Draximage. We also agreed with Draximage to maintain the confidentiality of each other s proprietary information, released each other from all other liability with respect to any claims under such agreements, and agreed to certain indemnification obligations with respect to third party claims.

ONCOSCINT CR/OV

In December 2002, we discontinued marketing, selling and producing ONCOSCINT CR/OV, a monoclonal antibody diagnostic imaging agent for the detection of the spread of colorectal and ovarian cancer. The market for ONCOSCINT CR/OV for colorectal cancer diagnosis was negatively affected by positron emission tomography, or PET , scans, which have been shown to have similar or higher sensitivity than the ONCOSCINT CR/OV scan.

RESEARCH AND DEVELOPMENT

AGGREGATE EXPENDITURES

Our research and development expenses over the past three years were:

2003 $ 6.1 million

2002 $ 10.5 million

2001 $ 10.4 million

We intend to pursue research and development activities having commercial potential and to review all of our programs to determine whether possible market opportunities provide an adequate return to justify the commitment of human and economic resources to their initiation or continuation. The major components of our research and development programs and expenditures are set forth below.

TECHNOLOGY

Prostate-Specific Membrane Antigen (PSMA)

PSMA is a transmembrane protein that is an important genetic marker associated with prostate cancer. Dr. Julius S. Horoszewicz identified the PSMA protein using a monoclonal antibody in 1987. The antibody technology developed by Dr. Horoszewicz was assigned to us. Later, researchers at the Sloan-Kettering Institute for Cancer Research identified and sequenced the gene encoding PSMA, and we acquired an exclusive worldwide license to that and related technologies. From these technologies, we have put one product on the market, PROSTASCINT, and we are building a pipeline of potential new products in research and development.

Table of Contents

These pipeline products are focused primarily on novel vaccine and antibody therapies for prostate and other cancers.

PSMA has also been found to be present at high levels in the new blood vessels or neovasculature formed in association with a variety of major solid tumors other than prostate cancers. Such neovasculature is necessary for the growth and survival of many types of solid tumors. We believe that, due to the unique characteristics of this antigen, technologies utilizing PSMA can yield novel products for the treatment and diagnosis of cancer. If PSMA-targeted therapies can destroy or prevent formation of these new blood vessels, we believe that such therapies may prove valuable in treating a broad range of cancers.

In 1993, we entered into an option and license agreement with the Sloan Kettering Institute for Cancer Research (SKICR), and began a development program with SKICR involving PSMA and our proprietary monoclonal antibody. In November 1996, we exercised our option and obtained an exclusive worldwide license to this technology. Under our agreement with SKICR, we received, or subsequently obtained, rights to patents and patent applications including: U.S. Pat. Nos. 5,538,866 (expiring July 23, 2013), 5,935,818 (expiring August 10, 2016), and 6,569,432 (expiring February 24, 2015), and U.S. Pat. Appln. Nos. 08/403,803 (filed March 17, 1995), 08/466,381 (filed June 6, 1995), 08/470,735 (filed June 6, 1995), 08/481,916 (filed June 7, 1995), 08/894,583 (filed February 23, 1998), 09/724,026 (filed November 28, 2000), 09/990,595 (November 21, 2001), 10/012,169 (filed October 24, 2001), 10/443,694 (filed May 21, 2003), and 10/614,625 (filed July 2, 2003). The filing, prosecution and maintenance of licensed patents, as defined in the agreement, is the responsibility of SKICR, but shall be at the discretion and expense of Cytogen. In the event that we decide not to file, prosecute or maintain any part of the licensed patents, SKICR may do so at its own expense.

The term of the license shall end on the date of expiration of the last to expire of the licensed patents unless it earlier terminates by operation of law or by acts of the parties in accordance with the terms of the agreement. The license agreement is also terminable by Cytogen upon 60 days notice to SKICR. Additionally, upon execution of an agreement with SKICR, we paid to SKICR an option fee, a license fee and reimbursement for patent expenses paid by SKICR. We remain obligated to make certain royalty payments, which are subject to certain minimum amounts and other annual payments to SKICR, for the term of the agreement.

In 2000, we executed a sublicense agreement with Northwest Biotherapeutics Inc. pursuant to which we granted Northwest the right to make and use PSMA for *ex vivo* prostate cancer immunotherapy. In December 2002, we announced that we had regained our rights to *ex vivo* prostate cancer immunotherapy using PSMA, in connection with the termination of our agreement with Northwest.

PSMA Development Company LLC

In 1999, we entered into a joint venture with Progenics Pharmaceuticals, Inc. to develop *in vivo* immunotherapeutic products utilizing PSMA. These product candidates currently include antibody-based immunotherapies for prostate cancer, a therapeutic prostate cancer vaccine utilizing the PSMA gene and a vector delivery system, and a recombinant form of the PSMA protein as a basis for immune stimulation. We believe that these product candidates, if successfully developed, could play an important role in the treatment of prostate cancer. We believe there are significant unmet needs for treatment and monitoring of this disease.

The joint venture is owned equally by Progenics and us. We have exclusively licensed to the joint venture certain immunotherapeutic applications of our PSMA patent rights and know-how. Progenics has funded the first $3.0 million of development costs, in addition to $2.0 million in supplemental capital contributions funded at certain dates. In connection with the licensing of our PSMA technology to the joint venture in June 1999, we recognized approximately $1.8 million in license fee revenue. Beginning in December 2001, we and Progenics began sharing costs of the program.

In 2003, we incurred expenses of $3.5 million relating to our half of the expenses for the programs at the joint venture, compared to $2.9 million in 2002. The joint venture is funded by equal capital contributions from

Table of Contents

each of Progenics and Cytogen in accordance with an annual budget approved by the joint venture representatives from each such party. In January 2004, we and Progenics: (i) agreed to a work plan governing the activities of the joint venture for the remainder of 2004; and (ii) agreed to a budget for the joint venture s operations for 2004 and certain related capital contributions of the parties. The joint venture s work plan, budget, and other operational and financial matters relating to periods after 2004 will require the further agreement of Progenics and us. During 2004, we expect to incur expenses of approximately $4.6 million relating to our half of the expenses for the joint venture. We have not committed to fund the joint venture beyond December 31, 2004 at this time, but for existing contractual commitments as of that date. Contract research and development services provided by Progenics to the joint venture during 2003 were in accordance with a services agreement between the parties which expired on January 31, 2004. Cytogen also provided minimal services to the joint venture. We are discussing the terms of a new services agreement with Progenics and we and Progenics continue to perform research and development in accordance with the approved annual budget and work plan for 2004. We believe that if mutual agreement is not achieved with respect to a new service agreement, the parties can successfully negotiate with outside third parties for necessary services.

We have North American marketing rights to products developed by the joint venture and a right of first negotiation with respect to marketing activities in any territory outside North America. We anticipate initiation of marketing efforts for any product developed upon approval by the FDA or requisite foreign regulatory bodies, as applicable. If approved, we anticipate marketing these products with our own sales force and will be reimbursed by the joint venture for these costs. We will split the net profit equally with Progenics for any products developed by the joint venture, assuming there is no change in our existing ownership interests.

Clinical Data Related to PSMA

In November 2003, the joint venture announced publication of new findings, published in the November 2003 issue of the *Proceedings of the National Academy of Sciences USA*, that PSMA exists on human cancer cells as a homodimer, a protein complex consisting of two identical PSMA chains. Importantly, researchers also found that when recombinant soluble PSMA (rsPSMA) was used as a cancer vaccine in an animal model, dimer but not monomer efficiently elicited antibodies that recognized PSMA-expressing tumor cells. In addition, researchers at the joint venture reported the discovery of fully human monoclonal antibodies that specifically recognize dimeric but not monomeric rsPSMA. Such antibodies represent candidates for therapy by virtue of their specificity for dimeric PSMA as found on tumor cells. The joint venture is currently conducting a Phase 1 clinical study of a therapeutic prostate cancer vaccine based on a novel proprietary form of dimeric rsPSMA.

We are currently pursuing three research and development programs at the joint venture:

Monoclonal Antibody Program. The PSMA monoclonal antibody program is currently in the preclinical development stage. The joint venture is utilizing fully human monoclonal antibodies, derived from Abgenix s Xenomouse™ technology, in conjunction with naked, radio-labeled and toxin-labeled approaches, to treat prostate cancer.

Viral Vector Vaccine Program. The joint venture is developing a novel, alphavirus vaccine for prostate cancer that induces both antibodies and cytotoxic T cells. The joint venture is currently working with AlphaVax and Greer Laboratories to use the Alphavax Replicon Vector(ArV) system to develop a prostate cancer vaccine using the PSMA antigen. To date, preclinical and clinical batches have been manufactured and stability and preclinical toxicology studies have been initiated and are ongoing.

Recombinant Soluble PSMA Vaccine Program. In December 2002, the joint venture announced the initiation of a Phase I clinical trial for the testing of a novel therapeutic prostate cancer vaccine directed against PSMA. This trial is being conducted through a physician s IND by the Memorial Sloan Kettering Cancer Center.

Strategic Relationships, Collaborations and Licensing Arrangements Related to PSMA

AlphaVax Human Vaccines, Inc. During 2001, the joint venture entered into a worldwide exclusive licensing agreement with AlphaVax Human Vaccines, Inc. to use the Alphavax Replicon Vector(ArV) system

Table of Contents

to create a therapeutic prostate cancer vaccine incorporating the PSMA antigen. In consideration for the license, the joint venture paid a nonrefundable, noncreditable license fee and is obligated to pay additional payments upon the occurrence of certain defined milestones associated with the development and commercialization program for products incorporating the ArV technology. In addition, the joint venture is required to pay an annual maintenance fee until the commencement of commercial sales of products and then royalties based on net sales of products. The joint venture has the right to terminate this agreement upon 30 days prior written notice. We believe that this technology, if successfully deployed, may have important advantages in targeting immune stimulating cells *in vivo* which impact on the progression of cancer.

Abgenix, Inc. During 2001, the joint venture entered into an agreement with Abgenix, Inc. regarding the development of fully human antibodies to PSMA using Abgenix s Xenomouse™ technology. In consideration for the license, the joint venture paid a nonrefundable, noncreditable license fee and is obligated to pay additional license fees on each of the first three anniversary dates and milestone payments upon the occurrence of certain defined milestones associated with the development and commercialization program for products incorporating an antibody generated utilizing the Xenomouse technology. In addition, the joint venture is required to pay royalties based upon net sales of antibody products sold thereunder. If not terminated early, the agreement continues until the expiration of the joint venture s obligation to pay royalties under the agreement to Abgenix. In August 2003, the joint venture entered into a manufacturing agreement with Abgenix for the production of clinical supplies in the PSMA human monoclonal antibody program. The joint venture has the right to terminate either of these agreements upon 30 days prior written notice.

In connection with the agreements discussed above, the joint venture has recognized contractual payments, including license fees, which are included in research and development expenses, totaling approximately $300,000, $200,000, and $400,000 for the years ended December 31, 2003, 2002, and 2001, respectively. In addition, as of December 31, 2003, remaining potential payments associated with milestones and defined objectives with respect to the above agreements total approximately $13.5 million. Future annual minimum royalties under the agreements described above are not significant.

AxCell Biosciences

Further research and development efforts are carried out through our subsidiary, AxCell Biosciences Corporation, which remains engaged in the research and development of novel biopharmaceutical products using its collection of proprietary signal transduction pathway information, despite significant reductions in AxCell s workforce in 2002.

AxCell uses its proprietary technology as a tool to provide academic, governmental and commercial collaborators with vital information about signal transduction pathways that can be used for drug discovery and development. AxCell provides this information rapidly and efficiently, using the proprietary methods and systems that AxCell developed to identify signal transduction pathways. We have successfully leveraged our technology through research collaborations with Mount Sinai School of Medicine, National Cancer Institute, Kimmel Cancer Center at Thomas Jefferson University, University of Muenster in Germany and Celgene Corporation. These collaborations increase our research resources, improve our technological strength and establish valuable development relationships with potential commercial opportunities.

A majority of the drugs on the market today are agents that interact with cell surface receptors. Surface receptors, however, are generally associated with multiple intracellular signaling pathways and, as a result, drugs targeting these receptors are less specific to the disease, which may lead to reduced efficacy and/or unwanted side effects. By targeting intracellular proteins downstream from the surface receptor, a drug can more precisely initiate the desired cellular response, which may lead to treatments with greater efficacy and fewer side effects. Many proteins along these intracellular pathways communicate with each other through structurally and functionally defined modules, called domains, and their respective binding partners called ligands. The

17

Table of Contents

modular and well-defined nature of these domain-ligand interactions makes them ideal drug targets for developing small inhibitory molecules.

One of the historical challenges to design small molecule inhibitors for domain-ligand interactions is the fact that domains are highly homologous within each domain family making it difficult to develop a highly specific inhibitor for a particular interaction. AxCell overcomes this problem through the exact determination of specificity boundaries for each domain-ligand interaction. This biochemical approach integrates parallel synthesis of peptides, protein expression and high-throughput screening methodology combined with tools of bioinformatics.

AxCell has the only high throughput platform for the systematic identification and characterization of domain-mediated intracellular pathways, which can be combined with many levels of biological information to understand how they work together in a systems biology approach. Using its proprietary technologies, AxCell has made significant technical progress over the past several years and is currently applying its pathway content and knowledge to accelerate the development of targeted drugs in certain therapeutic categories through both internal efforts and external research collaborations with corporate, government and academic institutions.

In March 1993, we entered into a license agreement with The University of North Carolina at Chapel Hill, pursuant to which UNC granted us an exclusive world-wide license with respect to certain technology, patents and patent applications which relate to certain aspects of proteomics technology, including phage display. These patents include: U.S. Pat. Nos. 5,498,538 (expiring March 12, 2013), 5,625,033 (expiring April 29, 2014), 5,747,334 (expiring May 5, 2015), 5,844,076 (expiring December 1, 2015), 5,852,167 (expiring December 22, 2015), 5,935,823 (expiring August 10, 2016), 6,011,137 (expiring April 3, 2016), 6,184,205 (expiring July 22, 2014), 6,303,574 (expiring July 22, 2014), 6,309,820 (expiring April 7, 2015), and 6,432,920 (expiring July 22, 2014), and U.S. Pat. Appln. Nos. 09/879,957 (filed June 13, 2001), 09/938,315 (filed August 23, 2001), 10/161,791 (filed May 31, 2002), and 10/185,050 (filed June 28, 2002). We are responsible for the costs of filing, prosecuting and maintaining domestic and foreign patents and patent applications under an agreement with UNC.

The agreement commenced on March 10, 1993 and will expire, unless earlier terminated as provided therein, upon the expiration of the last to expire of the licensed patents that cover a licensed product. Under the agreement, we are required to make certain milestone and royalty payments, which are subject to certain minimum amounts, to UNC.

OTHER STRATEGIC RELATIONSHIPS

Our strategy is to use alliances with other companies to increase our financial resources, reduce risk and retain an appropriate level of ownership of products currently in development. In addition, through alliances with other pharmaceutical and biotechnology companies, we may obtain funding, expand existing programs, learn of new technologies, and gain additional expertise in developing and marketing products.

Antisoma Research Limited. In September 2003, Antisoma Research Limited acquired certain royalty rights to its lead product, R1549 (formerly Pemtumomab), from Cytogen. In connection with Antisoma s acquisition of these rights, Antisoma made a cash payment to us of $500,000. Antisoma also agreed to make an additional payment of $500,000 to us upon the first commercial sale, if any, of the R1549 product. In return, we relinquished our right to receive royalties equivalent to 1.65% of future net sales, if any, of the R1549 product.

Elan Corporation, plc. In December 1995, we entered into a license agreement granting Elan worldwide rights to a group of peptides and associated technology for orally administered drugs that are transported across the gastrointestinal epithelium, as well as rights to other orally delivered drugs derived from related research programs. Elan is responsible for the further development and commercialization of this

technology. We are entitled to royalties from sales of any product developed and commercialized based on this technology. In addition, we are the co-owners with Elan of patents and patent applications developed under the agreement,

Table of Contents

including U.S. Pat. No. 6,703,362 (expiring May 15, 2018), and U.S. Pat. Appln. Nos. 09/079,678 (filed May 15, 1998) and 09/079,819 (filed May 15, 1998).

Northwest Biotherapeutics, Inc. In August 2002, we entered into an agreement with Northwest Biotherapeutics that gave Northwest Biotherapeutics a license to develop and commercialize *ex vivo* immunotherapy products for prostate cancer that are produced by pulsing isolated populations of a patient s antigen presenting cells, such as dendritic cells, with PSMA. Northwest Biotherapeutics advanced their program to the initiation of Phase III clinical trials before terminating the program in November 2002, which resulted in a termination of the license agreement and Cytogen regaining rights to *ex vivo* prostate cancer immunotherapy using PSMA. Based on data demonstrating a favorable safety and clinical response in prostate cancer patients treated to date using PSMA-based *ex vivo* immunotherapy, Cytogen is pursuing other collaborations or partnerships to realize the clinical and commercial potential of this approach.

PRODUCT CONTRIBUTION TO REVENUES

PROSTASCINT and QUADRAMET account for, and, prior to its discontinuation in January 2003, BRACHYSEED accounted for, a significant percentage of our total revenues. For the years ended December 31, 2003, 2002 and 2001, revenues related to PROSTASCINT accounted for approximately 47%, 61% and 65%, respectively, of our total revenues; revenues related to QUADRAMET accounted for approximately 28%, 14% and 18%, respectively, of our total revenues; and revenues related to BRACHYSEED accounted for approximately 2%, 19% and 7%, respectively, of our total revenues. In April 2003, we announced the termination of our agreements with Draximage with respect to the BRACHYSEED products.

CONCENTRATION OF SALES

During the year ended December 31, 2003, we received 69% of our total revenues from four customers, as follows: 23% from Berlex Laboratories, Inc., 14% from Mallinckrodt Inc., 8% from Amersham Health (formerly Medi-Physics), and 24% from Cardinal Health (formerly Syncor International Corporation).

COMPETITION

The biotechnology and pharmaceutical industries are subject to intense competition, including competition from large pharmaceutical companies, biotechnology companies and other companies, universities and research institutions. Our existing therapeutic and imaging/diagnostic products compete with the products of a wide variety of other firms, including firms that provide products used in more traditional therapies or procedures, such as external beam radiation, chemotherapy agents, narcotic analgesics and other imaging/diagnostics. In addition, our existing and potential competitors may be able to develop technologies that are as effective as, or more effective than those offered by us, which would render our products noncompetitive or obsolete. Moreover, many of our existing and potential competitors have substantially greater financial, marketing, sales, manufacturing, distribution and technological resources than we do. Our existing and potential competitors may be in the process of seeking FDA or foreign regulatory approval for their respective products or may also enjoy substantial advantages over us in terms of research and development expertise, experience in conducting clinical trials, experience in regulatory matters, manufacturing efficiency, name recognition, sales and marketing expertise and established distribution channels. We believe that competition for our products is based upon several factors, including product efficacy, safety, cost-effectiveness, ease of use, availability, price, patent position and effective product promotion.

We expect competition to intensify in the fields in which we are involved, as technical advances in such fields are made and become more widely known. We cannot assure you, however, that we or our collaborative partners will be able to develop our products successfully or that we will obtain patents to provide protection against competitors. Moreover, we cannot assure you that our competitors will not succeed in developing therapeutic or imaging/diagnostic products that circumvent our products or that these competitors will not

Table of Contents

succeed in developing technologies or products that are more effective than those developed by us. In addition, many of these companies may have more experience in establishing third-party reimbursement for their products. Accordingly, we cannot assure you that we will be able to compete effectively against existing or potential competitors or that competition will not have a material adverse effect on our business, financial condition and results of operations.

INTELLECTUAL PROPERTY

We believe that our success depends in part on our ability to protect our products and technology through patents and trade secrets. Accordingly, our policy is to pursue a vigorous program of securing and maintaining patent and trade secret protection to preserve our right to exploit the results of our research and development activities and, to the extent it may be necessary or advisable, to exclude others from appropriating our proprietary technology.

We aggressively protect our proprietary technology by selectively seeking patent protection in a worldwide program. In addition to the United States, we file patent applications in Canada, major European countries, Japan and additional foreign countries on a selective basis to protect inventions important to the development of our business. We believe that the countries in which we have obtained and are seeking patent coverage for our proprietary technology represent the major focus of the pharmaceutical industry in which we will market our respective products.

We also rely upon, and intend to continue to rely upon, trade secrets, unpatented proprietary know-how and continuing technological innovation to develop and maintain our competitive position. It is our policy to require our employees, consultants, licensees, outside scientific collaborators, sponsored researchers and other advisors to execute confidentiality agreements upon the commencement of employment or consulting relationships with us. These agreements also provide that all confidential information developed or made known to the individual during the course of the individual s relationship with us is to be kept confidential and not disclosed to third parties except in specific circumstances. In the case of employees, the agreements provide that all inventions conceived by the individual shall be our exclusive property. There can be no assurances, however, that these agreements will provide meaningful protection or adequate remedies for our trade secrets in the event of unauthorized use or disclosure of such information.

We believe that our valuable proprietary information is protected to the fullest extent commercially reasonable; however, we cannot assure you that:

- additional patents will be issued to us in any or all appropriate jurisdictions;
- litigation will not be commenced seeking to challenge our patent protection or that challenges will not be successful;
- our processes or products do not or will not infringe upon the patents of third parties; or
- the scope of patents issued will successfully prevent third parties from developing similar and competitive products.

The technology applicable to our products is developing rapidly. A substantial number of patents have been issued to other biotechnology companies relating to PSMA. In addition, competitors have filed applications for, have been issued, or may otherwise obtain patents and other

proprietary rights relating to products or processes that are competitive with ours. In addition, others may have filed patent applications and may have been issued patents relating to products and technologies potentially useful to us or necessary to commercialize our products or to achieve our business goals. We cannot assure you that we will be able to obtain licenses to such patents on commercially reasonable terms if at all. The failure to obtain licenses to such patents could prevent us from commercializing products or services covered by such patents.

Table of Contents

We cannot predict how any patent litigation will affect our efforts to develop, manufacture or market our products.

GOVERNMENT REGULATION

The development, manufacture and sale of medical products utilizing our technology are governed by a variety of federal, state and local statutes and regulations in the United States and by comparable laws and agency regulations in most foreign countries. Our two actively marketed products consist of a biologic (PROSTASCINT) and a drug (QUADRAMET). Future applications for these may include expanded indications and could result in additional drugs, biologics, devices or combination products. Our product development pipeline contains various other products, the majority of which will likely be classified as new drugs or biologics.

In the United States, medical products that we currently market or intend to develop are regulated by the Food and Drug Administration (FDA) under the Federal Food, Drug, and Cosmetic Act (FDC Act) and the Public Health Service Act, and the rules and regulations promulgated thereunder. These laws and regulations require, among other things, carefully controlled research and preclinical and clinical testing of products, government notification, review and/or approval or clearance prior to investigating or marketing the product, inspection of manufacturing and production facilities, adherence to current Good Manufacturing Practices (cGMP), and compliance with product and manufacturer specifications or standards, and requirements for reporting, advertising, promotion, export, packaging, and labeling, and other applicable regulations.

The FDC Act requires that our products be manufactured in FDA registered facilities subject to inspection. The manufacturer must be in compliance with cGMP, which imposes certain procedural, substantive, and recordkeeping requirements upon us and our manufacturing partners with respect to manufacturing and quality control activities, and, for devices, product design. To ensure full technical compliance with such regulations, a manufacturer must spend funds, time and effort in the areas of production and quality control. These regulations may also apply to Cytogen. Any failure by us or our manufacturing partners to comply with the requirements of cGMP could have a material adverse effect on our business, financial condition and results of operations.

FDA approval of our proposed products, including a review of the manufacturing processes, controls and facilities used to produce such products, will be required before such products may be marketed in the United States. The process required by the FDA before drug, biological or medical device products may be approved for marketing in the United States generally involves:

- preclinical laboratory and animal tests under the FDA s good laboratory practice regulations;
- submission to the FDA of an Investigational New Drug Application (IND) (for a drug or biologic) or Investigational Device Exemption (IDE) (for a device), which must become effective before clinical trials may begin; further, approval of the investigation by an Institutional Review Board (IRB) must also be obtained before the investigational product may be given to human subjects;
- human clinical trial(s) to establish the safety and efficacy of the product for its intended indication;
- submission to the FDA of a marketing application [New Drug Application (NDA) for a drug, Biologics License Application (BLA) for a biologic, and a premarket approval application (PMA) or premarket notification (510(k)) for a device]; and

FDA review and approval or clearance of the marketing application. Radiopharmaceutical drugs are subject to additional requirements pertaining to the description and support of their indications for use, and the evaluation of product effectiveness and safety, including, radiation safety. There is no assurance that the FDA review of marketing applications will result in product approval or clearance on a timely basis, or at all.

Clinical trials for drugs, devices, and biologics typically are performed in three phases to evaluate the safety and efficacy of the product. In Phase I, a product is tested in a small number of healthy subjects or patients

Table of Contents

primarily for safety at one or more dosages. Phase II evaluates, in addition to safety, the efficacy of the product against particular diseases in a patient population that is generally somewhat larger than Phase I. Clinical trials of certain diagnostic and cancer therapeutic agents may combine Phase I and Phase II into a single Phase I/II study. In Phase III, the product is evaluated in a larger patient population sufficient to generate data to support a claim of safety and efficacy within the meaning of the FDC Act. Permission by the FDA must be obtained before clinical testing can be initiated within the United States. This permission is obtained by submission of an IND/IDE application which typically includes, among other things, the results of *in vitro* and non-clinical testing and any previous human testing done elsewhere. The FDA has 30 days to review the information submitted and makes a final decision whether to permit clinical testing with the drug, biologic or device. However, this process can take longer if the FDA raises questions or asks for additional information regarding the IND/IDE application. Unless the FDA notifies the sponsor that the IND/IDE is subject to a clinical hold during the 30 day review period, the IND/IDE is considered effective and the trial may commence.

There can be no assurance that submission of an IND or IDE will result in the ability to commence clinical trials. In addition, after a trial begins, the FDA may place it on hold or terminate it if, among other reasons, it concludes that clinical subjects are being exposed to an unacceptable health risk. In addition, clinical trials require IRB approval before the drug may be given to subjects and are subject to continuing IRB review. An IRB may suspend or terminate approval if the IRB s requirements are not followed or if unexpected serious harm to subjects is associated with the trial. The FDA may decide not to consider, in support of an application for approval or clearance, any data that was collected in a trial without IRB approval and oversight. After completion of *in vitro*, non-clinical and clinical testing, authorization to market a drug, biologic or device must be granted by the FDA. The FDA grants permission to market through the review and approval or clearance of either an NDA, BLA, PMA, or 510(k). Historically, monoclonal antibodies have been regulated through the FDA s Center for Biologics Evaluation and Research (CBER) . As of late 2003, monoclonal antibodies, which include ProstaScint, were transferred to the Center for Drug Evaluation and Research (CDER), for regulation, review and approval.

An NDA is an application to the FDA to market a new drug. A BLA is an application to the FDA to market a biological product. An NDA or BLA, depending on the submission, must contain, among other things, information on chemistry, manufacturing controls and potency and purity; nonclinical pharmacology and toxicology; human pharmacokinetics and bioavailability; and clinical data. The new drug or biologic may not be approved for marketing in the United States until the FDA has determined that the NDA product is safe and effective or that the BLA product is safe, pure, and potent and the facility in which it is manufactured, processed, packed or held meets standards designed to assure its continued safety, purity, and potency. For both NDAs and BLAs, the application will not be approved until the FDA conducts a manufacturing inspection and approves the applicable manufacturing process for the drug or biologic. A PMA is an application to the FDA to market certain medical devices, which must be approved in order for the product to be marketed. It must be supported by valid scientific evidence, which typically includes extensive data, including pre-clinical data and clinical data from well-controlled clinical trials to demonstrate the safety and effectiveness of the device. Product testing, manufacturing, controls, specifications and information must also be provided, and a pre-approval inspection is normally conducted. NDA, BLA, and PMA submissions may be refused review if they do not meet submission requirements.

Both the studies and the preparation and prosecution of these applications in front of the FDA are expensive and time consuming, and each may take several years to complete. Difficulties or unanticipated costs may be encountered by us or our licensees or us in their respective efforts to secure necessary governmental approval or licenses, which could delay or preclude us or our licensees from marketing their products. There can be no assurance that approvals of our proposed products, processes or facilities will be granted on a timely basis, or at all. Limited indications for use or other conditions could also be placed on any approvals that could restrict the commercial applications of products. With respect to patented products or technologies, delays imposed by the government approval process may materially reduce the period during which we will have the exclusive right to exploit them, because patent protection lasts only for a limited time, beginning on the date the patent is first granted (in the case of United States patent applications filed prior to June 6, 1995) and when the patent

Table of Contents

application is first filed (in the case of patent applications filed in the United States after June 6, 1995, and applications filed in the European Economic Community). We intend to seek to maximize the useful lives of our patents under the Patent Term Restoration Act of 1984 in the United States and under similar laws if available in other countries.

Our new drug products may be subject to generic competition. Once a NDA is approved, the product covered thereby becomes a listed drug which can, in turn, be cited by potential competitors in support of approval of an abbreviated new drug application (ANDA). An ANDA provides for marketing of a drug product that has the same active ingredients in the same strengths and dosage form as the listed drug and has been shown through bioequivalence testing to be therapeutically equivalent to the listed drug. There is no requirement, other than the requirement for bioequivalence testing, for an ANDA applicant to conduct or submit results of pre-clinical or clinical tests to prove the safety or effectiveness of its drug product. Drugs approved in this way are commonly referred to as generic equivalents to the listed drug, are listed as such by the FDA, and can often be substituted by pharmacists under prescriptions written for the original listed drug. Federal law provides for a period of three years of exclusivity following approval of a listed drug that contains previously approved active ingredients but is approved in a new dosage, dosage form, route of administration or combination, or for a new use, the approval of which was required to be supported by new clinical trials conducted by or for the sponsor. During such three-year exclusivity period the FDA cannot grant approval of an ANDA to commercially distribute a generic version of the drug based on that listed drug. However, the FDA can approve generic equivalents of that listed drug based on other listed drugs, *(e.g.*, a generic that is the same in every way but its indication for use), and thus the value of such exclusivity may be undermined. Federal law also provides a period of five years following approval of a drug containing no previously approved active ingredients, during which ANDAs for generic versions of those drugs cannot be submitted unless the submission accompanies a challenge to a listed patent, in which case the submission may be made four years following the original product approval. Additionally, in the event that the sponsor of the listed drug has properly informed the FDA of patents covering its listed drug, applicants submitting an ANDA referencing that drug are required to make one of four certifications including that it believes one or more listed patents are invalid or not infringed. If a generic applicant certifies invalidity or non-infringement, it is required to provide notice of its filing to the NDA sponsor and the patent holder. If the patent holder then initiates a suit for patent infringement against the ANDA sponsor within 45 days of receipt of the notice, the FDA cannot grant effective approval of the ANDA until either 30 months has passed or there has been a court decision holding that the patents in question are invalid or not infringed. If the ANDA applicant certifies that it does not intend to market its generic product before some or all listed patents on the listed drug expire, then the FDA cannot grant effective approval of the ANDA until those patents expire. The first of the abbreviated new drug applicant(s) submitting substantially complete applications certifying that listed patents for a particular product are invalid or not infringed may qualify for a period of 180 days exclusivity running from when the generic product is first marketed, during which subsequently submitted ANDAs cannot be granted effective approval.

Certain of our future products may be regulated by the FDA as combination products. Combination products are products comprised of a combination of two or more different types of components, *(e.g.,* drug/device, device/biologic, drug/device/biologic), or are comprised of two or more separate different types of products packaged together for use, or two or more different types of products packaged separately but labeled for use in combination with one another. The regulation of a combination product is determined by the product s primary mode of action. For example, a combination drug/device that has a primary mode of action as a drug would be regulated by the Center for Drug Evaluation and Research under an NDA. In some cases, however, consultative reviews and/or separate approvals by each agency Center with jurisdiction over a component may be required. The product designation, approval pathway, and submission requirements for a combination product may be difficult to predict, and the approval process may be fraught with unanticipated delays and difficulties. In addition, post-approval requirements may be more extensive than for single entity products. Even if products such as ProstaScint or Quadramet that we intend to develop for use with other separately regulated products are not regulated as combination products, they may be subject to similar multi-Center consultative reviews and additional post-market requirements.

Table of Contents

Once the FDA approves a product, we are required to maintain approval status of the product by providing certain updated safety and efficacy information at specified intervals. Most product or labeling changes to drugs or biologics as well as any change in a manufacturing process or equipment that has a substantial potential to adversely affect the safety or effectiveness of the product for a drug or biologic, or, for a device, changes that affect safety and effectiveness, would necessitate additional FDA review and approval. Post approval changes in packaging or promotional materials may also necessitate further FDA review and approval. Additionally, we are required to meet other requirements specified by the FDC Act, including but not limited to, cGMPs, enforced by periodic inspections, adverse event reporting, requirements governing labeling and promotional materials and, for drugs, biologics and restricted and PMA devices, requirements regarding advertising, and the maintenance of records. Failure to comply with these requirements or the occurrence of unanticipated safety effects from the products during commercial marketing could result in product marketing restrictions, product withdrawal or recall and/or public notifications, or other voluntary or FDA-initiated action, which could delay further marketing until the products are brought into compliance. Similar laws and regulations apply in most foreign countries where these products may be marketed.

Violations of the FDC Act, Public Health Service Act, or regulatory requirements at any time during the product development process, approval process, or after approval may result in agency enforcement actions, including voluntary or mandatory recall, license suspension or revocation, new drug approval suspension or withdrawal, pre-market approval withdrawal, seizure of products, fines, injunction and/or civil or criminal penalties. Any agency enforcement action could have a material adverse effect on our business, financial condition and results of operations.

Orphan Drug Act

The Orphan Drug Act is intended to provide incentives to pharmaceutical companies to develop and market drugs and biologics for rare diseases or conditions affecting fewer than 200,000 persons in the United States at the time of application for orphan drug designation. A drug that receives orphan drug designation and is the first product to receive FDA marketing approval for a particular indication is entitled to orphan drug status, which confers a seven-year exclusive marketing period in the United States for that indication. Clinical testing requirements for orphan drugs are the same as those for products that have not received orphan drug designation but pharmaceutical companies may receive grants or tax credits for research, as well as protocol assistance. Under the Orphan Drug Act, the FDA cannot approve any application by another party to market an identical product for treatment of an identical indication unless the holder consents, the party has a license from the holder of orphan drug status, or the holder of orphan drug status is unable to assure an adequate supply of the drug. However, a drug that is considered by the FDA to be different from a particular orphan drug is not barred from sale in the United States during the seven-year exclusive marketing period even if it receives marketing approval for the same product claim. In addition, holders of orphan drug status must notify the FDA of any decision to discontinue active pursuit of drug approval or biologics license, or, if such approval or license is in effect, notify the FDA at least one year prior to any discontinuance of product production. If the holder of an orphan designation cannot assure the availability of sufficient quantities of the product to meet the needs of affected patients, the FDA may withdraw orphan drug status.

Fraud and abuse

We are subject to various federal and state laws pertaining to health care fraud and abuse, including anti-kickback laws and physician self-referral laws. Violations of these laws are punishable by criminal and/or civil sanctions, including, in some instances, imprisonment and exclusion from participation in federal and state health care programs, including Medicare, Medicaid and veterans health programs. Because of the far-reaching nature of these laws, there can be no assurance that the occurrence of one or more violations of these laws would not result in a material adverse effect on our business, financial condition and results of operations.

Anti-Kickback Laws. Our operations are subject to federal and state anti-kickback laws. Certain provisions of the Social Security Act prohibit entities such as us from knowingly and willingly offering, paying, soliciting or

24

Table of Contents

receiving any form of remuneration in return for the referral of items or services reimbursable by any federal health care program, or in return for the recommendation, arrangement, purchase, lease or order of items or services that are covered by federal health care programs. Violation of the federal anti-kickback law is a felony, punishable by criminal fines and imprisonment for up to five years or both. In addition, the Department of Health and Human Services may impose civil penalties and exclude violators from participation in federal health care programs such as Medicare and Medicaid. Many states have adopted similar prohibitions against payments intended to induce referrals of products or services paid by Medicaid or other third party payors.

Physician Self-Referral Laws. We are also subject to federal and state physician self-referral laws. Federal physician self-referral legislation (known as the Stark law) prohibits, subject to certain exceptions, a physician from referring Medicare or Medicaid patients to an entity providing designated health services, including, among other things, certain radiology and radiation therapy services and clinical laboratory services in which the physician or a member of his immediate family has an ownership or investment interest or has entered into a compensation arrangement. The Stark law also prohibits the entity receiving the improper referral from billing any good or service furnished pursuant to the referral. The penalties for violations include a prohibition on payment by these government programs and civil penalties of as much as $15,000 for each improper referral and $100,000 for participation in a circumvention scheme. Various state laws also contain similar provisions and penalties.

False Claims Laws. Under separate federal statutes, submission of claims for payment that are false or fraudulent may lead to civil money penalties, criminal fines and imprisonment, and/or exclusion from participation in federal health care programs. These false claims statutes include the Federal False Claims Act, which allows any person to bring suit alleging false or fraudulent claims against a federal program such as Medicare or Medicaid or other violations of the statute and to share in any amounts paid by the entity to the government in fines or settlement. Such suits, known as *qui tam* actions, have increased significantly in recent years, causing greater numbers of health care companies to face false claim actions, pay fines or be excluded from Medicare, Medicaid or other federal health care programs. Various state laws also contain similar prohibitions, penalties, and *qui tam* action mechanisms.

Other regulations

In addition to regulations enforced by the FDA, and federal and state laws pertaining to health care fraud and abuse, we are also subject to regulation under the state and local authorities and other federal statutes and agencies including the Occupational Safety and Health Act, the Environmental Protection Act, the Toxic Substances Control Act, the Resource Conservation and Recovery Act and the Nuclear Regulatory Commission.

Foreign regulatory approval

The regulatory approval process in Europe has changed over the past few years. There are two regulatory approval processes in Europe for products developed by us. Beginning in 1995, the centralized procedure became mandatory for all biotechnology products. Under this regulatory scheme, the application is reviewed by two scientific project leaders referred to as the rapporteur and co-rapporteur. Their roles are to prepare assessment reports of safety and efficacy and for recommending the approval for full European Union marketing.

The second regulatory scheme, referred to as the Mutual Recognition Procedure, is a process whereby a product s national registration in one member state within the European Union may be mutually recognized by other member states within the European Union.

Substantial requirements, comparable in many respects to those imposed under the FDC Act, will have to be met before commercial sale is permissible in most countries. There can be no assurance, however, as to whether or when governmental approvals, other than those already obtained, will be obtained or as to the terms or scope of those approvals.

Table of Contents

HEALTH CARE REIMBURSEMENT

Sales of our products depend in part on the availability of reimbursement by various payers, including federal health care programs, such as Medicare and Medicaid, as well as private health insurance plans. Whether a product receives such coverage depends upon a number of factors, including the payer s determination that the product is reasonable and necessary for the diagnosis or treatment of the illness or injury for which it is administered according to accepted standards of medical practice, cost-effective, safe, effective, and not otherwise excluded from coverage by law or regulation. There may be significant delays in obtaining coverage for newly-approved products, and coverage may be limited or expanded outside the purpose(s) for which the product is approved by the FDA.

Eligibility for coverage does not imply that any product will be reimbursed in all cases or at a rate that allows us or any healthcare provider to make a profit or even cover costs, including research, development, production, sales, and distribution costs. Although new laws require expedited coverage for new technology, interim payments for new products, if applicable, may also not be sufficient to cover our costs and may not be made permanent. Reimbursement rates may vary according to the approved and covered use of the product and the place of service in which it is used, may be based on payments allowed for lower-cost products that are already reimbursed, may be incorporated into existing payments for other products or services, and may reflect budgetary constraints and/or imperfections in Medicare or Medicaid claims data. Net prices for products may be reduced by mandatory discounts or rebates required by law under government health care programs or by any future relaxation of laws that restrict imports of certain medical products from countries where they may be sold at lower prices than in the U.S.

Third party payers often mirror Medicare coverage policy and payment limitations in setting their own reimbursement payment and coverage policy and may have sufficient market penetration to demand significant price reductions. Even if successful, securing reimbursement coverage at adequate payment levels from government and third party payers can be a time consuming and costly process that could require us to provide additional supporting scientific, clinical and cost-effectiveness data to permit payment and coverage of our products to payers. Our inability to promptly obtain product coverage and profitable reimbursement rates from government-funded and private payers could have a material adverse effect on our business, financial condition and our results of operations.

Although healthcare funding has and will continue to be closely monitored by the government, the ability to diagnose patients quickly and more effectively has been one of the few areas where the government has increased healthcare spending. Approval in payment of new technology has been another area with required spending outlined in the 2004 legislative requirements.

The Centers for Medicare and Medicaid Services (CMS) continually monitor and update product descriptors, coverage policies, product and service codes, payment methodologies, and reimbursement values. Although it is not possible to predict or identify all of the risks relating to such changes, we believe that such risks include, but are not limited to: (i) increasing price pressures (including those imposed by regulations and practices of managed care groups and institutional and governmental purchasers); and (ii) judicial decisions and government laws related to health care reform including radiopharmaceutical, pharmaceutical and device reimbursement. In addition, an increasing emphasis on managed care has and will continue to increase the pressure on pricing of these products and services.

Our business, financial condition and results of operations will continue to be affected by the efforts of governmental and third-party payers to contain or reduce the costs of health care. There have been, and we expect that there will continue to be, federal and state proposals to constrain expenditures for medical products and services, which may affect payments for therapeutic and diagnostic imaging agents. We rely heavily on the ability to monitor changes in reimbursement and coverage and proactively influence policy and legislative changes in the areas of health care that directly impact our products. We have proven our ability to monitor changes that impact our products and have worked with the government and private payers to take advantage of

26

Table of Contents

the opportunities offered by legislative and policy changes for our products. While we cannot predict if legislative or regulatory proposals will be adopted or the effects managed care may have on our business, the changes in reimbursement and the adoption of new healthcare proposals could have a material adverse effect on our business, financial condition and results of operations. Further, to the extent that changes in healthcare reimbursement have a material adverse effect on other prospective corporate partners, our ability to establish strategic alliances may be materially and adversely affected. In certain foreign markets, the pricing and profitability of our products are generally subject to governmental controls.

KEY EMPLOYEES

Michael D. Becker currently serves as our President and Chief Executive Officer. Mr. Becker joined Cytogen in April 2001 and has served in positions of increasing responsibility, including Chief Executive Officer of our AxCell Biosciences subsidiary, Vice President, Business Development and Industry Relations, and Vice President, Investor Relations Officer. Prior to joining Cytogen, he was with Wayne Hummer Investments LLC, a Chicago-based regional brokerage firm from July 1996 to April 2001, where he held senior positions as a biotechnology analyst, investment executive and portfolio manager in addition to participating in sales management activities. From October 1998 to April 2001, Mr. Becker also served on the board of directors for the Chicago Biotech Network, a nonprofit trade association for the biotechnology industry in Illinois. Mr. Becker attended DePaul University in Chicago, Illinois. Mr. Becker continues to serve on the board of the Biotechnology Council of New Jersey.

William F. Goeckeler, Ph.D. was promoted to Senior Vice President, Operations in December 2003. Previously, he served as Vice President, Operations since January 2003 and Vice President of Research and Development since June 2001. He joined Cytogen in March of 1994 as the Assistant Director, Pharmaceutical Development. In 1995 he was promoted to Associate Director, Technical Support Operations and in June 1997 became our Director, Pharmaceutical Development, a position he held until June 2001. Before joining us, Dr. Goeckeler spent nine years as a scientist in the Bioproducts Laboratory of Central Research and Development at The Dow Chemical Company. Dr. Goeckeler did his undergraduate and graduate work at the University of Missouri where he received his Ph.D. in Radiochemistry for research that involved the discovery of QUADRAMET and other skeletal targeting radiopharmaceuticals.

Christopher P. Schnittker, CPA, joined Cytogen in September 2003 as our Vice President and Chief Financial Officer. Prior to joining Cytogen, Mr. Schnittker served as Chief Financial Officer of Genaera Corporation (formerly Magainin Pharmaceuticals, Inc.) from June 2000 to August 2003. Prior to Genaera, Mr. Schnittker served as Director of Finance from August 1999 to May 2000 and Controller from December 1997 to August 1999 at GSI Commerce, Inc., a publicly-traded technology company. From June 1995 to December 1997, Mr. Schnittker held several positions of increasing responsibility at Rhône-Poulenc Rorer, Inc. (now Aventis). Prior to that, Mr. Schnittker held various positions at Price Waterhouse LLP s (now PricewaterhouseCoopers LLP) Life Sciences audit practice from 1990 to 1995. Mr. Schnittker is a certified public accountant licensed in the State of New Jersey.

Thu A. Dang was promoted to Vice President, Finance in January 2003. Ms. Dang joined Cytogen in September 1988 as our Senior Financial Reporting Accountant, and was promoted to Director of Finance in May 2000. Prior to joining Cytogen, Ms. Dang held numerous positions with Harrisburg Dairies for six years, serving ultimately as their Controller. Ms. Dang received her Bachelor of Science Degree in Accounting from Elizabethtown College.

Rita A. Auld was promoted to Vice President, Human Resources and Administration in January 2003 and became our Corporate Secretary in March 2003. Ms. Auld joined Cytogen as our Director of Human Resources in October 2000. For a period of six years prior to joining Cytogen, Ms. Auld was the Director of Human Resources of Flexpaq Corporation, where she established the Human Resources Department, developing procedures, handbooks and benefit and safety programs. Ms. Auld has over 20 years of experience with sales,

27

Table of Contents

manufacturing, accounting and engineering organizations, directing the activities of human resources and administrative functions, specializing in small sized companies, both public and private. Ms. Auld holds Associates and Bachelor of Science Degrees in Business Administration and is certified as a Human Resources Professional.

June Gobern, MBA, was promoted to Senior Director of Marketing in January 2003. She previously served as Director of Marketing. Ms. Gobern joined Cytogen in 1992 as Supervisor of Technical Services, in 1994 was promoted to Assistant Director of Marketing Services and in July of 1996 to Director of Sales and Marketing. Prior to joining Cytogen, Ms. Gobern worked for Bristol-Myers Squibb as a Technical Sales Associate for the Metro Region. She spent over 10 years in the hospital setting where she functioned in various Nuclear Medicine, MRI and Ultrasound supervisory roles and served on the Board of Directors for Putman Credit Union. She received both a BS in Medical Technology and a MBA in Management from Fairleigh Dickinson University. She also holds a Certificate in International Business from Wroxton College, England and a Nuclear Medicine AMA Certification, from the JFK School of Nuclear Medicine. Ms. Gobern is also a certified Nuclear Medicine Technologist.

Corey Jacklin, MBA, joined Cytogen in January 2003 as our Director of Business Development and in March 2003 became our Senior Director of Sales. He has held various sales and marketing positions in the biotechnology industry for the past 15 years including co-founding Polyprobe (now Genisphere), marketing bioreactors and fermenters for New Brunswick Scientific, selling contract research services for MDS Panlabs, and lastly as a Director of Business Development with Gene Logic, a provider of genomics and toxicogenomics information products. He received his Bachelor s degree in Molecular Biology from the University of California at Berkeley and his MBA in Industrial Marketing from Baruch College, CUNY.

EMPLOYEES

As of March 1, 2004, we employed 61 persons, 60 of whom are employed full-time and 1 of whom is employed part-time. Of such 61 persons, 36 were employed in sales and marketing, 5 in clinical activities, 2 in regulatory, 4 in our AxCell subsidiary and 14 in administration and management. The employees in sales and marketing included 8 Regional Oncology Specialists and 23 Regional and Territory Managers. We believe that we have been successful in attracting skilled and experienced employees. None of our employees is covered by a collective bargaining agreement. All of our employees have executed confidentiality agreements. We consider relations with our employees to be excellent.

ADDITIONAL FACTORS THAT MAY AFFECT FUTURE RESULTS

Investing in our common stock involves a high degree of risk. You should carefully consider the risks and uncertainties described below together with other information included or incorporated by reference in this Annual Report on Form 10-K in your decision as to whether or not to invest in our common stock. If any of the following risks or uncertainties actually occur, our business, financial condition or results of operations would likely suffer. In that case, the trading price of our common stock could fall, and you may lose all or part of the money you paid to buy our common stock.

We have a history of operating losses and an accumulated deficit and expect to incur losses in the future.

Given the high level of research and development and related expenditures associated with our business and our inability to generate revenues sufficient to cover such expenditures, we have had a history of operating losses since our inception. We had net losses of $9.4 million, $15.7 million, and $12.1 million for the years ended December 31, 2003, 2002 and 2001, respectively. We had an accumulated deficit of $366 million as of December 31, 2003.

In order to develop and commercialize our technologies, particularly our prostate specific membrane antigen technology, and expand our oncology products, we expect to incur significant increases in our expenses over the next several years. As a result, we will need to generate significant additional revenue to become profitable.

Table of Contents

To date, we have taken affirmative steps to rationalize our trend of operating losses. Such steps include, among other things:

- undergoing steps to realign and implement our focus as a product-driven, oncology-focused biopharmaceutical company;
- the establishment and maintenance of our in-house specialty sales force;
- the reacquisition of North American and Latin American marketing rights to QUADRAMET from Berlex Laboratories in August 2003;
- enhancing our marketed product portfolio through marketing alliances and strategic arrangements such as we have done with the COMBIDEX product, which we intend to market if this product is approved by the FDA; and
- the effective monitoring and management of expenses relating to research and development, selling and marketing, and other general and administrative matters.

Although we have taken these affirmative steps, we may never be able to successfully implement them, and our ability to generate and sustain significant additional revenues or achieve profitability will depend upon the factors discussed elsewhere in this section entitled, Additional Factors That May Affect Future Results. As a result, we may never be able to generate or sustain significant additional revenue or achieve profitability.

We depend on sales of PROSTASCINT and QUADRAMET for the majority of our near-term revenues.

We expect QUADRAMET and PROSTASCINT to account for a significant percentage of our product related revenues in the near future. For the year ended December 31, 2003, royalty and product revenues from QUADRAMET and sales revenues from PROSTASCINT accounted for approximately 35% and 60%, respectively, of our product related revenues. For the year ended December 31, 2002, royalties from QUADRAMET and product revenues from PROSTASCINT accounted for approximately 15% and 64%, respectively, of our product related revenues. If PROSTASCINT or QUADRAMET does not achieve broader market acceptance, either because we fail to effectively market such products or our competitors introduce competing products, we may not be able to generate sufficient revenue to become profitable.

We depend on acceptance of our products by the medical community for the continuation of our revenues.

Because our marketed products contribute the majority of our product related revenues, our business, financial condition and results of operations depend on their acceptance as safe, effective and cost-efficient alternatives to other available treatment and diagnostic protocols by the medical community, including:

- health care providers, such as hospitals and physicians; and
- third-party payors, including Medicare, Medicaid, private insurance carriers and health maintenance organizations.

With respect to PROSTASCINT, our customers, including technologists and physicians, must successfully complete our Partners in Excellence Program, a proprietary training program designed to promote the correct acquisition and interpretation of PROSTASCINT images. This product is technique-dependent and requires a learning commitment by technologists and physicians and their acceptance of this product as part of their treatment practices. With respect to QUADRAMET, we believe that challenges we may encounter in generating market acceptance for this product include the need to further educate patients and physicians about QUADRAMET s properties, approved uses and how QUADRAMET may be differentiated from other radiopharmaceuticals and used in combination with other treatments for the palliation of pain due to bone metastases, such as analgesics, opioids, bisphosphonates, and chemotherapeutics. If PROSTASCINT or QUADRAMET do not achieve broader market acceptance, we may not be able to generate sufficient revenue to become profitable.

Table of Contents

Generating market acceptance and sales of our products has proven difficult, time consuming and uncertain. We launched ONCOSCINT CR/OV in December 1992, PROSTASCINT in October 1996, QUADRAMET in March 1997, BRACHYSEED I-125 in February 2001, BRACHYSEED Pd-103 in May 2002 and NMP22 BLADDERCHEK in November 2002. Revenues for PROSTASCINT grew from $55,000 in 1996 to $6.5 million in 2003. Royalties from sales and product revenues for QUADRAMET grew from $3.3 million in 1997 to $3.9 million in 2003. Royalties from sales of QUADRAMET in the initial years of sales were supported by a guaranteed minimum revenue arrangement with the third party licensor of QUADRAMET. ONCOSCINT CR/OV selling activity was discontinued in December 2002 and selling activities for the BRACHYSEED products were discontinued in January 2003. We began marketing NMP22 BLADDERCHEK in November 2002 and sales of this product have been minimal to date. Currently, most of our revenues are derived from sales of PROSTASCINT and QUADRAMET, as well as certain license and contract revenues.

We rely heavily on our collaborative partners.

Our success depends largely upon the success and financial stability of our collaborative partners. We have entered into the following agreements for the development, sale, marketing, distribution and manufacture of our products, product candidates and technologies:

- a license agreement with The Dow Chemical Company relating to the QUADRAMET technology;
- a manufacturing and supply agreement for the manufacture of QUADRAMET with BMSMI;
- marketing, license and supply agreements with Advanced Magnetics, Inc. related to COMBIDEX;
- a distribution services agreement with CORD Logistics, Inc. for PROSTASCINT;
- various agreements which form and control our joint venture with Progenics Pharmaceuticals for the development of PSMA for *in vivo* immunotherapy for prostate and other cancers;
- a collaboration and manufacturing agreement between our joint venture and Abgenix, Inc.; and
- a license agreement between our joint venture and AlphaVax Human Vaccines, Inc.

Because our collaborative partners are responsible for certain manufacturing and distribution activities, among others, these activities are outside our direct control and we rely on our partners to perform their obligations. In the event that our collaborative partners are entitled to enter into third party arrangements that may economically disadvantage us, or breach their obligations under our agreements, our products may not be commercially successful. As a result, any success may be delayed and new product development could be inhibited with the result that our business, financial condition and results of operation could be significantly and adversely affected.

Our business could be harmed if certain agreements expire or are terminated early.

If our collaborative agreements expire or are terminated and we cannot renew or replace them on commercially reasonable terms, our business and financial results may suffer. For example, in January 2003, we provided Draximage Inc. with notice of our intent to terminate our product manufacturing and supply agreement and license agreement with Draximage relating to the BRACHYSEED products which represented 20% of our product related revenues for the year ended December 31, 2002. In April 2003, we entered into an agreement with Draximage formally terminating each of these agreements. We no longer market and sell the BRACHYSEED products.

We currently depend on the following agreements for our present and future operating results:

Dow Chemical. In May 1993, we obtained an exclusive license from The Dow Chemical Company to North American rights to use QUADRAMET as a therapeutic radiopharmaceutical for metabolic bone disease or tumor regression for cancer caused by metastatic or primary cancer in bone in humans, and for the treatment of disease characterized by osteoblastic response in humans. Our license was expanded to include Latin America in 1995.

Table of Contents

Our license agreement with Dow with respect to QUADRAMET shall remain in effect, unless earlier terminated pursuant to the terms thereof, for a term of twenty (20) years from May 30, 1993 or until the last to expire of the related patents. We currently anticipate such termination date to be May 30, 2013.

Bristol-Myers Squibb Medical Imaging, Inc. QUADRAMET is manufactured by BMSMI pursuant to the terms of a manufacturing and supply agreement with us effective as of January 1, 2004. Under this agreement, BMSMI has agreed to manufacture, supply and distribute QUADRAMET for us in exchange for a minimum payment of at least $4.2 million annually through 2008. The agreement shall thereafter renew for five successive one-year periods unless terminated by either party upon two years notice, or earlier terminated pursuant to the terms thereof. The agreement is terminable by either party, at any time, upon two years notice to the other. We also pay BMSMI a variable amount per month for each order placed to cover the cost of customer service and distribution.

Advanced Magnetics, Inc. In August 2000, we entered into a license and marketing agreement and a supply agreement with Advanced Magnetics, Inc. for COMBIDEX, an investigational magnetic resonance imaging contrast agent that assists in the differentiation of metastatic from non-metastatic lymph nodes. We hold exclusive United States marketing rights to COMBIDEX. Advanced Magnetics is continuing its discussions with the FDA relating to outstanding issues regarding an approvable letter received from the FDA dated June 2000, in an effort to bring COMBIDEX to market. Our license and marketing agreement with Advanced Magnetics will continue until August 25, 2010, and shall thereafter automatically renew for successive five year periods, unless notice of non-renewal or termination is given by us or Advanced Magnetics, 90 days prior to the commencement of any renewal period.

Sloan Kettering Institute for Cancer Research. In 1993, we began a development program with SKICR involving PSMA and our proprietary monoclonal antibody. In November 1996, we exercised an option for, and obtained, an exclusive worldwide license from the SKICR to its PSMA-related technology. The term of the license shall end on the date of expiration of the last to expire of the licensed patents unless it earlier terminates by operation of law or by acts of the parties in accordance with the terms of the agreement.

Agreement with Dr. Horoszewicz regarding PROSTASCINT. In 1989, we entered into an agreement with Dr. Julius S. Horoszewicz pursuant to which we assigned certain rights to the patent claiming the 7E11-C5 antibody, as well as additional patents relating to the PROSTASCINT product and commercialization rights thereto. Under our agreement, which we believe will remain in effect until the expiration of the last related patent, we have made, and may continue to make, certain payments to Dr. Horoszewicz.

The University of North Carolina at Chapel Hill. In March 1993, we entered into a license agreement with The University of North Carolina at Chapel Hill, pursuant to which UNC granted us and our affiliates an exclusive world-wide license with respect to certain technology, patents and patent applications related to certain aspects of proteomics technology, including phage display. The agreement commenced on March 10, 1993 and will expire, unless earlier terminated as provided therein, upon the expiration of the last to expire of the licensed patents that cover a licensed product.

Laureate Pharma, L.P. In January 2003, we entered into a contract manufacturing agreement with Laureate Pharma L.P., pursuant to which Laureate was obligated to manufacture PROSTASCINT for us through December 31, 2003. Although we do not plan to manufacture any PROSTASCINT in 2004, we do intend to negotiate with Laureate or another suitable contract manufacturer to supply us with PROSTASCINT in subsequent periods.

If the licenses and/or agreements described above are terminated, we may not be able to find suitable alternatives to them on a timely basis or on reasonable terms, if at all. The loss of the right to use these technologies that we have licensed or the loss of any services provided to us under

these agreements would significantly and adversely affect our business, financial condition and results of operations.

Table of Contents

Our intellectual property is difficult to protect.

In addition to our key agreements referenced above, our business and competitive positions are also dependent upon our ability to protect our proprietary technology. Because of the substantial length of time and expense associated with the development of new products, we, like the rest of the biopharmaceutical industry, place considerable importance on obtaining and maintaining patent and trade secret protection for new technologies, products and processes. We have filed patent applications for certain aspects of our technology for diagnostic and therapeutic products and/or the methods for their production and use.

In addition, the protection afforded by a duly issued patent is limited in duration. With respect to our PROSTASCINT product, we rely primarily on United States patent numbers 5,162,504 (expiring October 28, 2010), 4,741,900 (expiring June 9, 2004), 4,671,958 (expiring June 9, 2004), and 4,867,973 (expiring June 9, 2004). With respect to QUADRAMET, we rely primarily on United States patent numbers 4,898,724 (expiring March 28, 2011), 4,937,333 (expiring August 4, 2009), 4,897,254 (expiring January 30, 2007), 5,066,478 (expiring November 19, 2008), and 5,300,279 (expiring November 19, 2008), which were licensed to us by The Dow Chemical Company. In addition, we rely on United States patent number 5,495,042 (expiring November 4, 2013), which is assigned to us, and United States patent numbers 5,714,604 (expiring February 3, 2015) and 5,762,907 (expiring November 21, 2006).

The patent positions of pharmaceutical, biopharmaceutical and biotechnology companies, including us, are generally uncertain and involve complex legal and factual questions. Our patent applications may not protect our technologies and products because, among other things:

- there is no guarantee that any of our pending patent applications will result in issued patents;
- we may develop additional proprietary technologies that are not patentable;
- there is no guarantee that any patents issued to us, our collaborators or our licensors will provide a basis for a commercially viable product;
- there is no guarantee that any patents issued to us or our collaborators will provide us with any competitive advantage;
- there is no guarantee that any patents issued to us or our collaborators will not be challenged, circumvented or invalidated by third parties; and
- there is no guarantee that any patents previously issued to others or issued in the future will not have an adverse effect on our ability to do business.

In addition, patent law in the technology fields in which we operate is uncertain and still evolving. The degree of protection that may be afforded any patents we are issued or license from others may not be sufficient to protect our commercial interests. Furthermore, others may independently develop similar or alternative technologies, duplicate our technologies, or, if patents are issued to us, design around the patented technologies developed by us. We could incur substantial costs in litigation if we are required to defend ourselves in patent suits by third parties or if we initiate such suits. In addition, if challenged by others in litigation, the patents we have been issued, which we have been assigned or we have licensed from others may be found invalid. It is also possible that our activities may infringe patents owned by others. Defense and prosecution of patent matters can be expensive and time-consuming and, regardless of whether the outcome is favorable to us, can result in the diversion of substantial financial, managerial and other resources. An adverse outcome could:

subject us to significant liability to third parties;

require us to cease any related research and development activities and product sales; or

require us to obtain licenses from third parties.

Table of Contents

Any licenses required under any such third-party patents or proprietary rights may not be available on commercially reasonable terms, if at all. Moreover, the laws of certain countries may not protect our proprietary rights to the same extent as the laws of the United States. We cannot predict whether our or our competitors pending patent applications will result in the issuance of valid patents which may significantly and adversely affect our business, financial condition and results of operations.

There are risks associated with the manufacture and supply of our products.

If we are to be successful, our products will have to be manufactured by contract manufacturers in compliance with regulatory requirements and at costs acceptable to us. If we are unable to successfully arrange for the manufacture of our products and product candidates, either because potential manufacturers are not cGMP compliant, are not available or charge excessive amounts, we will not be able to successfully commercialize our products and our business, financial condition and results of operations will be significantly and adversely affected.

PROSTASCINT was manufactured at a cGMP compliant manufacturing facility operated by Laureate Pharma L.P. We had access to Laureate s facility for continued manufacturing of the product until December 31, 2003. We entered into a development and manufacturing agreement with DSM Biologics Company B.V. in July 2000, which we intended would replace our arrangement with Laureate with respect to PROSTASCINT. Our relationship with DSM has subsequently terminated. Our failure to maintain a long term supply agreement on commercially reasonable terms will have a material adverse effect on our business, financial condition and results of operations.

QUADRAMET is manufactured by BMSMI, pursuant to an agreement with Cytogen. Both primary components of QUADRAMET, particularly Samarium-153 and EDTMP, are provided to BMSMI by outside suppliers. Due to radioactive decay, Samarium-153 must be produced on a weekly basis. BMSMI obtains its requirements for Samarium-153 from a sole supplier and EDTMP from another sole supplier. Alternative sources for these components may not be readily available, and any alternative supplier would have to be identified and qualified, subject to all applicable regulatory guidelines. If BMSMI cannot obtain sufficient quantities of the components on commercially reasonable terms, or in a timely manner, it would be unable to manufacture QUADRAMET on a timely and cost-effective basis, which could have a material adverse effect on our business, financial condition and results of operations.

The Company, our contract manufacturers and testing laboratories are required to adhere to United States Food and Drug Administration regulations setting forth requirements for cGMP, and similar regulations in other countries, which include extensive testing, control and documentation requirements. Ongoing compliance with cGMP, labeling and other applicable regulatory requirements is monitored through periodic inspections and market surveillance by state and federal agencies, including the FDA, and by comparable agencies in other countries. Failure of our contract vendors or us to comply with applicable regulations could result in sanctions being imposed on us, including fines, injunctions, civil penalties, failure of the government to grant pre-market clearance or pre-market approval of drugs, delays, suspension or withdrawal of approvals, seizures or recalls of products, operating restrictions and criminal prosecutions any of which could significantly and adversely affect our business, financial condition and results of operations.

Our products, generally, are in the early stages of development and commercialization and we may never achieve the revenue goals set forth in our business plan.

We began operations in 1980 and have since been engaged primarily in research directed toward the development, commercialization and marketing of products to improve the diagnosis and treatment of cancer and other diseases. In October 1996, we introduced for commercial use our PROSTASCINT imaging agent. In March 1997, we introduced for commercial use our QUADRAMET therapeutic product. In November 2002, we began promoting NMP22 BLADDERCHEK to urologists in the United States, and now promote NMP22 BLADDERCHEK solely to

oncologists.

Table of Contents

Our PSMA technologies are still in the early stages of development. We have significantly reduced operations at our AxCell subsidiary, which is responsible for the development certain of our technologies. We may be unable to develop or commercialize these products and technologies in the future.

Our business is therefore subject to the risks inherent in an early-stage biopharmaceutical business enterprise, such as the need:

- to obtain sufficient capital to support the expenses of developing our technology and commercializing our products;
- to ensure that our products are safe and effective;
- to obtain regulatory approval for the use and sale of our products;
- to manufacture our products in sufficient quantities and at a reasonable cost;
- to develop a sufficient market for our products; and
- to attract and retain qualified management, sales, technical and scientific staff.

The problems frequently encountered using new technologies and operating in a competitive environment also may affect our business, financial condition and results of operations. If we fail to properly address these risks and attain our business objectives, our business could be significantly and adversely affected.

All of our potential oncology products will be subject to the risks of failure inherent in the development of diagnostic or therapeutic products based on new technologies.

Product development for cancer treatment involves a high degree of risk. The product candidates we develop, pursue or offer may not prove to be safe and effective, may not receive the necessary regulatory approvals, may be precluded by proprietary rights of third parties or may not ultimately achieve market acceptance. These product candidates will require substantial additional investment, laboratory development, clinical testing and regulatory approvals prior to their commercialization. We may experience difficulties, such as the inability to initiate clinical trials or receive timely regulatory approvals, that could delay or prevent the successful development, introduction and marketing of new products.

Before we obtain regulatory approvals for the commercial sale of any of our products under development, we must demonstrate through preclinical studies and clinical trials that the product is safe and efficacious for use in each target indication. The results from preclinical studies and early-stage clinical trials may not be predictive of results that will be obtained in large-scale, later-stage testing. Our clinical trials may not demonstrate safety and efficacy of a proposed product, and therefore, may not result in marketable products. A number of companies in the biotechnology industry have suffered significant setbacks in advanced clinical trials, even after promising results in earlier trials. Clinical trials or marketing of any potential diagnostic or therapeutic products may expose us to liability claims for the use of these diagnostic or therapeutic products. We may not be able to maintain product liability insurance or sufficient coverage may not be available at a reasonable cost. In addition, as we develop diagnostic or therapeutic products internally, we will have to make significant investments in diagnostic or therapeutic product development, marketing, sales and regulatory compliance resources. We will also have to establish or contract for the manufacture of

products, including supplies of drugs used in clinical trials, under the current Good Manufacturing Practices of the FDA. We cannot assure you that product issues will not arise following successful clinical trials and FDA approval.

The rate of completion of clinical trials also depends on the rate of patient enrollment. Patient enrollment depends on many factors, including the size of the patient population, the nature of the protocol, the proximity of patients to clinical sites and the eligibility criteria for the study. Delays in planned patient enrollment may result in increased costs and delays, which could have a harmful effect on our ability to develop the products in our

Table of Contents

pipeline. If we are unable to develop and commercialize products on a timely basis or at all, our business, financial condition and results of operations could be significantly and adversely affected.

Competition in our field is intense and likely to increase.

We face, and will continue to face, intense competition from one or more of the following entities:

- pharmaceutical companies;
- biotechnology companies;
- diagnostic companies;
- bioinformatics companies;
- academic and research institutions; and
- government agencies.

All of our products and product candidate are subject to significant competition from organizations that are pursuing technologies and products that are the same as or similar to our technology and products. Many of the organizations competing with us have greater capital resources, research and development staffs and facilities and marketing capabilities.

The markets for therapeutic and molecular imaging/diagnostic products that address prostate and bladder cancers are large. Our most significant competitors include various pharmaceutical and medical device companies, radiopharmaceutical distributors and biotechnology companies.

QUADRAMET primarily competes with Strontium-89 chloride in the radiopharmaceutical pain palliation market. Strontium-89 chloride is manufactured and marketed either as Metastron, by Amersham Health, or in a generic form by Bio-Nucleonics Pharma, Inc. Amersham manufactures Metastron and sells the product through its wholly-owned network of radiopharmacies, direct to end-users and through other radiopharmacy distributors. The generic version is distributed directly by the manufacturer or is sold through radiopharmacy distributors such as Cardinal Health and Custom Care Pharmacy. The first radiopharmaceutical introduced as a metastatic bone cancer pain palliation agent, Phosphorus-32 (P-32), is no longer routinely utilized clinically in the United States.

Competitive imaging modalities to PROSTASCINT include computed tomography (CT), magnetic resonance (MR) imaging, and position emission tomography (PET).

Polymedco manufactures BTAStat, a point of care urine-based test approved for monitoring bladder cancer patients. BTAStat, marketed by Mentor, competes with NMP22 BLADDERCHEK (a product of Matritech for which we are the sole distributor to oncologists in the United States). NMP22 BLADDERCHEK is, however, the only point of care urine-based test approved for both monitoring and diagnosis of bladder cancer. Matritech has retained rights to market NMP22 BLADDERCHEK directly to physicians other than oncologists, such as primary care physicians.

Additionally, we face competition in the development of PSMA-related technology and products primarily from Millennium Pharmaceuticals, Inc. and Medarex, Inc.

Before we recover development expenses for our products and technologies, the products or technologies may become obsolete as a result of technological developments by others or us. Our products could also be made obsolete by new technologies, which are less expensive or more effective. We may not be able to make the enhancements to our technology necessary to compete successfully with newly emerging technologies and failure to do so could significantly and adversely affect our business, financial condition and results of operations.

Table of Contents

We have limited sales, marketing and distribution capabilities for our products.

We have established an internal sales force that is responsible for marketing and selling PROSTASCINT, QUADRAMET and NMP22 BLADDERCHEK. However, such internal sales force has limited sales, marketing and distribution capabilities for our products, compared to those of many of our competitors. Effective August 1, 2003, we reacquired marketing rights to QUADRAMET from Berlex Laboratories, Inc. in North and Latin America, for an upfront payment of $8.0 million and the obligation to pay royalties to Berlex on future sales of QUADRAMET. If our internal sales force is unable to successfully market QUADRAMET, our business and financial condition may be adversely affected. If we are unable to establish and maintain significant sales, marketing and distribution efforts within the United States, either internally or through arrangements with third parties, our business may be significantly and adversely affected. In locations outside of the United States, we have not established a selling presence. To the extent that our sales force, from time to time, markets and sells additional products, we cannot be certain that adequate resources or sales capacity will be available to effectively accomplish these tasks.

Failure of consumers to obtain adequate reimbursement from third-party payors could limit market acceptance and affect pricing of our products.

Sales of our products depend in part on the availability of reimbursement by federal health care programs such as Medicare and Medicaid as well as private health insurance plans. Whether a product receives such coverage depends upon a number of factors, including the payor s determination that the product is reasonable and necessary for the diagnosis or treatment of the illness or injury for which it is administered according to accepted standards of medical practice, cost effective, not experimental or investigational, not found by the FDA to be less than effective, and not otherwise excluded from coverage by law or regulation. There may be significant delays in obtaining coverage for newly-approved products, and coverage may be more limited than the purposes for which the product is approved by the FDA.

Moreover, eligibility for coverage does not imply that any product will be reimbursed in all cases or at a rate that allows us to make a profit or even cover our costs, including research, development, production, sales, and distribution costs. Interim payments for new products, if applicable, may also not be sufficient to cover our costs and may not be made permanent. Reimbursement rates may vary according to the use of the product and the clinical setting in which it is used, may be based on payments allowed for lower-cost products that are already reimbursed, may be incorporated into existing payments for other products or services, and may reflect budgetary constraints and/or imperfections in Medicare or Medicaid data. Net prices for products may be reduced by mandatory discounts or rebates required by government health care programs or by any future relaxation of laws that restrict imports of certain medical products from countries where they may be sold at lower prices than in the United States.

Third party payors often follow Medicare coverage policy and payment limitations in setting their own reimbursement rates and may have sufficient market power to demand significant price reductions. Even if successful, securing coverage at adequate reimbursement rates from government and third party payors can be a time consuming and costly process that could require us to provide supporting scientific, clinical and cost-effectiveness data for the use of our products to each payor. Our inability to promptly obtain coverage and profitable reimbursement rates from government-funded and private payors for our products could have a material adverse effect on our business, financial condition and results of operations, and our ability to raise capital needed to commercialize products.

Our business, financial condition and results of operations will continue to be affected by the efforts of governments and third-party payors to contain or reduce the costs of health care. There have been, and we expect that there will continue to be, a number of federal and state proposals to regulate expenditures for medical products and services, which may affect payments for therapeutic and diagnostic imaging agents such as our products. In addition, an emphasis on managed care increases possible pressure on the pricing of these products. While we cannot predict whether these legislative or regulatory proposals will be adopted, or the effects these

36

Table of Contents

proposals or managed care efforts may have on our business, the announcement of these proposals and the adoption of these proposals or efforts could affect our stock price or our business. Further, to the extent these proposals or efforts have an adverse effect on other companies that are our prospective corporate partners, our ability to establish necessary strategic alliances may be harmed.

If we are unable to comply with applicable governmental regulation we may not be able to continue our operations.

Any products tested, manufactured or distributed by us or on our behalf pursuant to FDA approvals are subject to pervasive and continuing regulation by numerous regulatory authorities, including primarily the FDA. We may be slow to adapt, or we may never adapt to changes in existing requirements or adoption of new requirements or policies. Our failure to comply with regulatory requirements could subject us to enforcement action, including product seizures, recalls, withdrawal, suspension, or revocation of approvals, restrictions on or injunctions against marketing our products based on our technology, and civil and criminal penalties. We may incur significant costs to comply with laws and regulations in the future or compliance with laws or regulations may create an unsustainable burden on our business.

Numerous federal, state and local governmental authorities, principally the FDA, and similar regulatory agencies in other countries, regulate the preclinical testing, clinical trials, manufacture and promotion of any compounds or agents we or our collaborative partners develop, and the manufacturing and marketing of any resulting drugs. The product development and regulatory approval process is lengthy, expensive, uncertain and subject to delays.

The regulatory risks we face also include the following:

- any compound or agent, including generics, we or our collaborative partners develop must receive regulatory agency approval before it may be marketed as a drug in a particular country;
- the regulatory process, which includes preclinical testing and clinical trials of each compound or agent in order to establish its safety and efficacy, varies from country to country, can take many years and requires the expenditure of substantial resources;
- in all circumstances, approval of the use of previously unapproved radioisotopes in certain of our products requires approval of either the Nuclear Regulatory Commission or equivalent state regulatory agencies, which may be a lengthy process. A radioisotope is an unstable form of an element which undergoes radioactive decay, thereby emitting radiation which may be used, for example, to image or destroy harmful growths or tissue;
- data obtained from preclinical and clinical activities are susceptible to varying interpretations which could delay, limit or prevent regulatory agency approval; and
- delays or rejections may be encountered based upon changes in regulatory agency policy during the period of product development and/or the period of review of any application for regulatory agency approval. These delays could adversely affect the marketing of any products we or our collaborative partners develop, impose costly procedures upon our activities, diminish any competitive advantages we or our collaborative partners may attain and adversely affect our ability to receive royalties.

Regulatory agency approval for a product or agent may not be received and may entail limitations on the indicated uses that could limit the potential market for any such product. For example, as disclosed in our press releases and periodic filings, we have exclusive United States

marketing rights to COMBIDEX, an ultrasmall superparamagnetic iron oxide contrast agent for magnetic resonance imaging of lymph nodes, that is pending clearance by the United States Food and Drug Administration. In June 2000, Advanced Magnetics received an approvable letter from the FDA with respect to COMBIDEX. An approvable letter is a written communication to an applicant from the FDA stating that the agency will approve the application or abbreviated application if

Table of Contents

specific and satisfactory additional information or material is submitted or specific conditions are met. An approvable letter does not constitute approval of any part of an application or abbreviated application and does not permit marketing of the drug that is the subject of the application or abbreviated application. We are awaiting further information from the FDA regarding COMBIDEX.

If and when we obtain approval or clearance for our products, the marketing, manufacture, labeling, packaging, adverse event and other reporting, storage, advertising and promotion and record keeping related to our products would remain subject to extensive regulatory requirements. Discovery of previously unknown problems with a drug, its manufacture or its manufacturer may result in restrictions on such drug, manufacture or manufacturer, including withdrawal of the drug from the market.

The United States Food, Drug and Cosmetics Act requires: (i) that our products be manufactured in FDA registered facilities subject to inspection; and (ii) that we comply with cGMP, which imposes certain procedural and documentation requirements upon us and our manufacturing partners with respect to manufacturing and quality assurance activities. If we or our contract partners do not comply with cGMP or we do not comply with any of the FDA s other postmarket requirements we may be subject to sanctions, including fines, injunctions, civil penalties, recalls or seizures of products, total or partial suspension of production, product recalls, failure of the government to grant clearance or premarket approval for devices or premarket approval for drugs or biologics, suspension, revocation or withdrawal of marketing approvals and criminal prosecution.

From time to time, legislation is drafted and introduced in Congress that could significantly change the statutory provisions governing the approval, manufacturing and marketing of products regulated by the FDA. In addition, FDA regulations and guidance are often revised or reinterpreted by the agency in ways that may significantly affect our business and our products. It is impossible to predict whether legislative changes will be enacted, or FDA regulations, guidance or interpretations changed, or what the impact of such changes, if any, may be.

We depend on attracting and retaining key personnel.

We are highly dependent on the principal members of our management and scientific staff. The loss of their services might significantly delay or prevent the achievement of development or strategic objectives. Our success depends on our ability to retain key employees and to attract additional qualified employees. Competition for personnel is intense, and therefore we may not be able to retain existing personnel or attract and retain additional highly qualified employees in the future.

On December 17, 2002, we entered into a letter agreement with Michael D. Becker in connection with Mr. Becker s promotion to President and Chief Executive Officer of the Company. Under the terms of such letter agreement, Mr. Becker receives an annual base salary of $280,000. Mr. Becker is also eligible to participate in our Cytogen Corporation Performance Bonus Plan, as and if approved by our Board of Directors, with a target bonus rate of 30% of base salary based upon performance objectives. Mr. Becker is also entitled to all existing Company benefits, at the sole discretion of the Board of Directors. In addition, Mr. Becker was granted options to purchase 200,000 shares of our common stock under our 1995 Stock Option Plan. Pursuant to the terms of the letter agreement, in the event we terminate Mr. Becker s employment for reasons other than for cause, as defined therein, Mr. Becker shall be entitled to receive twelve month s base pay and continuation of benefits under COBRA, and a pro rata portion of any incentive benefits earned through the date of termination.

We do not carry key person life insurance policies and we do not typically enter into long-term arrangements with our key personnel. If we are unable to hire and retain personnel in key positions, our business financial condition and results of operations could be significantly and adversely affected unless qualified replacements can be found.

38

Table of Contents

Our business exposes us to potential liability claims that may exceed our financial resources, including our insurance coverage, and may lead to the curtailment or termination of our operations.

Our business is subject to product liability risks inherent in the testing, manufacturing and marketing of our products and product liability claims may be asserted against us, our collaborators or our licensees. While we currently maintain product liability insurance in the amount of $10.0 million, such coverage may not be adequate to protect us against future product liability claims. In addition, product liability insurance may not be available to us in the future on commercially reasonable terms, if at all. Although we have not had a history of claims payments that have exceeded our insurance coverage or available financial resources, if liability claims against us exceed our financial resources or coverage amounts, we may have to curtail or terminate our operations. In addition, while we currently maintain directors and officers liability insurance in the amount of $20.0 million, such coverage may not be available on commercially reasonable terms or be adequate to cover any claims that we may be required to satisfy in the future. Our insurance coverage is subject to industry standard and certain other limitations.

Our security measures may not protect our unpatented proprietary technology.

We also rely upon trade secret protection for some of our confidential and proprietary information that is not subject matter for which patent protection is available. To help protect our rights, we require all employees, consultants, advisors and collaborators to enter into confidentiality agreements that require disclosure, and in most cases, assignment to us, of their ideas, developments, discoveries and inventions, and that prohibit the disclosure of confidential information to anyone outside Cytogen or our subsidiaries. Although we are unaware of any unauthorized use or disclosure of our unpatented proprietary technology to date, these agreements may not provide adequate protection for our trade secrets, know-how or other proprietary information or prevent such unauthorized use or disclosure.

The reduced workforce at AxCell may not be able to implement AxCell s business plan.

In September 2002, we implemented the restructuring of our subsidiary, AxCell Biosciences Corporation, in an effort to reduce expenses and position Cytogen for stronger long-term growth in oncology. As a result, we reduced our staff at AxCell by seventy-five percent, suspended certain projects at AxCell and implemented other cost-saving measures.

The technologies under development at AxCell are complex and remain commercially unproven. Even if we are able to develop and commercialize a product through AxCell, there may be fewer than 100 pharmaceutical companies and biotechnology companies that are potential customers for such technology or product.

Although we believe that we have retained the AxCell personnel who are key to achieving AxCell s goals and implementing its strategies, such reduced workforce may not be able to implement AxCell s current business plan. The further loss of any of AxCell s personnel could have a material adverse effect on AxCell s ability to achieve its goals.

We may need to raise additional capital, which may not be available.

Our cash, cash equivalents and short-term investments were $30.2 million at December 31, 2003. We expect that our existing capital resources should be adequate to fund our operations and commitments at least into the middle of 2005.

We have incurred negative cash flows from operations since our inception and have expended, and expect to continue to expend in the future, substantial funds based upon the:

- success of our product commercialization efforts;

- success of any future acquisitions of complementary products and technologies we may make;

Table of Contents

magnitude, scope and results of our product development and research and development efforts;

progress of preclinical studies and clinical trials;

progress toward regulatory approval for our products;

costs of filing, prosecuting, defending and enforcing patent claims and other intellectual property rights;

competing technological and market developments; and

expansion of strategic alliances for the sale, marketing and distribution of our products.

Our business or operations may change in a manner that would consume available resources more rapidly than anticipated. We expect that we will have additional requirements for debt or equity capital, irrespective of whether and when we reach profitability, for further product development costs, product and technology acquisition costs, and working capital. To the extent that our currently available funds and revenues are insufficient to meet current or planned operating requirements, we will be required to obtain additional funds through equity or debt financing, strategic alliances with corporate partners and others, or through other sources. These financial sources may not be available when we need them or they may be available, but on terms that are not commercially acceptable to us. If adequate funds are not available, we may be required to delay, further scale back or eliminate certain aspects of our operations or attempt to obtain funds through arrangements with collaborative partners or others that may require us to relinquish rights to certain of our technologies, product candidates, products or potential markets. If adequate funds are not available, our business, financial condition and results of operations will be materially and adversely affected.

Our capital raising efforts may dilute stockholder interests.

If we raise additional capital by issuing equity securities or convertible debentures, the issuance will result in ownership dilution to our existing stockholders. The extent of such dilution will vary based upon the amount of capital raised.

We may need to raise funds other than through the issuance of equity securities.

If we raise additional funds through collaborations and licensing arrangements, we may be required to relinquish rights to certain of our technologies or product candidates or to grant licenses on unfavorable terms. If we relinquish rights or grant licenses on unfavorable terms, we may not be able to develop or market products in a manner that is profitable to us.

Our PSMA product development program is novel and, consequently, inherently risky.

We are subject to the risks of failure inherent in the development of product candidates based on new technologies, including our PSMA technology. These risks include the possibility that:

the technologies we use will not be effective;

our product candidates will be unsafe;

our product candidates will fail to receive the necessary regulatory approvals;

the product candidates will be hard to manufacture on a large scale or will be uneconomical to market; and

we will not successfully overcome technological challenges presented by our potential new products.

Our other research and development programs involve similarly novel approaches to human therapeutics. Consequently, there is no precedent for the successful commercialization of therapeutic products based on our

Table of Contents

PSMA technologies. If we fail to develop such products, our business financial condition and results of operations could be significantly and adversely affected.

We could be negatively impacted by future interpretation or implementation of federal and state fraud and abuse laws, including anti-kickback laws and, federal and state anti-referral laws.

We are subject to various federal and state laws pertaining to health care fraud and abuse, including anti-kickback laws and physician self-referral laws. Violations of these laws are punishable by criminal and/or civil sanctions, including, in some instances, imprisonment and exclusion from participation in federal and state health care programs, including Medicare, Medicaid, and veterans health programs. We have not been challenged by a governmental authority under any of these laws and believe that our operations are in compliance with such laws.

However, because of the far-reaching nature of these laws, we may be required to alter one or more of our practices to be in compliance with these laws. Health care fraud and abuse regulations are complex, and even minor, inadvertent irregularities can potentially give rise to claims that the law has been violated. Any violations of these laws could result in a material adverse effect on our business, financial condition and results of operations. If there is a change in law, regulation or administrative or judicial interpretations, we may have to change our business practices or our existing business practices could be challenged as unlawful, which could have a material adverse effect on our business, financial condition and results of operations.

We could become subject to false claims litigation under federal statutes, which can lead to civil money penalties, criminal fines and imprisonment, and/or exclusion from participation in federal health care programs. These false claims statutes include the False Claims Act, which allows any person to bring suit alleging false or fraudulent claims under federal programs or other violations of the statute and to share in any amounts paid by the entity to the government in fines or settlement. Such suits, known as *qui tam* actions, have increased significantly in recent years and have increased the risk that companies like us may have to defend a false claim action. We could also become subject to similar false claims litigation under state statutes. If we are unsuccessful in defending any such action, such action may have a material adverse effect on our business, financial condition and results of operations.

Our business involves environmental risks that may result in liability.

We are subject to a variety of local, state, federal and foreign government regulations relating to storage, discharge, handling, emission, generation, manufacture and disposal of toxic, infectious or other hazardous substances used to manufacture our products. If we fail to comply with these regulations, we could be liable for damages, penalties, or other forms of censure and our business could be significantly and adversely affected. We currently do not carry insurance for contamination or injury resulting from the use of such materials.

Two of our marketed products, PROSTASCINT and QUADRAMET utilize radioactive materials. PROSTASCINT is not manufactured or shipped as a radioactive material because the radioactive component is not added until the product has arrived at its final destination (a radiopharmacy). Laureate Pharma, our most recent contract manufacturer of PROSTASCINT, holds a radioactive materials license because such license is required for certain release and stability tests of the product.

QUADRAMET, however, is manufactured and shipped as radioactive, and therefore, the manufacturing and distribution of this product must comply with regulations promulgated by the U.S. Nuclear Regulatory Commission. BMSMI manufacturers and distributes QUADRAMET, and

is, therefore, subject to these regulations.

We are currently subject to patent litigation.

On March 17, 2000, we were served with a complaint filed against us in the United States District Court for the District of New Jersey by M. David Goldenberg and Immunomedics, Inc. (collectively Plaintiffs). The

Table of Contents

litigation claims that our PROSTASCINT product infringes a patent purportedly owned by Goldenberg and licensed to Immunomedics. The patent sought to be enforced in the litigation has now expired; as a result, the claim, even if successful, would not result in an injunction barring the continued sale of PROSTASCINT or affect any other of our products or technology. We believe that PROSTASCINT did not infringe this patent, and that the patent was invalid and unenforceable. The patent sought to be enforced in the litigation has now expired; as a result, the claim, even if successful, would not result in an injunction barring the continued sale of PROSTASCINT or affect any other of our products or technology. In addition, we have certain rights to indemnification against litigation and litigation expenses from the inventor of technology used in PROSTASCINT, which may be offset against royalty payments on sales of PROSTASCINT. However, given the uncertainty associated with litigation, we may incur material expenditures. On December 17, 2001, Cytogen filed a motion for summary judgment of non-infringement of the asserted claims of the patent-in-suit. The Plaintiffs opposed that motion and filed their own cross-motion for summary judgment of infringement. On July 3, 2002, the Court denied both parties summary judgment motions, with leave to renew those motions after presenting expert testimony and legal argument based upon that testimony. The parties subsequently presented expert testimony and submitted additional briefing. On April 29, 2003, our motion for summary judgment of non-infringement of all asserted claims was granted, plaintiffs motion for summary judgment of infringement was denied and the case was ordered closed. On May 12, 2003, Plaintiffs filed a Notice of Appeal regarding this decision to the U.S. Court of Appeals for the Federal Circuit, and subsequently filed their opening brief on July 28, 2003. On September 22, 2003, Cytogen filed its responsive brief. On October 23, 2003, Plaintiffs filed their reply brief in the Federal Circuit. The appeal is now fully briefed and oral argument was held on March 2, 2004. The Court has not indicated when it expects to issue a ruling, however, given the uncertainty associated with litigation, we cannot give any assurance that the litigation could not result in a material expenditure to us.

Our stock price has been and may continue to be volatile, and your investment in our stock could decline in value or fluctuate significantly.

The market prices for securities of biotechnology and pharmaceutical companies have historically been highly volatile, and the market has from time to time experienced significant price and volume fluctuations that are unrelated to the operating performance of particular companies. The market price of our common stock has fluctuated over a wide range and may continue to fluctuate for various reasons, including, but not limited to, announcements concerning our competitors or us regarding:

- results of clinical trials;
- technological innovations or new commercial products;
- changes in governmental regulation or the status of our regulatory approvals or applications;
- changes in earnings;
- changes in health care policies and practices;
- developments or disputes concerning proprietary rights;
- litigation or public concern as to safety of the our potential products; and
- changes in general market conditions.

These fluctuations may be exaggerated if the trading volume of our common stock is low. These fluctuations may or may not be based upon any of our business or operating results. Our common stock may experience similar or even more dramatic price and volume fluctuations which may continue indefinitely.

We have adopted various anti-takeover provisions which may affect the market price of our common stock and prevent or frustrate attempts by our stockholders to replace or remove our management team.

Our Board of Directors has the authority, without further action by the holders of common stock, to issue from time to time, up to 5,400,000 shares of preferred stock in one or more classes or series, and to fix the rights

Table of Contents

and preferences of the preferred stock. Pursuant to these provisions, we have implemented a stockholder rights plan by which one preferred stock purchase right is attached to each share of common stock, as a means to deter coercive takeover tactics and to prevent an acquirer from gaining control of us without some mechanism to secure a fair price for all of our stockholders if an acquisition was completed. These rights will be exercisable if a person or group acquires beneficial ownership of 20% or more of our common stock and can be made exercisable by action of our board of directors if a person or group commences a tender offer which would result in such person or group beneficially owning 20% or more of our common stock. Each right will entitle the holder to buy one one-thousandth of a share of a new series of our junior participating preferred stock for $20. If any person or group becomes the beneficial owner of 20% or more of our common stock (with certain limited exceptions), then each right not owned by the 20% stockholder will entitle its holder to purchase, at the right s then current exercise price, common shares having a market value of twice the exercise price. In addition, if after any person has become a 20% stockholder, we are involved in a merger or other business combination transaction with another person, each right will entitle its holder (other than the 20% stockholder) to purchase, at the right s then current exercise price, common shares of the acquiring company having a value of twice the right s then current exercise price.

We are subject to provisions of Delaware corporate law which, subject to certain exceptions, will prohibit us from engaging in any business combination with a person who, together with affiliates and associates, owns 15% or more of our common stock for a period of three years following the date that the person came to own 15% or more of our common stock unless the business combination is approved in a prescribed manner.

These provisions of the stockholder rights plan, our certificate of incorporation, and of Delaware law may have the effect of delaying, deterring or preventing a change in control of Cytogen, may discourage bids for our common stock at a premium over market price and may adversely affect the market price, and the voting and other rights of the holders, of our common stock. In addition, these provisions make it more difficult to replace or remove our current management team in the event our stockholders believe this would be in the best interest of the Company and our stockholders.

The liquidity of our common stock could be adversely affected if we are delisted from The Nasdaq National Market.

In the event that we are unable maintain compliance with all relevant Nasdaq Listing Standards, our securities may be subject to delisting from the Nasdaq National Market. If such delisting occurs, the market price and market liquidity of our common stock may be adversely affected.

Alternatively, if faced with such delisting, we may submit an application to transfer the listing of our common stock to the Nasdaq SmallCap Market. The Nasdaq SmallCap Market also has a $1.00 minimum bid price requirement.

If our common stock is delisted by Nasdaq, our common stock would be eligible to trade on the OTC Bulletin Board maintained by Nasdaq, another over-the-counter quotation system, or on the pink sheets where an investor may find it more difficult to dispose of or obtain accurate quotations as to the market value of our common stock. In addition, we would be subject to a rule promulgated by the Securities and Exchange Commission that, if we fail to meet criteria set forth in such rule, imposes various practice requirements on broker-dealers who sell securities governed by the rule to persons other than established customers and accredited investors. Consequently, such rule may deter broker-dealers from recommending or selling our common stock, which may further affect the liquidity of our common stock.

Delisting from Nasdaq would make trading our common stock more difficult for investors, potentially leading to further declines in our share price. It would also make it more difficult for us to raise additional capital. Further, if we are delisted, we would also incur additional costs under state blue sky laws in connection

43

Table of Contents

with any sales of our securities. These requirements could severely limit the market liquidity of our common stock and the ability of our shareholders to sell our common stock in the secondary market.

A large number of our shares are eligible for future sale which may adversely impact the market price of our common stock.

A large number of shares of our common stock are already outstanding, issuable upon exercise of options and warrants, or the achievement of certain milestones under previously completed acquisitions and may be eligible for resale. This availability of a significant number of additional shares of our common stock for future sale and issuance could depress the price of our common stock.

Because we do not intend to pay, and have not paid, any cash dividends on our shares of common stock, our stockholders will not be able to receive a return on their shares unless the value of our shares appreciates and they sell them.

We have never paid or declared any cash dividends on our common stock or other securities and intend to retain any future earnings to finance the development and expansion of our business. We do not anticipate paying any cash dividends on our common stock in the foreseeable future. Therefore, our stockholders will not be able to receive a return on their shares unless the value of our shares appreciates and they sell them.

Item 2. Properties

In August 2002, we moved our main offices from 600 College Road East to 650 College Road East in Princeton, New Jersey. On February 10, 2004, we entered into an amendment to our existing sublease agreement to increase the amount of space we occupy from approximately 11,500 square feet to approximately 16,100 square feet. Such amendment also extended the expiration date of our sublease to October 2007, with a 2 year option to renew thereafter. We intend to remain headquartered in Princeton, New Jersey for the foreseeable future.

We also lease approximately 9,200 square feet of laboratory and office space in Newtown, Pennsylvania, which is occupied by our AxCell Biosciences subsidiary. In February 2001, we expanded the AxCell facility by amending the lease to include approximately an additional 5,700 square feet, which additional lease space will expire in September 2006. We sublease approximately 2,400 square feet of the Axcell space to another company. Such sublease will expire in August 2006.

We own substantially all of the equipment used in our laboratories and offices. We believe our facilities are adequate for our operations at present.

Item 3. Legal Proceedings

On March 17, 2000, we were served with a complaint filed against us in the United States District Court for the District of New Jersey by M. David Goldenberg and Immunomedics, Inc. (collectively Plaintiffs). The litigation claims that our PROSTASCINT product infringes a patent purportedly owned by Goldenberg and licensed to Immunomedics. The patent sought to be enforced in the litigation has now expired; as a result, the claim, even if successful, would not result in an injunction barring the continued sale of PROSTASCINT or affect any other of our products or technology. We believe that PROSTASCINT did not infringe this patent, and that the patent was invalid and unenforceable. The patent sought

to be enforced in the litigation has now expired; as a result, the claim, even if successful, would not result in an injunction barring the continued sale of PROSTASCINT or affect any other of our products or technology. In addition, we have certain rights to indemnification against litigation and litigation expenses from the inventor of technology used in PROSTASCINT, which may be offset against royalty payments on sales of PROSTASCINT. However, given the uncertainty associated with litigation, we may incur material expenditures. On December 17, 2001, Cytogen filed

Table of Contents

a motion for summary judgment of non-infringement of the asserted claims of the patent-in-suit. The Plaintiffs opposed that motion and filed their own cross-motion for summary judgment of infringement. On July 3, 2002, the Court denied both parties summary judgment motions, with leave to renew those motions after presenting expert testimony and legal argument based upon that testimony. The parties subsequently presented expert testimony and submitted additional briefing. On April 29, 2003, our motion for summary judgment of non-infringement of all asserted claims was granted, plaintiffs motion for summary judgment of infringement was denied and the case was ordered closed. On May 12, 2003, Plaintiffs filed a Notice of Appeal regarding this decision to the U.S. Court of Appeals for the Federal Circuit, and subsequently filed their opening brief on July 28, 2003. On September 22, 2003, Cytogen filed its responsive brief. On October 23, 2003, Plaintiffs filed their reply brief in the Federal Circuit. The appeal is now fully briefed and oral argument was held on March 2, 2004. The Court has not indicated when it expects to issue a ruling, however given the uncertainty associated with litigation, we cannot give any assurance that the litigation could not result in a material expenditure to us.

Item 4. Submission of Matters to a Vote of Security Holders

Not applicable.

Table of Contents

PART II

Item 5. Market for the Company s Common Equity, Related Stockholder Matters and Company Purchases of Equity Securities

Our common stock is traded on the Nasdaq National Market under the trading symbol CYTO.

The table below sets forth the high and low bid information for our common stock for each of the calendar quarters indicated, as reported on the Nasdaq National Market. Such quotations reflect inter-dealer prices, without retail mark-up, mark-down or commission, may not represent actual transactions and have been adjusted to reflect the Company s one-for-ten reverse stock split executed October 25, 2002.

2002	High	Low
First Quarter	$ 34.40	$ 21.10
Second Quarter	$ 22.00	$ 9.10
Third Quarter	$ 11.00	$ 3.10
Fourth Quarter	$ 8.40	$ 3.30
2003		
First Quarter	$ 3.89	$ 2.51
Second Quarter	$ 8.59	$ 2.63
Third Quarter	$ 14.46	$ 7.78
Fourth Quarter	$ 13.40	$ 9.26

As of February 25, 2004, there were approximately 4,000 holders of record of our common stock and there were approximately 38,500 beneficial holders of our common stock.

We have never paid any cash dividends on our common stock and we do not anticipate paying any cash dividends on our common stock in the foreseeable future. We intend to retain any future earnings to fund the development and growth of our business. Any future determination to pay dividends will be at the discretion of the board of directors.

Table of Contents

Item 6. Selected Financial Data

The following selected financial information has been derived from our audited consolidated financial statements for each of the five years in the period ended December 31, 2003. The selected financial data set forth below should be read in conjunction with the consolidated financial statements, including the notes thereto, Management s Discussion and Analysis of Financial Condition and Results of Operations and other information provided elsewhere in this report.

	Year Ended December 31,				
	2003	2002	2001	2000	1999
Statements of Operations Data:	(All amounts in thousands, except per share data)				
Revenues:					
Product sales	$ 9,823	$ 10,626	$ 8,782	$ 7,523	$ 7,073
Royalties	1,105	1,842	2,063	2,004	1,060
License and contract	2,914	463	912	1,024	3,171
Total revenues	13,842	12,931	11,757	10,551	11,304
Operating Expenses:					
Cost of product related and contract manufacturing revenues	6,268	4,748	4,216	4,513	4,213
Selling, general and administrative	11,550	11,247	11,178	11,060	7,711
Research and development	2,659	7,605	10,091	6,957	3,849
Equity in loss of joint venture	3,452	2,886	332		
Impairment of intangible assets[1]	115	1,729			
Acquisition of marketing and technology rights[2]				13,241	1,214
Total operating expenses	24,044	28,215	25,817	35,771	16,987
Operating loss	(10,202)	(15,284)	(14,060)	(25,220)	(5,683)
Loss on investment		(516)			
Gain on sale of laboratory and manufacturing facilities					3,298
Other income (expense), net	(44)	101	857	611	412
Loss before income taxes and cumulative effect of accounting change	(10,246)	(15,699)	(13,203)	(24,609)	(1,973)
Income tax benefit	(888)				