Opko Health, Inc.
Form 10-K
March 31, 2008

UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
WASHINGTON, DC 20549

FORM 10-K

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

For the fiscal year ended December 31, 2007

OR

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

Commission file number 000-26648

OPKO HEALTH, INC.
(Exact Name of Registrant as Specified in Its Charter)

DELAWARE	75-2402409
(State or Other Jurisdiction of Incorporation or Organization)	(I.R.S. Employer Identification No.)

4400 Biscayne Blvd., Suite 1180, Miami, FL 33137
(Address of Principal Executive Offices, Zip Code)

Registrant's Telephone Number, Including Area Code: (305) 575-4138

Securities registered pursuant to section 12(b) of the Act:

Title of Each Class	Name of Each Exchange on Which Registered
Common Stock, $.01 par value per share	American Stock Exchange

Indicate by check mark if the registrant is a well-known seasoned issuer, as defined in Rule 405 of the Securities Act. Yes ¨ No þ

Indicate by check mark if the registrant is not required to file reports pursuant to Section 13 or Section 15(d) of the Act. Yes ¨ No þ

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 ¨ No þ

Indicate by check mark if disclosures 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 a large accelerated filer, an accelerated filer, a non-accelerated filer, or a smaller reporting company (as defined in Rule 12b-2 of the Exchange Act).

Large Accelerated filer ¨	Accelerated filer ¨	Non-Accelerated filer þ	Smaller Reporting Company ¨

Indicate by check mark whether the registrant is a shell company (as defined in Rule 12b-2 Act). Yes ¨ No þ

The aggregate market value of the voting and non-voting common equity held by non-affiliates computed by reference to the price at which the common equity was last sold, as of the last business day of the Registrant's most recently completed second fiscal quarter was: $236,986,298.

As of March 21, 2008 the registrant had 182,150,969 shares of common stock outstanding.

Documents Incorporated by Reference

Portions of the registrant's definitive proxy statement for its 2008 Annual Meeting of Stockholders are incorporated by reference in Items 10, 11, 12, 13, and 14 of Part III of this Annual Report on Form 10-K.

TABLE OF CONTENTS

CAUTIONARY STATEMENTS REGARDING FORWARD-LOOKING STATEMENTS

This Annual Report on Form 10-K contains "forward-looking statements," as that term is defined under the Private Securities Reform Act of 1995, or PSLRA, Section 27A of the Securities Act of 1933, as amended, and Section 21E of the Securities Exchange Act of 1934, as amended. Forward-looking statements include statements about our expectations, beliefs or intentions regarding our product development efforts, business, financial condition, results of operations, strategies or prospects. You can identify forward-looking statements by the fact that these statements do not relate strictly to historical or current matters. Rather, forward-looking statements relate to anticipated or expected events, activities, trends or results as of the date they are made. Because forward-looking statements relate to matters that have not yet occurred, these statements are inherently subject to risks and uncertainties that could cause our actual results to differ materially from any future results expressed or implied by the forward-looking statements. Many factors could cause our actual activities or results to differ materially from the activities and results anticipated in forward-looking statements. These factors include those described below and in "Item 1A-Risk Factors" of this Annual Report on Form 10-K. We do not undertake any obligation to update forward-looking statements. We intend that all forward-looking statements be subject to the safe-harbor provisions of the PSLRA. These forward-looking statements are only predictions and reflect our views as of the date they are made with respect to future events and financial performance.

Risks and uncertainties, the occurrence of which could adversely affect our business, include the following:

- We have a history of operating losses and we do not expect to become profitable in the near future.
- Our technologies are in an early stage of development and are unproven.
- Our drug research and development activities may not result in commercially viable products.
- We are highly dependent on the success of our lead product candidate, bevasiranib, and we cannot give any assurance that it will receive regulatory approval or be successfully commercialized.
- The results of previous clinical trials may not be predictive of future results, and our current and planned clinical trials may not satisfy the requirements of the FDA or other non-United States regulatory authorities.
- We will require substantial additional funding, which may not be available to us on acceptable terms, or at all.
- If our competitors develop and market products that are more effective, safer or less expensive than our future product candidates, our commercial opportunities will be negatively impacted.
- The regulatory approval process is expensive, time consuming and uncertain and may prevent us or our collaboration partners from obtaining approvals for the commercialization of some or all of our product candidates.
- Failure to recruit and enroll patients for clinical trials may cause the development of our product candidates to be delayed.
- Even if we obtain regulatory approvals for our product candidates, the terms of approvals and ongoing regulation of our products may limit how we manufacture and market our product candidates, which could materially impair our ability to generate anticipated revenues.
- We may not meet regulatory quality standards applicable to our manufacturing and quality processes.
- We may be unable to resolve issues relating to an FDA warning letter in a timely manner.

- Even if we receive regulatory approval to market our product candidates, the market may not be receptive to our products.

- If we fail to attract and retain key management and scientific personnel, we may be unable to successfully develop or commercialize our product candidates.

- As we evolve from a company primarily involved in development to a company also involved in commercialization, we may encounter difficulties in managing our growth and expanding our operations successfully.

- If we fail to acquire and develop other products or product candidates at all or on commercially reasonable terms, we may be unable to diversify or grow our business.

- We have no experience manufacturing our pharmaceutical product candidates and we therefore rely on third parties to manufacture and supply our pharmaceutical product candidates, and would need to meet various standards necessary to satisfy FDA regulations when we commence manufacturing.

- We currently have no pharmaceutical marketing, sales or distribution organization. If we are unable to develop our sales and marketing and distribution capability on our own or through collaborations with marketing partners, we will not be successful in commercializing our pharmaceutical product candidates.

- Independent clinical investigators and contract research organizations that we engage to conduct our clinical trials may not be diligent, careful or timely.

- The success of our business may be dependent on the actions of our collaborative partners.

- If we are unable to obtain and enforce patent protection for our products, our business could be materially harmed.

- If we are unable to protect the confidentiality of our proprietary information and know-how, the value of our technology and products could be adversely affected.

- We will rely heavily on licenses from third parties.

- We license patent rights to certain of our technology from third-party owners. If such owners do not properly maintain or enforce the patents underlying such licenses, our competitive position and business prospects will be harmed.

- Our commercial success depends significantly on our ability to operate without infringing the patents and other proprietary rights of third parties.

- Medicare prescription drug coverage legislation and future legislative or regulatory reform of the health care system may affect our ability to sell our products profitably.

- Failure to obtain regulatory approval outside the United States will prevent us from marketing our product candidates abroad.

- Acquisitions may disrupt our business, distract our management and may not proceed as planned; and we may encounter difficulties in integrating acquired businesses.

- Non-United States governments often impose strict price controls, which may adversely affect our future profitability.

- Our business may become subject to economic, political, regulatory and other risks associated with international operations.

- The market price of our common stock may fluctuate significantly.

- Directors, executive officers, principal stockholders and affiliated entities own a significant percentage of our capital stock, and they may make decisions that you do not consider to be in your best interests or in the best interests of our stockholders.

·Compliance with changing regulations concerning corporate governance and public disclosure may result in additional expenses.

- If we are unable to satisfy the requirements of Section 404 of the Sarbanes-Oxley Act of 2002, as they apply to us, or our internal controls over financial reporting are not effective, the reliability of our financial statements may be questioned and our common stock price may suffer.

- We may be unable to maintain our listing on the American Stock Exchange, which could cause our stock price to fall and decrease the liquidity of our common stock.

- Future issuances of common stock and hedging activities may depress the trading price of our common stock.

- Provisions in our charter documents and Delaware law could discourage an acquisition of us by a third party, even if the acquisition would be favorable to you.

- We do not intend to pay cash dividends on our common stock in the foreseeable future.

PART I

Unless the context otherwise requires, all references in this Annual Report on Form 10-K to the "Company", "OPKO", "we", "our", "ours", and "us" refers to OPKO Health, Inc., a Delaware corporation, including our wholly-owned subsidiaries.

ITEM 1. BUSINESS

OVERVIEW

We are a specialty healthcare company focused on the discovery, development and commercialization of proprietary pharmaceuticals, drug delivery technologies, diagnostic systems, and instruments for the treatment, diagnosis and management of ophthalmic disorders. Our business presently consists of the development of ophthalmic pharmaceuticals and the development, commercialization and sale of ophthalmic diagnostic and imaging systems and instrumentation products. Our objective is to establish industry-leading positions in large and rapidly growing segments of ophthalmology by leveraging our preclinical and development expertise and our novel and proprietary technologies. We actively explore opportunities to acquire complementary pharmaceuticals, compounds, and technologies, which could, individually or in the aggregate, materially increase the scale of our business. We also intend to explore strategic opportunities in other medical markets that would allow us to benefit from our business and global distribution expertise, and which have operational characteristics that are similar to ophthalmology, such as dermatology. We intend to expand under the following strategic objectives.

Leverage R&D strengths to develop our pharmaceutical product pipeline. We plan to leverage our strengths in siRNA drug development, RNAi technology, and all phases of pharmaceutical research and development to further develop and commercialize a pipeline of pharmaceutical products used in the treatment of ophthalmic disorders with unmet medical needs, such as Age-Related Macular Degeneration, or AMD, glaucoma, diabetic retinopathy, and dry eye, among others.

Develop novel diagnostic and disease management technologies. We plan to invest in and develop novel technologies and products to diagnose ophthalmic disorders at the earliest stages and to monitor the disease state and track the impact of intervention over time and during the course of treatment. We believe these technologies will improve our understanding of disease processes, help individualize treatment options, improve clinical decision making and enhance clinical outcomes and quality of life for patients with a variety of ocular disorders, including AMD, diabetic retinopathy and glaucoma.

Utilize expertise and resources to develop other ophthalmic products. We also plan to use our expertise and resources to develop and commercialize other types of ophthalmic products beyond pharmaceutical products and diagnostic and imaging systems, including without limitation, drug delivery systems and other ophthalmic devices which aid in the management of ocular disorders.

Acquire additional ophthalmic businesses, therapies and technologies and expand into complementary businesses. We continue to seek to expand our current operations by acquiring additional ophthalmic businesses and therapeutic and diagnostic technologies. We also intend to explore strategic opportunities in other medical markets that would allow us to benefit from our business and global distribution expertise, and which have operational characteristics that are similar to ophthalmology, such as dermatology. While we have not yet made any definitive plans to acquire any dermatology-related businesses, we believe that there are opportunities to apply our expertise to this field.

Utilize expertise and resources to enhance our competitive position. We intend to utilize our wide-ranging technological innovation and proprietary position to enhance our competitive position in the ophthalmic products market. For example, we intend to utilize our diagnostic and instrumentation products to measure disease progression and treatment outcomes of our pharmaceutical products in clinical trials.

Key elements of our strategy are to:

- Obtain regulatory approval for our lead product candidate, bevasiranib, for Wet AMD;
- Develop a focused commercialization capability in the United States;
- Strategically utilize our R&D resources to advance our product pipeline;

- Develop and grow our instrumentation business beyond diagnostic and imaging systems to include drug delivery devices and other therapeutic devices and technologies;

- Utilize our ophthalmic expertise to identify and acquire companies with innovative ophthalmic technologies; and

- Expand into other medical markets, including dermatology, which we believe are complementary to and synergistic with our ophthalmology business.

Corporate Information

We were originally incorporated in Delaware in October 1991 under the name Cytoclonal Pharmaceutics, Inc., which was later changed to eXegenics, Inc. On March 27, 2007, we were part of a three-way merger with Froptix Corporation, or Froptix, a research and development company, and Acuity Pharmaceuticals, Inc., or Acuity, a research and development company. This transaction was accounted for as a reverse merger between Froptix and eXegenics, with the combined company then acquiring Acuity. eXegenics was previously involved in the research, creation, and development of drugs for the treatment and/or prevention of cancer and infectious diseases; however, eXegenics had been a public shell company without any operations since 2003. On June 8, 2007, we changed our name to OPKO Health, Inc.

On November 28, 2007, we acquired Ophthalmic Technologies, Inc., or OTI, an Ontario corporation pursuant to a definitive share purchase agreement with OTI and its shareholders. As a result of this agreement, we have entered into the ophthalmic instrumentation market and have begun generating revenue from this business.

Our shares are publicly traded on the American Stock Exchange under the ticker “OPK”. Our principal executive offices are located in Miami, Florida. Our clinical operations are based in Morristown, New Jersey. OTI has offices in Toronto, Ontario, Canada, with a research and development branch office in Kingston, Ontario, Canada. OTI also maintains a research and development office in the United Kingdom at the University of Kent. We maintain a website at www.OPKO.com.

BUSINESS

We presently have eight compounds and technologies in research and development for the ophthalmic pharmaceutical market. Our most advanced drug candidate is bevasiranib, which we are developing for the treatment of Wet AMD. In July 2007, we initiated the first of two required pivotal Phase III trials for bevasiranib. Bevasiranib is the first therapy in late stage clinical development based on the Nobel Prize-winning RNA interference, or RNAi technology, and we believe it is the most advanced siRNA-based drug currently in development. Bevasiranib is administered locally to the eye through an intravitreal injection, and is designed to require administration every eight to 12 weeks. Lucentis®, an FDA approved treatment for the treatment of Wet AMD currently on the market, is recommended to be administered through intravitreal injection every four weeks. We are also researching and developing several novel pharmaceutical products for ophthalmic disorders, including Dry AMD, diabetic retinopathy and Diabetic Macular Edema, or DME, dry eye, viral conjunctivitis, and prevention of ocular infection. The following table lists our most advanced pharmaceutical product candidates, the initial indications that we plan to address through their development, and their development stage.

Product Candidate	Initial Indication	Development Stage
Bevasiranib	Wet AMD	Phase III
Bevasiranib	Diabetic Retinopathy/DME	Phase I / II
Civamide	Dry Eye	Phase I/II

ACU-HHY-011	Wet AMD, Diabetic Retinopathy/DME	Pre-Clinical
ACU-XSP-001	Allergy and Inflammation	Pre-Clinical
Wound Dressing	Post-surgical Wound Healing	Late Stage Research
ACU-HTR-028	Wound-Healing-Antifibrotic	Pre-Clinical
Dry-AMD Compound	AMD	Pre-Clinical
N-Chlorotaurine	Viral Conjunctivitis	Late Stage Research

In April 2007, we acquired 33% of Ophthalmic Technologies, Inc., or OTI, and in November 2007, we acquired the remaining 67% of OTI. Through OTI, we presently market four ophthalmic diagnostic systems and instrumentation products in over 60 countries worldwide. We offer innovative systems with advanced imaging capabilities and tools designed to meet the needs of eye care professionals.

We offer a full line of advanced imaging products and ultrasound used by eye care professionals for both routine and specialized care. These technologically advanced systems are routinely used in the screening and management of major eye diseases, provide key information for treatment decisions, and complement our therapeutic products. In the future, for example, we expect that patient outcomes will be significantly optimized by the use of our instrumentation products in individualizing treatment as well as monitoring and tracking disease progression and treatment outcomes. We believe our OCT / SLO system is an innovative product offering significant advantages over current technology and providing a flexible platform that can process a wide variety of diagnostic tests. OTI has offices in Canada and the United Kingdom, and a growing distributor network that currently covers more than 60 countries.

OPHTHALMIC PHARMACEUTICAL MARKET

In the developed world, major vision threatening disorders include cataracts, glaucoma, AMD, and diabetic retinopathy/DME. To date, we have primarily focused our resources on developing drugs to prevent and treat AMD, as well as diabetic retinopathy/DME.

The ophthalmic pharmaceutical market in the developed world is driven by:

- An aging population and increased life expectancy;
- Increased incidence of chronic and age-related disorders with vision destroying characteristics, such as Diabetes (Type I and II), and other metabolic syndromes;
- Better understanding of the pathophysiology of diseases;
- Emerging technologies to diagnose, treat and manage ophthalmic diseases; and
- Improved access to medical care.

Age Related Macular Degeneration ("AMD")

AMD is a back-of-the-eye disease involving the retina, macula and fovea, which is characterized by loss of central visual acuity. AMD affects the central part of the retina, known as the macula. The extent of vision loss is dependent on the degree to which the center of the macula, the fovea, is affected. The fovea is responsible for vision acuity. The rest of the retina outside of the macular area is responsible for peripheral vision, which is usually unaffected in AMD patients. Untreated AMD can significantly impact an affected individual's quality of life.

AMD accounts for approximately 55% of blindness in the United States. Direct and indirect costs attributed to the treatment of AMD in the United States are approximately $30 to $40 billion annually, according to the National Eye Institute, a division of the National Institutes of Health. Age is the primary risk factor for AMD, and the number of cases of AMD is expected to increase significantly as the population ages. AMD afflicts approximately 9 million Americans, and the current Wet AMD treatment market is approaching 2 million patients in the United States. There are two forms of AMD, Dry and Wet. Wet AMD is the result of the formation of new, leaky, poorly organized blood vessels under the retina, which is known as neovascularization. The blood vessels are delicate and break easily, causing bleeding, swelling and the formation of scar tissue, which results in visual impairment and/or blindness. Although more common than Wet AMD, Dry AMD typically results in a less severe, more gradual loss of vision. Wet AMD is considered a more serious disease, with clinically demonstrated vision loss occurring within three to six months of diagnosis. Currently there is no known proven pharmaceutical therapy for Dry AMD.

Diabetic Retinopathy/Diabetic Macular Edema

Diabetic retinopathy is the most common diabetic eye disease. It is caused by damage to blood vessels in the retina. Diabetic Macular Edema, or DME, a medical condition which occurs when the damaged blood vessels leak fluid and lipids onto the macula, the portion of the retina that allows us to see detail, is present in approximately 25% of all diabetic retinopathy cases. DME can occur at any stage in diabetic retinopathy development, and it is possible for advanced diabetic retinopathy and DME to occur simultaneously in the same patient. DME is the leading cause of visual impairment for people with diabetic retinopathy, and the population suffering from DME is expected to grow as a result of an increasing incidence of Type II diabetes in the United States.

OPHTHALMIC PHARMACEUTICAL BUSINESS

We have concentrated significant resources to address ophthalmic disease in large and growing markets by employing a powerful and rapidly progressing technology, known as RNAi, to develop our lead product candidate, bevasiranib. In October 2006, the Nobel prize in Medicine was awarded to the two individuals who discovered RNAi. We have taken advantage of this major scientific breakthrough by inventing and developing siRNAs that shut down the production of proteins that cause ophthalmic diseases. We believe we are a pioneer in this area as we conducted the first clinical trials ever with an siRNA and obtained the first clinical proof of concept with a siRNA. We intend to market bevasiranib, which is our most advanced therapeutic compound, as a treatment for Wet AMD. Bevasiranib is a first in class siRNA drug designed to silence the genes that cause vascular endothelial growth factor, or VEGF, which is believed to be largely responsible for the vision loss associated with Wet AMD and other related ocular conditions. We believe that bevasiranib is the most advanced siRNA-based drug currently in development. We believe that RNA-interference based drugs have the potential to be a significant advancement over the VEGF inhibitors presently on the market because they block the synthesis of VEGF as opposed to merely neutralizing existing VEGF. In addition, RNA-interference based drugs should require less frequent administration than VEGF inhibitors and have a better safety profile.

We have utilized our expertise in ophthalmology and RNAi technology to take bevasiranib from the laboratory through animal models into clinical trials. We have completed two Phase II clinical trials studying the use of bevasiranib as a treatment for Wet AMD and DME. Bevasiranib demonstrated safety and potential to show efficacy in our Phase II clinical trial for Wet AMD in 129 patients. Results showed bevasiranib to be safe and well-tolerated, with a dose-related effect evident across multiple endpoints including near vision, choroidal neovascularization, or CNV, size and time to rescue.

In July 2007, we commenced our pivotal multi-national Phase III COBALT, or Combining Bevasiranib And Lucentis® Therapy, clinical trial of bevasiranib for the treatment of Wet AMD. The trial will include more than 330 Wet AMD patients and will assess whether bevasiranib administered every eight or 12 weeks is safe and has equivalent efficacy in preventing vision loss as Lucentis® administered every four weeks. Interim analysis of safety and efficacy will be made at week 60.

We believe that bevasiranib will be an improvement over existing and anticipated therapies for Wet AMD as it addresses the underlying source of VEGF production, rather than merely neutralizing existing VEGF. Currently marketed drugs for the treatment of Wet AMD are antagonist-based and are only designed to neutralize existing VEGF. We also believe bevasiranib has a better safety profile than VEGF inhibitors in that we do not believe it has the serious systemic side effects associated with VEGF inhibitors in some patients.

We are also developing product candidates for additional ophthalmic disorders, including the treatment of dry eye, diabetic retinopathy and DME, complications of ocular surgery, viral conjunctivitis, and the fibrotic component of Wet AMD and Dry AMD. In order to treat these disorders, we are using compounds that induce lacrimation, are anti-angiogenic, anti-inflammatory, anti-fibrotic and anti-Drusen. These products address eye diseases with large markets and major unmet medical needs, and range in developmental stage from clinical to preclinical.

Bevasiranib Commercial Potential

We have an exclusive license to commercialize bevasiranib. We believe there are three primary potential therapeutic profiles for bevasiranib in the marketplace: maintenance therapy, primary therapy and preventative treatment.

Maintenance Therapy. We anticipate that bevasiranib will be used by itself as a maintenance therapy to inhibit VEGF production following an initiation therapy with an approved VEGF antagonist drug. After the antagonist has absorbed extracellular VEGF, bevasiranib could be used to suppress the formation of new VEGF and maintain a patient's vision.

Primary Therapy. It is possible that not all patients will require the VEGF antagonist initiation regimen due to low VEGF load at time of diagnosis. These patients may get the full benefit from bevasiranib alone. Additionally, not all patients respond favorably to the currently marketed VEGF antagonist. Finally, when used in combination with other therapies bevasiranib's sustained VEGF suppression may add to the antagonist's activity and provide a better outcome than that of the VEGF antagonist alone.

Preventative Therapy. Certain patients who do not yet have the wet form of AMD may be determined to be at high-risk for progressing to the wet form. Bevasiranib may prevent these high-risk patients from progressing to Wet AMD. The current VEGF antagonist products will not likely provide any benefit to this type of patient because of the lack of any VEGF to absorb.

Clinical Results and Program Status of Bevasiranib

The following table summarizes the status of our material clinical trials of bevasiranib to date:

Indication	Trial Name	Phase	Objectives	Number of Patients	Enrollment Status
Wet AMD	CARBON study	Phase III	Dose ranging, Safety and Efficacy	~500	Initiation planned for 2009
Wet AMD	COBALT study	Phase III	Safety and Efficacy	~330	Initiated July 2007
Wet AMD	CARE Trial	Phase II	Safety / Dosage / Efficacy	129	Complete
Wet AMD	NA	Phase I	Safety	15	Complete
DME	RACE Trial	Phase II	Safety / Dosage / Efficacy	48	Complete

Clinical Trials for the Treatment of Wet AMD

The COBALT Study. In July 2007, we initiated this pivotal Phase III study of bevasiranib for the treatment of Wet AMD. The multi-national COBALT study is currently open and enrolling patients. The trial will include approximately 330 wet AMD patients and will assess whether bevasiranib administered every eight or 12 weeks is safe and has equivalent efficacy in preventing vision loss as Lucentis® administered every four weeks. This study has been designed to show that bevasiranib is safe and efficacious for the treatment of wet AMD following an initiation with Lucentis®. Additionally, the study has been designed to demonstrate that in patients that receive an initiation therapy with Lucentis®, a less frequent administration of bevasiranib is equivalent or superior to monthly treatments of Lucentis®.

We currently anticipate initiating a second Phase III clinical trial of bevasiranib in or around 2009. This clinical trial of bevasiranib for the treatment of Wet AMD will be referred to as the CARBON study. The trial will include more than ~500 Wet AMD patients and will compare the safety and efficacy of three doses of bevasiranib administered every eight weeks to Lucentis®, an approved treatment for Wet AMD, administered every four weeks.

The CARE™ Trial, a Phase II Clinical Trial for Wet AMD. The "Cand5 Anti-VEGF RNAi Evaluation, or CARE study," a 129 patient Phase II clinical study in patients with predominantly and minimally classic Wet AMD, was completed successfully. The results of the CARE study demonstrated that bevasiranib is safe and well-tolerated for doses up to 3.0 mg/eye. An important measure of Wet AMD is choroidal neovascularization, or CNV. In the CARE study, bevasiranib was shown to inhibit the growth of CNV, and demonstrated the effects of RNA interference-based VEGF suppression.

Phase I Clinical Trial for Wet AMD. This Phase I trial was an open label, dose escalation study that included 15 patients and tested five dose levels administered by intravitreal injection at six-week intervals. Bevasiranib was shown to be safe and well-tolerated following repeated administration of escalating doses, up to 3.0 mg per eye. Further, this study indicated that the study drug was below the limit of detection in the peripheral blood at any of the doses tested. The absence of systemic exposure to bevasiranib is significant because anti-VEGF agents have been shown to have serious systemic side effects in some patients.

Clinical Trials for the Treatment of DME

The R.A.C.E.™ Trial, a Pilot Phase II Clinical Trial for DME. The RNAi Assessment of bevasiranib in Diabetic Macular Edema, or R.A.C.E. trial, was a pilot phase II investigation of the safety and preliminary efficacy of bevasiranib in patients with DME. This 48 patient multi-center, double-masked and randomized trial studied three dose levels of bevasiranib.

In this pilot study, there was a trend showing a decrease in macular thickness between weeks eight and twelve, where the higher doses result in a larger reduction in thickness than the lowest dose. This trial also showed no detectable levels of bevasiranib in patients at all doses and time-points. These results further support the findings of the CARE study and serve as a confirmation of the safety and biologic activity in a second VEGF-driven ocular condition.

ACU-HHY-011 for the Treatment of Wet AMD

We have a worldwide exclusive license to commercialize ACU-HHY-011, which is an siRNA targeting HIF-1 , believed to be the most important transcription factor involved in the cellular response to hypoxia, a key step in the neovascularization process which occurs in Wet AMD. HIF-1 is upstream of the target for bevasiranib and preclinical data suggests that targeting HIF-1 may have advantages over other approaches to treating Wet AMD. HIF-1 modulates the expression of more than 60 genes, including multiple angiogenic factors under hypoxic conditions, such as VEGF, angiopoietin-1, angiopoietin-2, placental growth factor, and platelet-derived growth factor-B.

ACU-HTR-028 for the Treatment of Fibrosis

We have a worldwide exclusive license to commercialize siRNAs targeting transforming growth factor-b receptor Type II, or TbRII, which is an important mediator of wound healing and has been shown to play a significant causative role in ocular inflammation and scarring. This compound may have a therapeutic application as an eye drop to prevent complications from ocular surgery, and will also be developed as an adjunct therapy to bevasiranib or ACU-HHY-011 in Wet AMD patients to reduce the damage caused by the fibrotic component of Wet AMD.

Compounds for the Treatment of Dry AMD

We have worldwide exclusive licenses to commercialize compounds from the University of Florida Research Foundation which have potential to treat Dry AMD by eliminating disease-causing accumulations of protein molecules at the back of the eye. Proteins must fold into their correct three-dimensional conformation to achieve their biological function. The loss of vision associated with Dry AMD is thought to be caused by the destructive effects of the misfolded protein and debris aggregates likes lipofuscin. Autophagy is a cellular process by which cellular protein aggregates and dysfunctional organelles like mitochondria are degraded. If methods for increasing autophagy were available, they might enhance the elimination of misfolded proteins, and eliminate the destructive effects associated with their accumulation. These compounds may mitigate retinal degeneration by causing the elimination or reduction of drusen in patients with Dry AMD.

Civamide for the Treatment of Dry Eye

In September 2007, we acquired worldwide rights to commercialize products containing civamide for the treatment of ophthalmic conditions in humans, particularly dry eye. There is only one FDA approved prescription product available for dry eye. Dry eye syndrome is caused by a variety of conditions, such as insufficient tear production. Nine million Americans are estimated to suffer from moderate to severe dry eye. An additional 20 to 30 million people may have a mild form of the condition. Dry eye syndrome is more common with advancing age and the incidence appears to be increasing with our aging population and the increasing popularity of procedures that can cause dry eye, such as vision-correction surgery and cosmetic eyelid surgery.

Wound Dressing

In October 2007, we acquired worldwide rights to commercialize an ocular product for use following invasive retinal procedures to prevent the development of endophthalmitis, a devastating complication that can lead to blindness and loss of the affected eye. There are estimated to be over 1.5 million invasive retinal procedures, including both surgeries and intravitreal injections, being currently performed in the U.S. alone. While most patients suffer no adverse effects from intravitreal injections, all patients who receive invasive retinal procedures are at risk of developing endophthalmitis. The product is in late-stage research.

N-chlorotaurine

In April 2006, we entered into a license agreement with Pathogenics, Inc. (“Pathogenics”) under which we were granted an exclusive, irrevocable license, with the right to sublicense, under Pathogenics intellectual property to make, have

made, use, sell, offer for sale, import, or otherwise commercialize N-chlorotaurine and licensed products for the treatment of ophthalmic disease or infection in any territory. We were also granted non-exclusive rights to all data resulting from a phase I clinical trial with N-chlorotaurine in Austria. We are obligated to use commercially reasonable efforts to develop and commercialize the licensed product, including commercially reasonable efforts to initiate pre-clinical activities necessary to file an IND with the FDA to initiate a phase I clinical trial for N-chlorotaurine for an ophthalmic indication. Pathogenics will have a non-exclusive right to such information for the treatment of non-ophthalmic diseases or infections.

OPHTHALMIC INSTRUMENTATION MARKET

The market for ophthalmic instrumentation, including imaging systems and other devices, is approximately $1.5 billion and growing at a rate of approximately 10% annually. This growth is primarily driven by an aging patient population, technological innovation and improvement in treatment options, as well as improved awareness in patients actively seeking treatment. Ophthalmic instruments, imaging products, and other medical devices are sold to a variety of eye care practitioners, including retinal and glaucoma specialists, ophthalmologists, optometrists, retail optometry chain outlets, teaching institutions, and military hospitals.

OPHTHALMIC INSTRUMENTATION BUSINESS

Our instrumentation business consists of the development, commercialization and sale of ophthalmic diagnostic and imaging systems and instrumentation products. Currently, the instrumentation business is primarily based on the technology platform established by Ophthalmic Technologies, Inc. (OTI), which offers innovative systems with advanced diagnostic imaging capabilities and tools that meet the needs of eye care professionals. We continue to build our presence in the international marketplace currently covering more than 60 countries using the distributor network built by OTI. Additionally, we are developing our own direct sales force in the United States to sell our products primarily to retinal and glaucoma specialists and ophthalmologists.

We plan to utilize our expertise and resources to expand our business to include other types of ophthalmic products. These efforts may lead to our acquiring or developing products which aid in the prevention, diagnosis, treatment, and management of ocular disorders. The product types may include diagnostic and imaging instruments, other instrumentation products, and drug delivery systems and technologies.

We plan to develop and sell novel technologies utilized to diagnose ophthalmic diseases at the earliest stages and track them for change over time, and during the course of treatment. We expect these technologies to improve physician treatment decisions and enhance outcomes for a variety of ocular disorders, including AMD, diabetic retinopathy, and glaucoma, among others.

Optical Coherence Tomography / Confocal Scanning Ophthalmoscopy

We have developed a spectral imaging system which combines Spectral Optical Coherence Tomography, together with a Confocal Scanning Ophthalmoscope, or OCT / SLO, in a single platform that is used in the diagnosis of a variety of ocular disorders. We believe this is an innovative product that offers significant advantages over current technology in resolution and functionality. OCT technology is being rapidly adopted by the eye care community for diagnosing AMD and diabetic retinopathy and also tracking the course of treatment. The OCT / SLO is unique in that it offers microperimetry capability, which provides the physician with the ability to correlate loss of visual function with abnormalities in the retina. Additionally, the OCT / SLO diagnostic platform offers a foundation upon which to build a multitude of diagnostic tests. In the future, we plan to incorporate a number of imaging and other diagnostic test modalities into the OCT / SLO platform.

Ultrasound

We develop, manufacture, market and sell a full line of advanced ophthalmic ultrasound systems used by eye care professionals for both routine and specialized care. Our ultrasound systems include A-scans, B-scans, and Ultrasound Bio-microscope, or UBM, high frequency B-scan systems. A-scan technology is principally used for eye axial length measurement in the calculation of the power for an intraocular lens implant. These systems are routinely used prior to cataract surgery.

The B-scan system displays internal structures of the eye, often when these structures are not visible by traditional light-based imaging methods. This system has the ability to pass through opacities and reveal internal structures.

The UBM system is a high frequency ultrasound device that provides detailed structural assessment of the anterior segment of the eye and is typically used in glaucoma evaluation and certain refractive surgeries that require precise positioning of lens implantation.

Research and development program expenses

To date, the majority of our research and development expenses have been incurred to develop our bevasiranib programs. During 2006, our research and development expenses of $0.5 million reflect the sponsored research between Froptix and the University of Florida. During 2007, we incurred $10.9 million in research and development expenses, a majority of which reflects costs to develop bevasiranib. In addition, during 2007 we recorded $243.8 million for acquired in process research and development related to our acquisition of Acuity.

INTELLECTUAL PROPERTY

We believe that technology innovation is driving breakthroughs in vision healthcare. We have adopted a comprehensive intellectual property strategy which blends the efforts to innovate in a focused manner with the efforts of our business development activities to strategically in-license intellectual property rights. We develop, protect, and defend our own intellectual property rights as dictated by the developing competitive environment. We value our intellectual property assets and believe we have benefited from early and insightful efforts at understanding the disease and the molecular basis of potential pharmaceutical intervention.

We actively seek, when appropriate and available, protection for our products and proprietary information by means of United States and foreign patents, trademarks, trade secrets, copyrights, and contractual arrangements. Patent protection in the pharmaceutical field, however, can involve complex legal and factual issues. Moreover, broad patent protection for new formulations or new methods of use of existing chemical entities is sometimes difficult to obtain, primarily because the active ingredient and many of the formulation techniques have been known for some time. Consequently, some patents claiming new formulations or new methods of use for old drugs may not provide meaningful protection against competition. There can be no assurance that any steps taken to protect such proprietary information will be effective.

We own or have exclusively licensed more than eight issued patents in the United States and five foreign patents, as well as more than 100 United States and foreign patent applications. Our acquisition of OTI has given us access to an additional seven U.S. patents in the field of ophthalmic instrumentation, as well as ten U.S. patent applications and 18 foreign patent applications.

We have exclusively licensed technology, patents, and patent applications from the University of Pennsylvania related to siRNA directed to specific mRNA targets for therapeutic use. These applications include targeting VEGF, HIF-1 , and intracellular adhesion molecules, or ICAM, among other therapeutic targets. In particular, we have exclusively licensed two issued U.S. patents that cover bevasiranib and methods of using bevasiranib.

In addition, we have exclusively licensed technology, patents, and patent applications related to (i) the treatment of ophthalmic disorders characterized by excessive neovascularization, angiogenesis or leakage, (ii) siRNA targeting TGF-bRI; and (iii) compounds or technologies to treat a variety of ocular disorders, including without limitation, Dry AMD and retinitis pigmentosa, viral conjunctivitis, dry eye, and ocular infection. See “Licenses and Collaborative Relationships”.

LICENSES AND COLLABORATIVE RELATIONSHIPS

Our strategy is to develop a portfolio of product candidates through a combination of internal development and external partnerships. Collaborations are key to our strategy and we continue to build relationships and forge partnerships with companies both inside and outside of ophthalmology. We have completed strategic deals with the Trustees of the University of Pennsylvania, the University of Illinois, the University of Florida Research Foundation, Pathogenics, Inc., and Intradigm Corporation, among others.

The Trustees of the University of Pennsylvania

In March 2003, we entered into two world-wide exclusive license agreements with The Trustees of the University of Pennsylvania to commercialize siRNA targeting VEGF, HIF-1 , ICAM, and other therapeutic targets. In consideration for the licenses, we are obligated to make certain milestone payments to the University of Pennsylvania. We also agreed to pay the University of Pennsylvania earned royalties based on the number of products we sell that use the inventions claimed in the licensed patents. We agreed to use commercially reasonable efforts to develop, commercialize, market, and sell such products covered by the license agreements.

The term of the agreements is for the later of the expiration or abandonment of the last patent or ten years after the first commercial sale of the first licensed product. We may terminate either of the agreements upon 60 days’ prior written notice. The University of Pennsylvania may terminate either of the agreements if we are more than 90 days late in a payment owed to the University of Pennsylvania, we breach the agreements and do not cure within 90 days after receiving written notice from the University of Pennsylvania, if we become insolvent or we are involved in bankruptcy proceedings.

Intradigm Corporation

In June 2005, we entered into a license and collaboration agreement with Intradigm Corporation, or Intradigm, for intellectual property covering the treatment of ophthalmic diseases characterized by excessive neovascularization, angiogenesis, or leakage. Under the terms of the agreement, we have agreed to jointly develop a topical siRNA compound. After selection the topical siRNA compound, we are obligated to use commercially reasonable efforts to market, distribute, and sell the topical siRNA in the United States and any selected foreign country. We have agreed to pay to Intradigm certain milestone payments upon the achievement of specified milestones and royalty payments on all net sales of the topical siRNA and other licensed products.

The term of the agreement is 20 years, unless earlier terminated in accordance with the agreement. Either party may terminate upon mutual written consent, upon written notice by a party if the other party dissolves or enters into bankruptcy or insolvency proceedings, or upon 90 days prior written notice of a material breach of the agreement without cure.

The Board of Trustees of the University of Illinois

In August 2006, we entered into an exclusive worldwide license agreement with The Board of Trustees of the University of Illinois to commercialize intellectual property related to ophthalmic siRNA targeting TGF-bRII for the treatment of ophthalmic disease. In September 2007, the license was amended to include all other fields of use beyond the treatment of ophthalmic disease. The license agreement obligates us to pay to the University of Illinois certain milestone payments and royalty payments on all net sales of licensed products and an annual license fee payment.

University of Florida Research Foundation

In April 2006, we entered into three world-wide exclusive license agreements with the University of Florida Research Foundation. The license agreements obligate us to pay to University of Florida Research Foundation royalty payments on all net sales of licensed products. We agreed to use our commercially reasonable activities to commercialize products. The technology licensed from the University of Florida Research Foundation includes autophagy inducing compounds which are designed to enhance the elimination of misfolded proteins, and eliminate the destructive effects associated with their accumulation, compounds that affect important intracellular pathways which lead to the accumulation of properly folded mutant proteins, and potential drug candidates that are designed to recruit stem cells which may aid in delaying or reversing the damage at the back of the eye associated with several retinal diseases including Dry AMD and retinitis pigmentosa. The term of each of the agreements is for the earlier of the date that no licensed patent remains an enforceable patent or the payment of earned royalties under the agreement once begun, ceases for more than two calendar quarters. We may terminate any of the agreements upon 60 days' prior written notice. The University of Florida Research Foundation may terminate any of the agreements if we are more than 60 days late, after written demand, for a payment owed to the University of Florida Research Foundation, if we breach the agreements and do not cure within 60 days after receiving written notice from the University of Florida Research Foundation, or if we become involved in bankruptcy proceedings.

Civamide License

In September 2007, we entered into an exclusive worldwide license to commercialize intellectual property related to pharmaceutical compositions or preparations containing civamide for the treatment of ophthalmic conditions in humans, particularly dry eye. The license agreement obligates us to pay the licensor certain milestone payments and royalty payments on all net sales of licensed products thereunder and all costs of research and development necessary to obtain marketing authorizations for such licensed products. There is only one FDA approved prescription product available for dry eye. Dry eye syndrome is caused by a variety of conditions, such as insufficient tear production. Nine million Americans are estimated to suffer from moderate to severe dry eye. An additional 20 to 30 million people may have a mild form of the condition. Dry eye syndrome is more common with advancing age and the incidence appears to be increasing with our aging population and the increasing popularity of procedures that can cause dry eye, such as vision-correction surgery and cosmetic eyelid surgery. We intend to evaluate the safety and efficacy of civamide in patients with moderate to severe dry eye. A Phase I/II proof of principal study in moderate to severe dry eye is being planned in 2008.

Theta Research Consultants

In October 2007, we entered into an exclusive worldwide license to commercialize intellectual property related to an ocular product for use following invasive retinal procedures to prevent the development of endophthalmitis, a

devastating complication that can lead to blindness and loss of the affected eye. The license agreement obligates us to make royalty payments on all net sales of licensed products thereunder and all costs of research and development necessary to obtain marketing authorizations for such licensed products. Experts believe that the incidence of endophthalmitis is growing as a result of the rising number of ocular surgeries being performed, the widespread adoption of sutureless surgical techniques, and a significant increase in the number of intravitreal injections. While most patients suffer no adverse effects from intravitreal injections, all patients who receive invasive retinal procedures are at risk of developing endophthalmitis.

Pathogenics

In April 2006, we entered into a license agreement with Pathogenics under which we were granted an exclusive, irrevocable license, with the right to sublicense, under Pathogenics' intellectual property to make, have made, use, sell, offer for sale, import, or otherwise commercialize N-chlorotaurine and licensed products for the treatment of ophthalmic disease or infection in any territory. We were also granted non-exclusive rights to all data resulting from a phase I clinical trial with N-chlorotaurine in Austria. We are obligated to use commercially reasonable efforts to develop and commercialize the licensed product, including commercially reasonable efforts to initiate pre-clinical activities necessary to file an IND with the FDA to initiate a phase I clinical trial for N-chlorotaurine for an ophthalmic indication. Pathogenics will have a non-exclusive right to such information for the treatment of non-ophthalmic diseases or infections.

We are obligated to pay to Pathogenics certain milestone payments upon the achievement of specified milestones and royalty payments on all net sales of licensed products. We are also obligated to pay Pathogenics an annual minimum payment if the total payments made for such year are less than a specified minimum amount. The term of the agreement is for the shorter of twenty years or the last to expire of the Pathogenics intellectual property. We may terminate the agreement for any reason upon written notice. The agreement may be terminated upon mutual written consent of the parties, by either party upon written notice if either party dissolves or is involved in a bankruptcy or insolvency proceeding or upon ninety days prior written notice if the other party is in material breach and fails to cure.

COMPETITION

Wet AMD

The Wet AMD treatment market is highly competitive with each competitive company eager to expand market share. Several pharmaceutical and biotechnology companies are actively engaged in research and development related to new treatments for Wet AMD. We intend to leverage our technological innovation and proprietary position utilizing RNAi and other platform technologies to effectively compete in the ophthalmic drug market. Additionally, we intend to couple diagnostic tests together with therapeutics in clinical trials to further enhance our competitive position.

Genentech, Allergan, Alcon Laboratories, Novartis, Alnylam, Regeneron and QLT all have products or development programs for Wet AMD. For Wet AMD, we currently believe that Genentech and Allergan are or will be our primary competitors. Genentech's Lucentis® and Avastin® products are both based on antibody technology to block VEGF protein after it is produced. While both of the drugs provide most patients with an effective treatment, we believe that bevasiranib has distinct advantages over these approaches, which will result in its use and contribute to a significant market share.

Lucentis® and Avastin® block VEGF protein only after it is produced. Additionally, Lucentis® and Avastin® are designed to require monthly injections for optimal effectiveness and include cautions about potential arterial thromboembolic events. Bevasiranib is designed to reduce injection frequency to bi-monthly or quarterly, and we do not believe it has the systemic side effect risks associated with anti-VEGF antibodies. By using siRNA and stopping the production of VEGF, we believe bevasiranib will provide a Wet AMD patient with a longer-lasting and safer maintenance treatment following an initiation therapy with either Lucentis® or Avastin®.

Allergan is presently developing an siRNA based therapy with a product licensed from Merck (formerly Sirna). This siRNA based therapy targets a particular VEGF receptor and due to the fact that there are multiple receptors for VEGF, it is unclear whether that approach will yield a clinical benefit in Wet AMD. Additionally this program is at an earlier stage than our bevasiranib program.

Diabetic Retinopathy

We believe that the primary competitors in the diabetic retinopathy/DME market include Bausch & Lomb with its Fluocinolone acetonide product, Allergan with its Dexamethasone product, Surmodics with its Triamcinolone acetonide product, and Psividia/Alimeira Sciences with its Fluocinolone acetonide product. Many of these competitors have significantly greater financial resources than we do to fund further research and development.

Optical Coherence Tomography

We have several competitors located in the United States and abroad. These include companies with a far more diverse product offering than ours with significantly greater market presence. Our primary competition for medical devices include Carl Zeiss Meditec, Topcon Corporation, and Heidelberg Engineering. There are a number of competitors and smaller start-up companies that may also have competing technologies and products.

The ophthalmic device market is highly competitive. We intend to leverage our technological innovations to effectively compete in the ophthalmic device market. We differentiate our products on the basis of scan quality, precise image registration, software functionality, and on a diagnostic test known as microperimetry. Microperimetry allows the clinician to obtain both structure and function from a single device. Additionally, in the future we intend to utilize diagnostic tests to further refine and guide therapeutic treatments in clinical trials in order to further enhance our competitive position.

GOVERNMENT REGULATION OF OUR DRUG AND DEVICE DEVELOPMENT ACTIVITIES

The United States federal government regulates healthcare through various agencies, including but not limited to the following: (i) the FDA, which administers the FDCA, as well as other relevant laws; (ii) the Centers for Medicare & Medicaid Services, or CMS, which administers the Medicare and Medicaid programs; (iii) the Office of Inspector General, or OIG, which enforces various laws aimed at curtailing fraudulent or abusive practices, including by way of example, the Anti-Kickback Law, the Anti-Physician Referral Law, commonly referred to as the Stark law, the Anti-Inducement Law, the Civil Money Penalty Law, and the laws that authorize the OIG to exclude healthcare providers and others from participating in federal healthcare programs; and (iv) the Office of Civil Rights, which administers the privacy aspects of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). All of the aforementioned are agencies within the Department of Health and Human Services (HHS). Healthcare is also provided or regulated, as the case may be, by the Department of Defense through its TriCare program, the Department of Veterans Affairs, especially through the Veterans Health Care Act of 1992, the Public Health Service within HHS under Public Health Service Act § 340B (42 U.S.C. § 256b), the Department of Justice through the Federal False Claims Act and various criminal statutes, and state governments under the Medicaid and other state sponsored or funded programs and their internal laws regulating all healthcare activities.

The testing, manufacture, distribution, advertising, and marketing of drug products and medical devices are subject to extensive regulation by federal, state, and local governmental authorities in the United States, including the FDA, and by similar agencies in other countries. Any product that we develop must receive all relevant regulatory approvals or clearances, as the case may be, before it may be marketed in a particular country. The PMA clearance processes for drugs differ from those for devices.

The regulatory process, which includes overseeing preclinical studies and clinical trials of each pharmaceutical compound to establish its safety and efficacy and confirmation by the FDA that good laboratory, clinical, and manufacturing practices were maintained during testing and manufacturing, can take many years, requires the expenditure of substantial resources, and gives larger companies with greater financial resources a competitive advantage over us. Delays or terminations of clinical trials that we undertake would likely impair our development of product candidates. Delays or terminations could result from a number of factors, including stringent enrollment criteria, slow rate of enrollment, size of patient population, having to compete with other clinical trials for eligible patients, geographical considerations, and others.

The FDA review processes can be lengthy and unpredictable, and we may encounter delays or rejections of our applications when submitted. Generally, in order to gain FDA approval, we must first conduct preclinical studies in a laboratory and in animal models to obtain preliminary information on a compound and to identify any safety problems. The results of these studies are submitted as part of an IND application that the FDA must review before

human clinical trials of an investigational drug can commence.

Clinical trials are normally done in three sequential phases and generally take two to five years or longer to complete. Phase I consists of testing the drug product in a small number of humans, normally healthy volunteers, to determine preliminary safety and tolerable dose range. Phase II usually involves studies in a limited patient population to evaluate the effectiveness of the drug product in humans having the disease or medical condition for which the product is indicated, determine dosage tolerance and optimal dosage, and identify possible common adverse effects and safety risks. Phase III consists of additional controlled testing at multiple clinical sites to establish clinical safety and effectiveness in an expanded patient population of geographically dispersed test sites to evaluate the overall benefit-risk relationship for administering the product and to provide an adequate basis for product labeling. Phase IV clinical trials may be conducted after approval to gain additional experience from the treatment of patients in the intended therapeutic indication.

After completion of clinical trials of a new drug product, FDA and foreign regulatory authority marketing approval must be obtained. Assuming that the clinical data support the product's safety and effectiveness for its intended use, an NDA is submitted to the FDA for its review. Generally, it takes one to three years to obtain approval. If questions arise during the FDA review process, approval may take a significantly longer period of time. The testing and approval processes require substantial time and effort and we may not receive approval on a timely basis, if at all, or the approval that we receive may be for a narrower indication than we had originally sought, potentially undermining the commercial viability of the product. Even if regulatory approvals are obtained, a marketed product is subject to continual review, and later discovery of previously unknown problems or failure to comply with the applicable regulatory requirements may result in restrictions on the marketing of a product or withdrawal of the product from the market as well as possible civil or criminal sanctions. For marketing outside the United States, we also will be subject to foreign regulatory requirements governing human clinical trials and marketing approval for pharmaceutical products. The requirements governing the conduct of clinical trials, product licensing, pricing, and reimbursement vary widely from country to country.

None of our pharmaceutical products under development has been approved for marketing in the United States or elsewhere. We may not be able to obtain regulatory approval for any such products under development in a timely manner, if at all. Failure to obtain requisite governmental approvals or failure to obtain approvals of the scope requested will delay or preclude us, or our licensees or marketing partners, from marketing our products, or limit the commercial use of our products, and thereby would have a material adverse effect on our business, financial condition, and results of operations. See "Risk Factors—The results of previous clinical trials may not be predictive of future results, and our current and planned clinical trials may not satisfy the requirements of the FDA or other non-United States regulatory authorities."

Devices are subject to varying levels of premarket regulatory control, the most comprehensive of which requires that a clinical evaluation be conducted before a device receives approval for commercial distribution. The FDA classifies medical devices into one of three classes: Class I devices are relatively simple and can be manufactured and distributed with general controls; Class II devices are somewhat more complex and require greater scrutiny; Class III devices are new and frequently help sustain life.

In the United States, a company generally can obtain permission to distribute a new device in one of two ways. The first applies to any device that is substantially equivalent to a device first marketed prior to May 1976, or to another device marketed after that date, but which was substantially equivalent to a pre-May 1976 device. These devices are either Class I or Class II devices. To obtain FDA permission to distribute the device, the company generally must submit a section 510(k) submission, and receive an FDA order finding substantial equivalence to a predicate device (pre-May 1976 or post-May 1976 device that was substantially equivalent to a pre-May 1976 device) and permitting commercial distribution of that device for its intended use. A 510(k) submission must provide information supporting a claim of substantial equivalence to the predicate device. If clinical data from human experience are required to support the 510(k) submission, these data must be gathered in compliance with investigational device exemption, or IDE, regulations for investigations performed in the United States. The 510(k) process is normally used for products of the type that the Company proposes distributing. The FDA review process for premarket notifications submitted pursuant to section 510(k) takes, on average, about 90 days, but it can take substantially longer if the FDA has concerns, and there is no guarantee that the FDA will "clear" the device for marketing, in which case the device cannot be distributed in the United States. There is also no guarantee that the FDA will deem the applicable device subject to the 510(k) process, as opposed to the more time-consuming, resource-intensive and problematic, PMA process described below.

The second, more comprehensive, approval process applies to a new device that is not substantially equivalent to a pre-1976 product or that is to be used in supporting or sustaining life or preventing impairment. These devices are normally Class III devices. For example, most implantable devices are subject to the approval process. Two steps of FDA approval are generally required before a company can market a product in the United States that is subject to

approval, as opposed to clearance. First, a company must comply with IDE regulations in connection with any human clinical investigation of the device. These regulations permit a company to undertake a clinical study of a "non-significant risk" device without formal FDA approval. Prior express FDA approval is required if the device is a significant risk device. Second, the FDA must review the company's PMA application, which contains, among other things, clinical information acquired under the IDE. The FDA will approve the PMA application if it finds there is reasonable assurance that the device is safe and effective for its intended use. The PMA process takes substantially longer than the 510(k) process and it is conceivable that the FDA would not agree with our assessment that a device that we propose to distribute should be a Class I or Class II device. If that were to occur we would be required to undertake the more complex and costly PMA process. However, for either the 510(k) or the PMA process, the FDA could require us to run clinical trials, which would pose all of the same risks and uncertainties associated with the clinical trials of drugs, described above.

Even when a clinical study has been approved by the FDA or deemed approved, the study is subject to factors beyond a manufacturer's control, including, but not limited to the fact that the institutional review board at a given clinical site might not approve the study, might decline to renew approval which is required annually, or might suspend or terminate the study before the study has been completed. Also, the interim results of a study may not be satisfactory; leading the sponsor to terminate or suspend the study on its own initiative or the FDA may terminate or suspend the study. There is no assurance that a clinical study at any given site will progress as anticipated; there may be an insufficient number of patients who qualify for the study or who agree to participate in the study or the investigator at the site may have priorities other than the study. Also, there can be no assurance that the clinical study will provide sufficient evidence to assure the FDA that the product is safe and effective, a prerequisite for FDA approval of a PMA, or substantially equivalent in terms of safety and effectiveness to a predicate device, a prerequisite for clearance under 510(k). Even if the FDA approves or clears a device, it may limit its intended uses in such a way that manufacturing and distributing the device may not be commercially feasible.