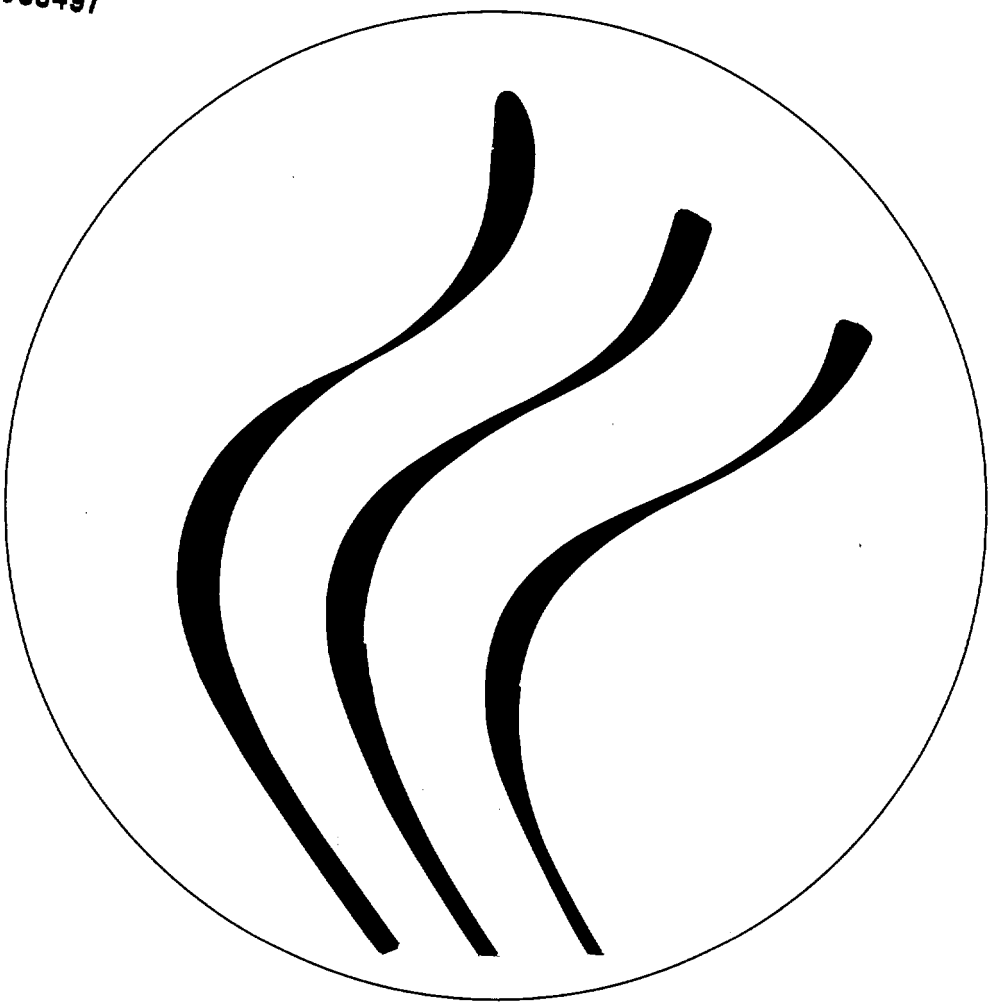
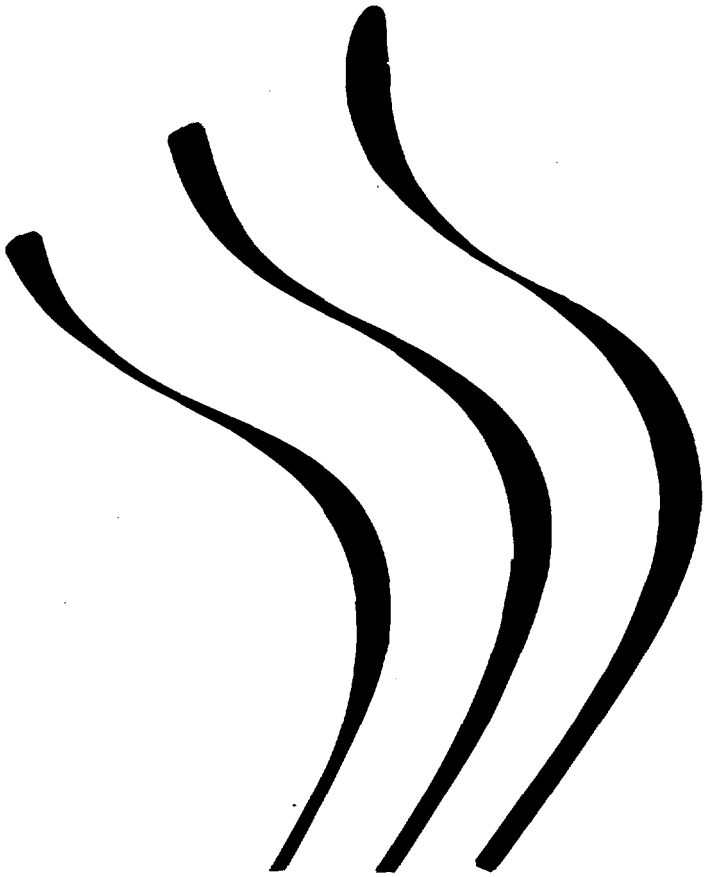


What do you see?

INSPIRE 2005 ANNUAL REPORT



Corporate Profile Inspire is a biopharmaceutical company dedicated to discovering, developing and commercializing prescription pharmaceutical products in disease areas with significant commercial potential and unmet medical needs. Our research and development programs are driven by extensive scientific experience in the therapeutic areas of ophthalmology and respiratory/allergy, and supported by expertise in the field of P2 receptors. We are currently developing drug candidates for dry eye, cystic fibrosis, allergic rhinitis and acute cardiac care. Our U.S. specialty sales force promotes *Elestat*® (epinastine HCl ophthalmic solution) 0.05% for allergic conjunctivitis and *Restasis*® (cyclosporine ophthalmic emulsion) 0.05% for dry eye, ophthalmology products developed by Allergan, Inc.

We see opportunity.

Why We Exist We aspire to be an innovative, financially self-sustaining biopharmaceutical company with products that make a difference to patients. We encourage a culture that promotes efficiency, creativity, collaboration and personal responsibility. We strive to be a good corporate citizen and have a reputation for high ethical standards.

To Our Stockholders:

While we have faced various challenges over the years, we continue to forge ahead in leveraging our strengths to achieve success. We are focused on our core therapeutic areas of Ophthalmology and Respiratory/Allergy and have aligned our organization in this way. We believe this targeted approach will bring us many opportunities.

Christy L. Shaffer, Ph.D.
President and Chief Executive Officer

2005 Financial Summary

We have been very pleased with the ability of our specialized commercial organization to grow co-promotion revenues of *Elestat*® and *Restasis*®, two ophthalmology products developed by Allergan, Inc. *Elestat* is currently the second most prescribed allergic conjunctivitis product in the United States, amid strong competitors with well-known brands. The success of *Elestat*, in a short period of time, is a tribute to the product and to the capabilities of our team. We have also shared in the success of *Restasis*, as we and Allergan strive to further increase awareness among physicians and their patients who suffer from dry eye disease.

During 2005, we recognized $23 million of co-promotion revenue, covering our marketing and sales expenses for the year. We managed our total expenses carefully and maintained our cash burn at the low end of our expected range for the year. Thus, we ended 2005 with a healthy capital position of $122 million in cash and investments. We aim to manage our financial position and liquidity effectively and to judiciously allocate our resources to achieve the maximum potential return for our stockholders.

R&D Challenges and Opportunities

Ophthalmology

In June of 2005, we submitted an amendment to our New Drug Application (NDA) for diquafosol tetrasodium, our clinical candidate being studied for dry eye, and in December of 2005 we received a second approvable letter from the U.S. Food and Drug Administration (FDA). We met with the FDA in March of 2006. Based upon this meeting, we are providing the FDA with additional information to facilitate ongoing discussions related to diquafosol. While we have encountered significant clinical and regulatory challenges in our dry eye program, we continue to believe that there is an important unmet medical need in the dry eye patient community.

Respiratory/Allergy

In October of 2005, we announced the completion of a second Phase 2 clinical trial and two six-month animal toxicology studies of denufosol tetrasodium for cystic fibrosis (CF). We held a productive End-of-Phase 2 meeting with the FDA in January of 2006 and plans are underway for initiation of a first Phase 3 trial and a required carcinogenicity study in animals. Also, in early 2006, we received orphan drug designation for denufosol for the treatment of CF from the European Medicines Agency. We are excited about the tremendous interest within the CF community for a potential early intervention therapy, such as denufosol, that could represent a novel approach to treating this devastating disease. This is an attractive market opportunity for Inspire since global sales of existing CF lung disease treatments exceed more than $550 million annually.

In February of 2006, we announced a development and license agreement with Boehringer Ingelheim International GmbH, in which we obtained certain exclusive rights to develop and commercialize intranasal epinastine for the treatment or prevention of rhinitis in the United States and Canada. This program will provide us with the opportunity to build on our respiratory and allergy franchise, while leveraging our success in the market with the ocular form of epinastine, *Elestat*. This is an attractive opportunity since we have a substantial understanding of this compound and extensive experience in the large allergy therapeutic market. We expect to move this program into Phase 2 clinical development in 2006, depending on the outcome of our initial meeting with the FDA, which is scheduled for May of 2006.

Other Programs

Our expertise in P2 receptors led to the discovery of INS50589 Antiplatelet, a reversible $P2Y_{12}$ receptor antagonist being developed as an intravenous inhibitor of platelet aggregation for the use in the acute treatment of cardiovascular diseases. Studies have shown INS50589 to be a fast-acting and reversible compound that may provide advantages over non-reversible platelet aggregation inhibitors. In June of 2005, we announced positive results in a Phase 1 clinical trial of INS50589 for acute cardiac care and we have recently initiated a Phase 2 trial in patients undergoing coronary artery bypass graft surgery. In addition, in March of 2006, we were issued a related patent for the composition and method for inhibiting platelet aggregation.

As part of our ongoing process to prioritize our R&D program investments and target our clinical resources to the most promising opportunities, we made the decision to discontinue enrollment in several pilot trials. We discontinued the retinal disease program, ending enrollment in two Phase 2 pilot clinical trials of denufosol tetrasodium intravitreal injection in patients with macular edema, and we discontinued enrollment in a Phase 2 pilot clinical trial of diquafosol for corneal epithelial wound healing.

Potential Opportunities Ahead

Looking ahead to 2006 and beyond, we expect to leverage our commercial organization, make progress in our clinical development programs, pursue potential new strategic partnerships and support our ongoing novel discovery efforts. We believe our continued investment in R&D has the potential to drive substantial future value for Inspire. Additionally, we believe that having a commercial operation gives us a strategic advantage and will help drive new business development opportunities. As demonstrated by our recent in-licensing agreement for intranasal epinastine, we plan to supplement our in-house assets through the pursuit of in-licensing and out-licensing agreements that could enhance our ability to build value in our key therapeutic areas of Ophthalmology and Respiratory/Allergy.

The Inspire team is enthusiastic, capable and experienced. Most importantly, we are dedicated to turning our many opportunities into value for stockholders and the medical community. This dedication was epitomized by one of our senior executives, Dr. Richard Evans. Our organization was deeply saddened when Richard passed away recently, but we will remember his caring nature, team spirit and tremendous contributions to Inspire.

In closing, we recognize that 2006 and the next several years represent a critical time in the life of Inspire. Our success will depend in great part on our ability to recognize and capitalize on our opportunities with skill, tenacity and integrity. We look forward to this challenge and to sharing with stockholders our progress throughout the year.

Sincerely,

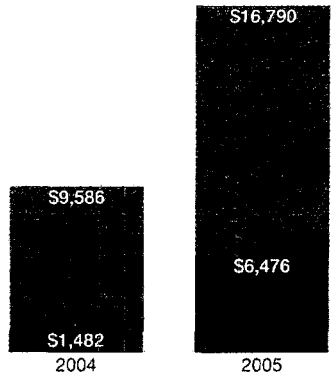
Christy L. Shaffer, Ph.D.
President and Chief Executive Officer

April 2006

INSPIRE PRODUCT PORTFOLIO AND R&D PIPELINE

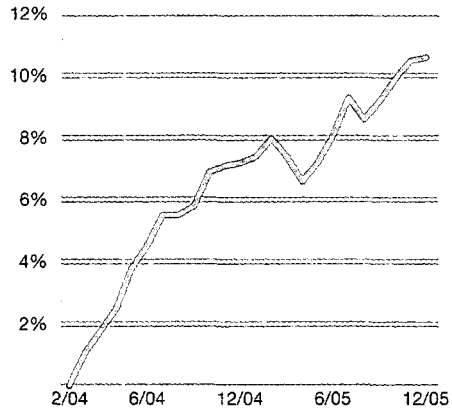
	OPHTHALMOLOGY	RESPIRATORY/ALLERGY	OPPORTUNISTIC
MARKETED PRODUCTS	*ELESTAT*® FOR ALLERGIC CONJUNCTIVITIS *RESTASIS*® FOR DRY EYE		
DEVELOPMENT PRODUCT CANDIDATES	DIQUAFOSOL TETRASODIUM FOR DRY EYE	DENUFOSOL TETRASODIUM FOR CYSTIC FIBROSIS	INS50589 ANTIPLATELET FOR ACUTE CARDIAC CARE
PRECLINICAL & DISCOVERY PROGRAMS	GLAUCOMA	INTRANASAL EPINASTINE FOR SEASONAL ALLERGIC RHINITIS	ORAL ANTIPLATELET

We see product revenues combined with an attractive R&D pipeline.



Inspire's Co-Promotion Revenue
(in thousands)

Elestat® Co-promotion Revenue
Restasis® Co-promotion Revenue



Elestat® Market Share of Prescriptions in Ocular Allergy Market

Based on IMS National Prescription Audit data measuring top prescription products for allergic conjunctivitis

Elestat® and Restasis® are trademarks owned by Allergan, Inc.

What do you see?

We see opportunity.

2005 FORM 10-K

UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
Washington, D.C. 20549

FORM 10-K

ANNUAL AND TRANSITION REPORTS PURSUANT TO SECTIONS 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934

(Mark One)

☒ **ANNUAL REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934**
For the fiscal year ended December 31, 2005

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 No. 000-31135

INSPIRE PHARMACEUTICALS, INC.
(Exact Name of Registrant as Specified in Its Charter)

Delaware	**04-3209022**
(State or Other Jurisdiction of Incorporation or Organization)	(I.R.S. Employer Identification No.)
4222 Emperor Boulevard, Suite 200, Durham, North Carolina	**27703-8466**
(Address of Principal Executive Offices)	(Zip Code)

(919) 941-9777
(Registrant's telephone number, including area code)

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

Title of Each Class	Name of Each Exchange on Which Registered
None	None

Securities registered pursuant to Section 12(g) of the Act:
Common Stock, $.001 par value
(Title of Class)

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

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 ☒

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 ☐

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 a large accelerated filer, an accelerated filer, or a non-accelerated filer. See definition of "accelerated filer and large accelerated filer" in Rule 12b-2 of the Exchange Act. (Check one)

Large accelerated filer ☐ Accelerated filer ☒ Non-accelerated filer ☐

Indicate by check mark whether the Registrant is a shell company (as defined in Rule 12b-2 of the Act). Yes ☐ No ☒

State 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, or the average bid and asked price of such common equity, as of the last business day of the registrant's most recently completed second fiscal quarter. $351,555,065.

Indicate the number of shares outstanding of each of the Registrant's classes of common stock, as of January 31, 2006.

Class	Number of Shares
Common Stock, $.001 par value	42,210,593

Documents incorporated by reference

Document Description	10-K Part III
Portions of the Registrant's proxy statement to be filed pursuant to Regulation 14A within 120 days after Registrant's fiscal year end of December 31, 2005 are incorporated by reference into Part III of this report.	Items 10, 11, 12, 13, 14

INSPIRE PHARMACEUTICALS, INC.
2005 FORM 10-K ANNUAL REPORT

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PART I

Item 1. Business.

Overview

We are a biopharmaceutical company dedicated to discovering, developing and commercializing prescription pharmaceutical products in disease areas with significant commercial potential and unmet medical needs. Our goal is to build and commercialize a sustainable pipeline of innovative new treatments based upon our technical and scientific expertise, focusing in the ophthalmic and respiratory/allergy therapeutic areas. Our portfolio of products and product candidates include:

PRODUCTS AND PRODUCT CANDIDATES	THERAPEUTIC AREA/ INDICATION	COLLABORATIVE PARTNER	CURRENT STATUS
Products			
Elestat®	Allergic conjunctivitis	Allergan	Co-promoting in the United States since February 2004
Restasis®	Dry eye disease	Allergan	Co-promoting in the United States since January 2004
Product Candidates in Clinical Development			
diquafosol tetrasodium (INS365 Ophthalmic)	Dry eye disease	Allergan and Santen Pharmaceutical	Phase 3; Second FDA approvable letter received December 2005
denufosol tetrasodium (INS37217 Respiratory)	Cystic fibrosis	None	Entering Phase 3
INS50589 Antiplatelet	Acute cardiac care	None	Entering Phase 2
Product Candidates in Preclinical Development			
Intranasal epinastine	Seasonal allergic rhinitis	Boehringer Ingelheim	Pre-IND
Outflow enhancer	Glaucoma	None	Pre-IND

We co-promote *Elestat*® and *Restasis*® in the United States under agreements with Allergan, Inc., or Allergan, and we receive co-promotion revenue based upon net sales of these products. In January 2004, we began co-promoting *Restasis*® for the treatment of dry eye disease. In February 2004, we launched *Elestat*® for the treatment of allergic conjunctivitis. *Elestat*® and *Restasis*® are trademarks owned by Allergan.

Our ophthalmic products and product candidates are currently concentrated in the allergic conjunctivitis, dry eye disease and glaucoma indications. Our respiratory/allergy product candidates are currently concentrated in the treatment of respiratory complications of cystic fibrosis and seasonal allergic rhinitis. In addition, we also have an antiplatelet product candidate that we are testing in cardiopulmonary bypass procedures but it could be useful in other cardiovascular indications.

We were incorporated in October 1993 and commenced operations in March 1995 following our first substantial financing and licensing of the initial technology from The University of North Carolina at Chapel Hill, or UNC. We are located in Durham, North Carolina, adjacent to the Research Triangle Park.

Our Strategy

Our business objective is to become a leading biopharmaceutical company focused on discovering, developing and commercializing new treatments for diseases primarily in the ophthalmic and respiratory/allergy areas. We intend to build and commercialize a sustainable pipeline of innovative new treatments based on our technical and scientific expertise. Our strategy is to advance product candidates in areas where we have significant expertise, through drug discovery, clinical trials, strategic alliances and in-licensing, and to be involved in the marketing and sale of our products. The principle elements of our strategy are to:

- **Aggressively Advance Our Product Candidates.** We focus significant energy and resources to rapidly and efficiently develop our existing product candidates. We target therapeutic markets and pursue product candidates where current therapy is not optimal and where we perceive significant market opportunities to exist.
- **Establish Strategic Relationships that Enhance and Complement Our Own Product Development and Commercial Organization.** Collaborations are, and we believe will continue to be, a key component of our corporate strategy. We have entered or plan to enter into alliances with pharmaceutical companies for the commercialization of our products, especially to address markets outside North America where we do not intend to develop infrastructure to commercialize our products. In addition, we intend to continue to develop alliances with leading pharmaceutical companies to enrich our product candidate pipeline and optimize our commercial efforts.
- **Successfully Commercialize Products Through a Concentrated Sales and Marketing Effort in Our Target Markets.** A key element of our strategy is to be involved in the sales and marketing activities of our products in North America. To that end, we have developed a specialty sales and marketing organization to support the commercialization of *Elestat®* and *Restasis®* to ophthalmologists, optometrists and allergists in the United States.
- **Develop or In-License New Products Outside Our Original Proprietary P2 Technology Platform.** Our research focus is to discover new pharmaceutical products that expand beyond our P2 receptor technology. We have internal programs and sponsored research and development agreements with universities to discover, develop and in-license new pharmaceutical products. In addition, we continue to be opportunistic with regard to in-licensing products in various stages of development in our core therapeutic areas.
- **Protect and Enhance Our Technology Leadership Position.** We have a substantial intellectual property position related to our technology. We currently have 57 issued patents: 35 exclusively owned, 7 jointly owned and exclusively licensed, 12 exclusively licensed, and 3 non-exclusively licensed. We also have other U.S. patents pending and multiple foreign patents issued and pending. We intend to continue to pursue an aggressive patent strategy to protect our expanding proprietary discoveries.

Elestat®

Overview. Elestat® (epinastine HCl ophthalmic solution) 0.05%, a topical antihistamine with mast cell stabilizing and anti-inflammatory activity, was developed by Allergan for the prevention of ocular itching associated with allergic conjunctivitis. In December 2003, we entered into an agreement with Allergan to co-promote *Elestat®* to ophthalmologists, optometrists and allergists in the United States. Under the agreement, we have the responsibility for selling, promoting and marketing *Elestat®* in the United States and paying the associated costs. In addition, we have the right to and may conduct Phase 4 clinical trials and other studies in collaboration with Allergan relating to *Elestat®*. We receive co-promotion revenue from Allergan on the U.S. net sales of *Elestat®*. Allergan records sales of *Elestat®* and is responsible for other product costs.

Elestat® was approved by the U.S. Food and Drug Administration, or FDA, in October 2003 for the prevention of itching associated with allergic conjunctivitis. *Elestat®* is indicated for adults and children at least three years old. *Elestat®* is a seasonal product with product demand mirroring seasonal trends for topical allergic

conjunctivitis products whereby there is usually a large increase in sales during the Spring and a lesser increase during the Summer and Fall In February 2004, we launched *Elestat®* in the United States and are promoting it to ophthalmologists, optometrists and allergists. We work with Allergan collaboratively on overall product strategy and management in the United States.

Market Opportunity. Allergies affect more than 40 million people in the United States annually. We estimate that allergic conjunctivitis may occur in up to 90% of those patients suffering from allergies. The 2005 annual U.S. market for prescription ocular allergy products was approximately $420 million, and has experienced a growth rate, in terms of dollars, of approximately 10% over 2004, based on data compiled and reported by IMS Health.

Co-Promotion Agreement. Under the terms of the agreement, we paid Allergan an up-front payment and Allergan pays co-promotion revenue to us on U.S. net sales of *Elestat®*. Allergan retains the licensing rights relating to promotion of *Elestat®* to U.S. prescribers other than ophthalmologists, optometrists and allergists. However, we have a right of first refusal to obtain such rights in the event Allergan decides to engage a third party to undertake such activities. In the event that a third party is engaged by Allergan to promote *Elestat®* to prescribers outside of our field, we will be paid a proportionate share of U.S. net sales of *Elestat®* based upon filled prescriptions written by ophthalmologists, optometrists and allergists. Allergan also retains rights to all international sales and marketing activities relating to the drug.

The agreement with Allergan to co-promote *Elestat®* will be in effect until the earlier of: (i) the approval and launch of the first generic epinastine product; or (ii) the approval and launch of the first over-the-counter epinastine product. The commercial exclusivity period for *Elestat®* under the Hatch-Waxman Act will expire in October 2008, after which time *Elestat®* could face generic or over-the-counter competition if there is no other intellectual property protection covering *Elestat®*. The agreement also provides for early termination under certain circumstances. See "—Collaborative Agreements."

Restasis®

Overview. Restasis® (cyclosporine ophthalmic emulsion) 0.05% is the first approved prescription product in the United States for the treatment of dry eye disease. It is indicated to increase tear production in patients whose tear production is presumed to be suppressed due to ocular inflammation associated with keratoconjunctivitis sicca, or dry eye disease. In June 2001, we entered into a joint license, development and marketing agreement with Allergan to develop and commercialize diquafosol tetrasodium (INS365 Ophthalmic) for the treatment of dry eye disease. The agreement also provided us with a specified royalty on net sales of Allergan's *Restasis®* and granted us the right to co-promote *Restasis®* in the United States. In December 2002, *Restasis®* was approved for sale by the FDA and Allergan launched *Restasis®* in the United States in April 2003.

In the third quarter of 2003, we exercised our right to co-promote *Restasis®* under the joint license, development and marketing agreement with Allergan. In January 2004, we began co-promotion of *Restasis®* to eye care professionals and allergists in the United States and began receiving co-promotion revenue on net sales of *Restasis®* beginning in April 2004. Commercial exclusivity for *Restasis®* under the Hatch-Waxman Act has expired. However, the manufacture and sale of *Restasis®* is protected under a use patent which expires in August 2009 and a formulation patent which expires in May 2014. In October 2005, Allergan executed an agreement with NPS Pharmaceuticals, Inc. to promote *Restasis®* to rheumatologists in the United States, which is expected to generate additional revenue for *Restasis®*.

Market Opportunity. Other than *Restasis®*, the current treatments for dry eye disease in the major markets consist of artificial tear solutions and lubricant eye drops. In some cases, small plugs are inserted by physicians in the tear duct to slow tear drainage. Dry eye disease is associated with various factors including aging, environmental factors, autoimmune disorders and various medications. Since dry eye disease is more prevalent among the elderly and post-menopausal women, this market is expected to grow as populations age. We estimate,

based on an extrapolation from U.S. data, that dry eye disease affects approximately thirty million people in the eight major international prescription pharmaceutical markets, of which approximately nine million are in North America. For the years ending December 31, 2005, 2004, and 2003, Allergan has recognized $191 million, $100 million, and $38 million, respectively, of revenue from net sales of *Restasis®*.

Collaborative Agreement. In December 2003, we amended the joint license, development and marketing agreement to reduce the co-promotion revenue rates that we would receive on net sales of *Restasis®* upon obtaining co-promotion rights to *Elestat®*. The agreement, as it applies to *Restasis®*, will be in effect until all patents relating to *Restasis®* licensed under the agreement have expired. The agreement also provides for early termination under certain circumstances. See "—Collaborative Agreements."

Diquafosol tetrasodium (INS365 Ophthalmic)

Treatment of dry eye disease

Overview. Diquafosol is a dinucleotide that we discovered, which functions as an agonist at the $P2Y_2$ receptor and is being developed for the treatment of dry eye disease. Diquafosol stimulates the release of three components of natural tears – mucin, lipids and fluid. To date, we have completed four Phase 3 clinical trials of diquafosol for the treatment of dry eye disease. In total, we have conducted placebo-controlled clinical trials of diquafosol in more than 2,000 subjects.

We are developing diquafosol as an eye drop for dry eye disease. If approved, diquafosol could be the second FDA approved pharmacologically active agent to treat dry eye disease and the first one with this mechanism of action. Since diquafosol and *Restasis®* have different mechanisms of action, we consider them complementary products and, if diquafosol is approved by the FDA, we believe there is commercial opportunity for both of these products.

Development Status. In June 2003, we filed a New Drug Application, or NDA, with the FDA for diquafosol for the treatment of dry eye disease. In response to that NDA, we were granted a "Priority Review" designation and subsequently, received an approvable letter in December 2003. In June 2005, we submitted an amendment to our diquafosol NDA and received a second approvable letter in December 2005. We have scheduled a meeting with the FDA in late March 2006 to discuss the process and requirements to potentially obtain approval for diquafosol for the treatment of dry eye disease. Based upon this meeting, we plan to provide an update on the diquafosol program by late April 2006. In addition, our partner, Santen Pharmaceutical Co., Ltd., or Santen, is developing diquafosol in Japan and nine other Asian countries. Diquafosol is currently in Phase 2 clinical trials in Japan.

Pursuant to our agreement with Allergan, Allergan is responsible for regulatory approval of diquafosol in Europe. We are working with Allergan to determine a European regulatory filing strategy for diquafosol for the treatment of dry eye disease.

Depending on the outcome of our March 2006 meeting with the FDA, estimated subsequent costs necessary to amend our diquafosol NDA submission and resubmit the application for commercial approval in the United States are projected to be in the range of $1 million to $8 million, depending on whether additional Phase 3 testing is required for approval, excluding the cost of pre-launch inventory. This range includes costs for regulatory and consulting activities and for potentially completing an additional Phase 3 clinical trial, salaries for development personnel, and other unallocated development costs. Costs of other diquafosol clinical trials are excluded from this projection. If we are required to do more than one Phase 3 clinical trial, our costs will likely be higher than the projected range. The projected costs associated with diquafosol are difficult to determine due to the uncertainty of future regulatory requirements prior to our meeting with the FDA, and the actual costs are likely to differ. For a more detailed discussion of the risks associated with the development of diquafosol and our other development programs, including factors that could result in a delay of a program and increased costs associated with such a delay, please see the Risk Factors described elsewhere in this report.

Collaborative Agreements. Under the joint license, development and marketing agreement with Allergan, we have continued our efforts to develop and commercialize diquafosol. Under this agreement, we have received up-front and milestone payments of $11 million and may receive up to an additional $28 million in milestone payments assuming the successful completion of all remaining milestones under this agreement. We will also receive co-promotion revenue from Allergan on net sales, if any, of diquafosol worldwide, excluding most larger Asian markets. In the third quarter of 2003, we exercised our right under the Allergan agreement to co-promote diquafosol with Allergan in the United States and expect to begin promoting this product if and when we receive FDA approval and the product is launched. Our partner, Santen, is developing diquafosol in Japan and nine other Asian countries. Diquafosol is currently in Phase 2 clinical trials in Japan. See "—Collaborative Agreements."

Treatment of corneal wound healing

In April 2005, we initiated enrollment in a Phase 2 pilot clinical trial designed to evaluate the efficacy of diquafosol versus placebo in improving corneal wound healing following photorefractive keratectomy, or PRK, surgery. The target enrollment was approximately 30 subjects undergoing bilateral myopic PRK. The single clinical trial site, located in New Orleans, was seriously impacted by Hurricane Katrina in August 2005, and we were unable to continue to enroll additional participants in the clinical trial. Enrollment was less than 50% complete at the time enrollment was discontinued. Based on a review of the limited data available and discussions with the principal investigator, we do not plan to pursue a specific indication for PRK at this time.

Denufosol tetrasodium (INS37217 Respiratory) for the treatment of cystic fibrosis

Overview. We are developing denufosol tetrasodium (INS37217 Respiratory) as an inhaled product candidate for the treatment of cystic fibrosis. We believe that our product candidate could be the first FDA approved product that mitigates the underlying ion transport defect in the airways of patients with cystic fibrosis. If approved, we expect denufosol to be an early intervention therapy for the treatment of cystic fibrosis. This product candidate has been granted orphan drug status and fast-track review status by the FDA in the United States, and in January 2006, denufosol was granted orphan drug status in Europe. Denufosol is designed to enhance the lung's innate mucosal hydration and mucociliary clearance mechanisms, which in cystic fibrosis patients are impaired due to a genetic defect. By hydrating airways and stimulating mucociliary clearance through activation of the $P2Y_2$ receptor, we expect denufosol to help keep the lungs of cystic fibrosis patients clear of thickened mucus, reduce infections and limit the damage that occurs as a consequence of the prolonged retention of thick and tacky infected secretions.

Cystic fibrosis is a life-threatening disease involving a genetic mutation that disrupts the cystic fibrosis transmembrane regulator protein, an ion channel. In cystic fibrosis patients, a defect in this ion channel leads to poorly hydrated lungs and severely impaired mucociliary clearance. Chronic secondary infections invariably occur, resulting in progressive lung dysfunction and deterioration. Respiratory infections and complications account for more than 95% of the morbidity and mortality associated with this disease. According to the U.S. Cystic Fibrosis Foundation, the median life expectancy for patients is 35 years.

Development Status. In 2003, we initiated a multi-center Phase 2 clinical trial, Trial 08-103, in 90 patients with mild cystic fibrosis lung disease that was conducted in collaboration with the Cystic Fibrosis Foundation Therapeutics, Inc., or the CFFT. In April 2004, we announced top line results and in October 2004, we presented detailed results of this clinical trial at the North American Cystic Fibrosis Conference. Trial 08-103 was a double-blind, placebo-controlled, randomized trial. The primary purpose of this clinical trial was to determine safety and tolerability of three times daily nebulizer doses of up to 60 mg denufosol versus placebo over a four-week treatment period. All three doses were well tolerated over the four-week treatment period. Lung function was assessed by multiple standard pulmonary lung function measurements and statistical significance was achieved on all of the spirometric measures employed in the clinical trial. Patients receiving denufosol (pooled results across three doses) had significantly better lung function than patients receiving placebo after 28 days of treatment.

In the fourth quarter of 2004, we began two six-month toxicology studies in two animal species required by the FDA prior to initiating a Phase 3 program. In October 2005, we announced the completion of

these toxicology studies. Based on our internal review and our consulting toxicologists' review of the results of these toxicology studies, we believe that the safety profile of denufosol is acceptable for advancement into Phase 3 clinical trials. In addition, a 12-month animal inhalation toxicology study is currently ongoing and is expected to be completed by mid-year 2006.

In January 2005, we began enrollment in an additional Phase 2 clinical trial, Trial 08-104, in 72 patients with cystic fibrosis lung disease in order to broaden our patient experience prior to our initiation of a Phase 3 program. The purpose of Trial 08-104 was to gain a greater understanding of the safety and tolerability of denufosol in a different population of cystic fibrosis patients than those enrolled in Trial 08-103. In contrast to Trial 08-103, Trial 08-104 enrolled patients with lower lung function and patients using multiple concomitant medications, including oral and inhaled antibiotics. Trial 08-104 consisted of a double-blind, randomized comparison of two doses of denufosol (20 mg and 60 mg) to placebo administered three-times daily for 28 days by standard air jet nebulizer in cystic fibrosis patients at 17 clinical centers across the United States. Trial 08-104 was not designed or powered to demonstrate statistically significant differences between denufosol and placebo with respect to efficacy, and no statistically significant differences were observed.

In October 2005, we announced the results of Trial 08-104. The 20 mg dose was generally well tolerated across all patients enrolled in Trial 08-104. As observed in previous clinical trials, both the 20 mg and 60 mg doses of denufosol were generally well tolerated in the patient population with milder disease. Patients with lower lung function reported more respiratory adverse events across all treatment groups compared to patients with milder disease. Some of these events were acute transient declines in lung function following initial dosing that led to clinical trial withdrawals, in particular in the 60 mg group. These observations are consistent with the expected pharmacologic activity of denufosol in enhancing airway hydration and mucociliary clearance. In the subset of patients using *Pulmozyme®*, positive trends in efficacy were observed when compared to placebo, but they were not statistically significant. The interpretation of results for patients on inhaled tobramycin was complex, due to the small size of the clinical trial and the logistics of intermittent inhaled tobramycin treatment.

In July 2005, we initiated a two-center, 15 patient pediatric double-blind, randomized, placebo-controlled, 28-day Phase 2 clinical trial in five to seven year-old cystic fibrosis patients. Enrollment is ongoing and is expected to be completed by mid-year 2006.

In January 2006, we completed an End-of-Phase 2 meeting with the FDA and plan to initiate a Phase 3 program to advance denufosol for the treatment of cystic fibrosis. The focus of our Phase 3 program will be to develop denufosol as an early intervention therapy for treatment of patients with mild lung disease. According to the Cystic Fibrosis Foundation's 2004 Patient Registry, approximately two-thirds of cystic fibrosis patients have lung disease defined as mild as measured by the standard pulmonary function test, FEV_1 (Forced Expiratory Volume over one second) > 70% predicted. In the pediatric population under 18 years of age, approximately 80% of patients have mild or early lung disease.

Based on the End-of-Phase 2 meeting with the FDA, we plan to conduct two pivotal Phase 3 clinical trials in cystic fibrosis patients with changes in FEV_1 as the primary endpoint. Secondary endpoints will most likely include, but are not limited to, pulmonary exacerbations, other lung function parameters and quality of life. We plan to run these clinical trials in parallel, with initiation of the first clinical trial targeted to begin mid-year 2006. We also intend to use the first pivotal efficacy clinical trial to fulfill the long-term safety requirement to study denufosol in a specified number of patients for one year. The FDA has indicated that it is not necessary for the second pivotal clinical trial to have the identical study duration. We plan to seek input from the FDA in finalizing the clinical trial protocols. It is anticipated that patients on standard cystic fibrosis therapies, including *Pulmozyme®*, *TOBI®*, and digestive enzymes will be included in this clinical trial. Patients using hypertonic saline, a non standard therapy, will not be included in the clinical trial.

We are required to conduct a single two-year inhalation carcinogenicity study in one animal species. The time from initiation of the study to receipt of the final study report is expected to be up to three years. This study is expected to be initiated before the end of 2006, following FDA review of the toxicology protocol.

In addition, although not requested by the FDA, we may conduct further clinical trials to evaluate denufosol in patients with lower lung function, to gain a better understanding of the initial dose tolerability of denufosol in a patient population with more significant airflow obstruction.

Estimated subsequent costs necessary to submit an NDA for denufosol for the treatment of cystic fibrosis are projected to be in the range of $35 million to $60 million, excluding the cost of pre-launch inventory and any potential development milestones payable to the CFFT. This estimate includes completing any ongoing or additional Phase 2 clinical trials, conducting two Phase 3 clinical trials and any required toxicology and carcinogenicity studies, manufacturing denufosol for clinical trials, toxicology and carcinogenicity studies, producing qualification lots consistent with current Good Manufacturing Practice, or cGMP, standards, salaries for development personnel, other unallocated development costs and regulatory preparation and filing costs. These costs are difficult to project and actual costs could be materially different from our estimate. For example, clinical trials, toxicology and carcinogenicity studies may not proceed as planned, results from future clinical trials may change our planned development program, additional Phase 3 clinical trials may be necessary, other parties may assist in the funding of our development costs, and an anticipated NDA filing could be delayed. For a more detailed discussion of the risks associated with our development programs, please see the Risk Factors described elsewhere in this report.

Market Opportunity. The current therapeutic approaches to address cystic fibrosis mainly treat the symptoms and are aimed at reducing respiratory infections and breaking up thickened mucous secretions that cause airflow obstruction and harbor bacteria. For example, *TOBI®* is an inhaled antibiotic that treats the infection, and *Pulmozyme®* is an inhaled protein that breaks up excessive DNA in cystic fibrosis mucus that reduces the thickness and tackiness of the respiratory secretions. While both products are approved for the treatment of cystic fibrosis, neither product is designed to address the genetic underlying ion-transport defect, which results in dehydrated mucus and severely impaired mucociliary clearance.

There are approximately 30,000 diagnosed cystic fibrosis patients in the United States and we estimate approximately 75,000 in the world. We estimate annual sales of the two prescription pharmaceutical products to treat cystic fibrosis lung disease, *Pulmozyme®* and *TOBI®*, to be approximately $375 million in the United States and $550 million on an aggregate worldwide basis, based on 2005 data compiled and reported by IMS Health.

We currently plan to retain commercial rights for denufosol for the treatment of cystic fibrosis in North America and to secure a corporate partner to develop and commercialize this product candidate outside of North America.

Collaborative Agreement. In October 2002, we entered into a study funding agreement with the CFFT pursuant to which they funded the majority of the external costs of our first Phase 2 clinical trial for the treatment of cystic fibrosis in exchange for certain milestone payments. These milestone payments are contingent upon FDA approval, potential commercialization and achievement of certain aggregate sales volume in the first five years following product approval. In the event of FDA approval, we are obligated to pay to the CFFT, over a period of five years, an amount equal to a multiple of the clinical trial costs incurred by the CFFT as a development milestone payment, which is currently estimated to be approximately $12 million. Additionally, in the event aggregate sales of the product exceed a certain level in the first five years subsequent to regulatory approval, we are obligated to pay the CFFT an additional $4 million sales milestone, payable over two years. See "—Collaborative Agreements."

Denufosol tetrasodium (INS37217 Ophthalmic) for the treatment of retinal disease

During 2005, we began investigation of denufosol tetrasodium (INS37217 Ophthalmic), a $P2Y_2$ receptor agonist given as an intravitreal injection, for the treatment of diseases associated with accumulation of fluid in or around the retina. We initiated two Phase 2 pilot clinical trials in patients with macular edema in the second and third quarters of 2005. The first clinical trial was to enroll patients with persistent macular edema associated with

uveitis, and the second clinical trial was to enroll patients with persistent macular edema following cataract surgery. In January 2006, we announced that we discontinued these two Phase 2 pilot clinical trials. Although we did not identify any significant safety or tolerability issues, the data did not demonstrate improvement in either reduction of retinal thickness or improvement in visual acuity. We have no current plans to conduct any further studies of denufosol for the treatment of retinal disease.

INS50589 Antiplatelet for use in acute cardiac care

Overview. INS50589 Antiplatelet is a selective and reversible inhibitor of the platelet $P2Y_{12}$ adenosine diphosphate receptor and is being developed to reduce complications in patients undergoing surgeries involving cardiopulmonary bypass. During bypass procedures, blood is diverted out of the body through a bypass pump, causing activation of platelets that results in subsequent platelet dysfunction following surgery. Platelets are components of the blood which, when activated, contribute to the formation of blood clots that help to stop bleeding. Platelet activation and post-operative platelet dysfunction may contribute to complications such as the need for blood transfusions, cognitive disorders, and pulmonary or renal dysfunction, among others. Unlike currently marketed products used for the prevention of blood clots during bypass procedures, INS50589 Antiplatelet has been shown in preclinical studies and our Phase 1 clinical trial to both inhibit platelet aggregation and to be reversible. This unique profile could provide for platelet aggregation inhibition and protection from activation during the bypass procedures and for restoration of normal platelet function following the procedure when intravenous administration of the drug is stopped.

Development status. In November 2004, we filed an Investigational New Drug Application, or IND, and in December 2004, we initiated a Phase 1 clinical trial of the tolerability, pharmacokinetics and pharmacodynamics of INS50589 Antiplatelet in healthy volunteers. The Phase 1 single-center clinical trial assessed the safety and tolerability of four doses of INS50589 Antiplatelet administered by continuous intravenous infusion over four hours in 36 healthy volunteers. The clinical trial included an initial open-label portion involving 12 subjects, followed by a double blind, placebo-controlled portion involving an additional 24 subjects. All 36 subjects completed the clinical trial. The clinical trial assessed the pharmacokinetics and biological activity of the compound using various platelet function tests. As announced in June 2005, INS50589 Antiplatelet was well-tolerated in this clinical trial and demonstrated dose-dependent evidence of pharmacological effect, as previously observed in preclinical studies. The clinical trial results were statistically significant compared to placebo at all doses and demonstrated complete inhibition of platelet aggregation within 15 to 30 minutes for the three highest doses. Depending on the dose and test method, platelet function returned to near baseline levels within minutes to hours following discontinuation of the infusion.

In August 2005, we completed a proof-of-concept preclinical study evaluating INS50589 Antiplatelet in an animal model of cardiopulmonary bypass surgery, which confirmed our expectations around preservation of platelet function, reduction of post operative blood loss and reduction of transfusions. Both the Phase 1 clinical trial and the proof-of-concept preclinical study demonstrated an adequate safety profile and biologic activity. We have designed and plan to initiate a Phase 2 proof-of-concept clinical trial in the first half of 2006.

In addition to the intravenous formulation of INS50589 Antiplatelet, we are actively working on a lead series of orally bioavailable $P2Y_{12}$ receptor antagonist molecules that, like INS50589 Antiplatelet, are fully reversible and may potentially have some advantages over existing therapies.

Estimated subsequent costs necessary to submit an NDA for INS50589 Antiplatelet are projected to be in the range of $30 million to $50 million, excluding the cost of pre-launch inventory. This estimate includes completing the remaining components of our Phase 2 program, conducting a Phase 3 clinical program, manufacturing INS50589 Antiplatelet for clinical trials and toxicology studies, producing qualification lots consistent with current cGMP standards, salaries for development personnel, other unallocated development costs and regulatory preparation and filing costs. These costs are difficult to estimate and actual costs could be materially different from our estimate. For example, clinical trials and toxicology studies may not proceed as

planned, results from future clinical trials may change our planned development program, other parties may assist in the funding of our development costs, and an anticipated NDA filing could be delayed. For a more detailed discussion of the risks associated with our development programs, please see the Risk Factors described elsewhere in this report.

In order to fully optimize our intravenous and oral antiplatelet programs on a global basis, we are currently exploring potential collaborative partnerships for these programs. Given the limited data available and the early stage of development of the oral series molecules, we are currently unable to reasonably project the future dates and costs that may be associated with clinical trials or a prospective NDA filing.

Market Opportunity. The near term opportunity for INS50589 Antiplatelet is in the reduction of complications as a result of perioperative blood loss and the need for blood transfusions associated with patients who undergo coronary artery bypass grafts surgery, or CABG. Based on our internal estimate of the number of CABG procedures, as well as current treatments and trends, we believe the market for this indication to be approximately $200 million in peak annual sales in the United States. In addition, we believe other opportunities may exist for INS50589 Antiplatelet use in valve replacement/repair procedures and thoracic aortic surgery. Our internal estimate of these markets, combined with the CABG market, based on current treatments and trends is potentially $470 million in peak annual sales in the United States.

Product Candidates in Preclinical Development

Intranasal epinastine

On February 17, 2006, we entered into a development and license agreement with Boehringer Ingelheim International GmbH, or Boehringer Ingelheim. The agreement grants us certain exclusive rights to develop and market an intranasal dosage form of epinastine, in the United States and Canada, for the treatment or prevention of rhinitis. We plan to meet with the Pulmonary Division of the FDA to discuss an IND application for intranasal epinastine, which we would intend to submit after that meeting. While we expect to initiate Phase 2 testing of intranasal epinastine in 2006 based on the work already completed by Boehringer Ingelheim, this will be dependent upon the pre-IND meeting with the FDA. See "—License Agreements."

Market Opportunity. The current market for nasal treatment of allergic rhinitis is approximately $2.8 billon in annual prescription sales in the United States, growing at approximately 10% based on 2005 data compiled and reported by IMS Health.

Outflow enhancer

As part of the research agreement under the technology licensed from Wisconsin Alumni Research Foundation, or WARF, in 2004, we have made significant progress in synthesizing compounds that are active in disrupting the acto-cytoskeleton of the trabecular meshwork as potential treatments for glaucoma. Our hypothesis is that the mechanism of action may result in reduction of intraocular pressure by affecting the primary outflow pathway for aqueous humor. See "—License Agreements."

Market Opportunity. The current market for treatment of glaucoma, the largest market in ophthalmic pharmaceuticals, is approximately $1.6 billion in annual sales in the United States based on 2005 data compiled and reported by IMS Health.

Additional discussion of the costs and expenses associated with all of our research and development programs is discussed below in "Management's Discussion and Analysis of Financial Condition and Results of Operations—Results of Operations—Years Ended December 31, 2005, 2004 and 2003—Costs and Expenses."

Collaborative Agreements

Allergan, Inc.—Elestat®

In December 2003, we entered into an agreement with Allergan to co-promote *Elestat®* to ophthalmologists, optometrists and allergists in the United States. *Elestat®* was approved by the FDA in October 2003 for the prevention of itching associated with allergic conjunctivitis. We have the primary responsibility for selling, promoting and marketing *Elestat®* in the United States and paying the associated costs. In addition, we have the right to and may conduct Phase 4 clinical trials and other studies in collaboration with Allergan relating to *Elestat®*. We work with Allergan collaboratively on overall product strategy and management in the United States. Allergan records sales of *Elestat®* and is responsible for other product costs, as well as retaining responsibility for all international marketing and selling activities. Allergan also retains the licensing rights relating to promotion of *Elestat®* to U.S. prescribers other than ophthalmologists, optometrists and allergists. However, we have a right of first refusal to obtain such rights in the event Allergan decides to engage a third party to undertake such activities. We have established a joint commercialization committee with Allergan to coordinate and oversee the broad strategies, promotion activities and manage the relationship. Allergan is responsible for supply chain management, managed healthcare, customer order processing and regulatory compliance. Under the terms of the agreement, we paid Allergan an up-front payment and Allergan pays co-promotion revenue to us on U.S. net sales of *Elestat®*. In the event that a third party is engaged by Allergan to promote *Elestat®* to prescribers outside of our field, we will be paid a proportionate share of U.S. net sales of *Elestat®* based upon filled prescriptions written by ophthalmologists, optometrists and allergists. Under the terms of the agreement, we are required to achieve certain performance minimums to receive some or all of co-promotion revenue contemplated.

The agreement will be in effect until the earlier of: (i) the approval and launch of the first generic epinastine product; or (ii) the approval and launch of the first over-the-counter epinastine product; in each case after expiration of the patents and market exclusivities for *Elestat®* listed in the FDA's publication "Approved Drug Products with Therapeutic Equivalence Evaluations" (generally known as the "Orange Book"). Either Allergan or we may terminate the agreement in the event of a material breach of the agreement by the other or in the event of the other's insolvency. Allergan can terminate the agreement if we fail to meet a defined minimum of net sales in any given year, or upon a change of control where we become an affiliate of a direct competitor of Allergan's as that term is defined in the agreement. We can terminate the agreement in the event that *Elestat®* is withdrawn from the market for more than ninety days.

Allergan, Inc. – Restasis® and diquafosol

In June 2001, we entered into a joint license, development and marketing agreement with Allergan to develop and commercialize diquafosol. The agreement also provided us with a specified royalty on net sales of *Restasis®* and granted us the right to co-promote *Restasis®* in the United States. In December 2003, at the time we entered into the co-promotion agreement relating to *Elestat®*, we amended the joint license, development and marketing agreement to reduce the co-promotion revenue rates that we would receive upon the sale of *Restasis®*.

Under the terms of the amended agreement, Allergan obtained an exclusive license to develop and commercialize diquafosol worldwide, with the exception of Japan and nine other Asian countries covered by our agreement with Santen. In return, we will receive co-promotion revenue from Allergan on net sales of *Restasis®* and diquafosol, if any, worldwide, excluding most larger Asian markets. In December 2002, *Restasis®* was approved for sale by the FDA and Allergan launched *Restasis®* in the United States in April 2003. In the third quarter of 2003, we exercised our right under the Allergan agreement to co-promote diquafosol and *Restasis®*. We began promoting *Restasis®* in January 2004 and began receiving co-promotion revenue on net sales of *Restasis®* in April 2004. We have received milestone payments under this agreement related to our development of diquafosol and will promote diquafosol if and when we receive FDA approval.

We have established a joint development committee with Allergan to oversee the joint development program and a joint commercialization committee to establish the broad strategies and manage the relationship.

Under the terms of the agreement, we provide bulk active drug substance while diquafosol is in development and Allergan is responsible for obtaining or manufacturing all of its bulk active drug substance requirements for commercial supply of the product.

We are responsible for conducting, in collaboration with Allergan, the Phase 3 clinical trials for diquafosol for dry eye disease needed for potential approval and for filing the U.S. NDA. Allergan is responsible for all other development activities under the agreement, including all development and regulatory activities needed for potential approval outside the United States and in its territories, and for ex-U.S. regulatory submissions, filings, and approvals relating to products. Allergan is responsible for all commercial costs except for the cost of our sales force in the United States. Allergan is required to use commercially reasonable efforts to conduct these development activities, seek ex-U.S. regulatory approvals and market and sell diquafosol.

Unless earlier terminated pursuant to other terms of the agreement, the agreement will expire as to each product (*Restasis®* or diquafosol, as the case may be) in each applicable country on the later of (i) the 10th anniversary of the first commercial sale of such product in the applicable country, or (ii) the date on which the sale of such product ceases to be covered by any claim of any applicable Inspire or Allergan patent. The agreement will expire in its entirety upon the expiration of the agreement with respect to all products in all countries in all applicable countries. Either Allergan or we may terminate the agreement in the event of a material breach of the agreement. In addition, we have the right to terminate the agreement by giving 180 days prior notice if we determine, subject to the joint commercialization committee's review and arbitration, that Allergan has not made reasonably sufficient progress in the commercialization of our product. If Allergan breaches the agreement, becomes insolvent or we terminate for failure to make progress with the commercialization of our product, Allergan's license will terminate and Allergan must provide us with all data and information relating to our product and must assign or permit us to cross-reference all regulatory filings and approvals.

The co-promotion revenue that we receive on the net sales of *Restasis®* is based upon a percentage of net sales of *Restasis®* in the United States, for which this percentage will increase in April 2006 and again in April 2007, and upon a percentage of net sales of *Restasis®* outside the United States, except in Japan, Taiwan, Korea, Hong Kong and the Peoples Republic of China. In the event that the Allergan/Inspire joint development committee decides to terminate the development program for diquafosol, and any other Inspire product under development pursuant to the agreement, and we do not within six months of the termination of the development program fulfill our obligations under the co-promotion provisions for *Restasis®*, including providing a required minimum percentage of the budgeted sales force effort for *Restasis®*, the royalty that we receive on net sales of *Restasis®*, both with respect to sales in the United States and elsewhere, will be reduced, but not eliminated.

Santen Pharmaceutical Co., Ltd.

In December 1998, we entered into a development, license and supply agreement with Santen for the development of diquafosol for the therapeutic treatment of ocular surface diseases, such as dry eye disease, in Asia. Under the agreement, we granted Santen an exclusive license to market diquafosol for ocular surface diseases in Japan, China, South Korea, the Philippines, Thailand, Vietnam, Taiwan, Singapore, Malaysia and Indonesia.

We established a coordinating committee to review and evaluate Santen's progress in the development and commercialization of potential products. Santen is responsible for all development, regulatory submissions, filings and approvals, and all marketing of potential products. We are obligated to supply Santen with its requirements of diquafosol in bulk drug substance form for all preclinical studies, clinical trials and commercial requirements at agreed-upon prices.

Under the terms of the agreement, we received an up-front equity investment of $1.5 million for shares of our preferred stock in December 1998, that were subsequently converted into shares of our common stock.

During 2000, we received a milestone payment under the Santen Agreement of $500,000 based on achievement of a regulatory milestone by Santen. In addition, depending on whether all milestones are met, we could receive additional payments of up to $4.25 million, as well as royalties on net sales of licensed products.

The agreement will terminate when all patents licensed under the agreement have expired. Either Santen or we may terminate the agreement if the other materially breaches the agreement. In addition, we have the right to terminate the agreement at any time if we determine, subject to the coordinating committee's review and arbitration, that Santen has not made reasonably sufficient progress in the development or commercialization of potential products. If Santen breaches the agreement, or if we terminate the agreement because Santen has not made sufficient progress, Santen's license will terminate. Santen will provide us with all data and information relating to our products, and will assign or permit us to cross-reference all regulatory filings and approvals.

Cystic Fibrosis Foundation Therapeutics, Inc.

In October 2002, we entered into a study funding agreement with the CFFT, a non-profit drug development affiliate of the Cystic Fibrosis Foundation, for the funding of one Phase 2 clinical trial for denufosol for the treatment of cystic fibrosis. Under the agreement, the CFFT provided the majority of funding of external costs for one Phase 2 clinical trial of denufosol, which we completed in April 2004, in exchange for post-commercialization development and sales milestone payments. If denufosol ultimately receives FDA approval for the treatment of cystic fibrosis, we would be obligated to pay a development milestone to the CFFT, calculated as a multiple of the clinical trial costs incurred by the CFFT. In addition, we would be obligated to pay a sales milestone if the product candidate achieves a certain aggregate sales volume in the first five years following product approval. The development milestone is currently estimated to be approximately $12 million, payable over five years, and the sales milestone would be an additional $4 million, payable over two years.

The agreement will terminate no later than the expiration of all payment obligations under the agreement. Either the CFFT or we may terminate the agreement if the other materially breaches the agreement.

License Agreements

The University of North Carolina at Chapel Hill

In March 1995, September 1998, and January 2002, we entered into three separate agreements with UNC granting us exclusive worldwide licenses to develop, make, use and sell products based on UNC patented technology relating to the use of P2Y receptor agonists and antagonists for respiratory therapeutics, such as diquafosol tetrasodium for respiratory diseases; respiratory diagnostics, such as INS316 Diagnostic; and cardiovascular uses, such as INS50589 Antiplatelet. Development programs for diquafosol tetrasodium for respiratory diseases and INS316 Diagnostic are not currently active. In connection with these license agreements, we have paid an aggregate of $720,000 in license initiation fees, up-front milestone payments, and annual license preservation payments, and may have to pay additional milestone payments totaling $650,000. In addition, we would be obligated to pay royalties based on net sales of certain licensed products as defined in the agreements. A fourth agreement, entered into in March 1995, granted us a non-exclusive worldwide license to use other UNC patented technology as a research tool to identify agonists and antagonists for P2Y receptors.

If we fail to meet performance milestones relating to the timing of regulatory filings or pay the minimum annual payments under our respective UNC licenses, UNC may terminate the applicable license.

Wisconsin Alumni Research Foundation

In November 2004, we licensed several patents for use in developing and commercializing new treatments for glaucoma from WARF. Under the terms of the agreement, we paid an upfront licensing payment of $150,000 and are obligated for additional contingent payments of up to an aggregate of $1.8 million upon the achievement of development milestones, and royalties on sales of any regulatory approved product utilizing the licensed patents.

We will design and fund all future research, development, testing, regulatory filings and potential marketing activities related to any product candidate under development or product developed from the license. Unless terminated earlier, the agreement will expire on a country-by-country basis upon the expiration of the patents in such country.

If we fail to meet performance milestones relating to the timing of regulatory filings or pay the minimum annual payments under this license, WARF may terminate the license.

Boehringer Ingelheim International GmbH

On February 17, 2006, we entered into a development and license agreement with Boehringer Ingelheim. The agreement grants us certain exclusive rights to develop and market an intranasal dosage form of epinastine, in the United States and Canada, for the treatment or prevention of rhinitis.

Under the terms of the agreement, we will have full responsibility for the intranasal epinastine development program and regulatory filings in the United States and Canada. Upon the receipt of appropriate regulatory approvals for an intranasal epinastine product, we will be responsible for the commercialization of such product in the United States and Canada. Boehringer Ingelheim has retained the rights to develop and commercialize intranasal epinastine outside the United States and Canada, based on any future results of our intranasal epinastine development program.

In addition to funding all development activities under the terms of the agreement, we are required to pay Boehringer Ingelheim (a) an upfront license fee of $2.5 million, and (b) high single digit royalties on net sales of an intranasal epinastine product in the United States and Canada. If Boehringer Ingelheim commercializes our intranasal epinastine product outside of the United States and Canada, it will be obligated to pay royalties to us on net sales of the product.

In general, the exclusive license granted to us will expire and convert into a perpetual, fully paid-up, non-exclusive license on December 31, 2022. Certain other rights and royalty obligations will continue beyond such date. For a period of five (5) years following December 31, 2022, Boehringer Ingelheim shall have the right, but not the obligation, to switch a product developed under the agreement from a prescription product to an over-the-counter, or OTC, product. Following such a switch, Boehringer Ingelheim will have the right to commercialize such product in the United States and/or Canada. In connection with such a switch, Boehringer Ingelheim will be required to pay an OTC switch payment and ongoing royalties to us.

Research and Development

Since our inception, we have made substantial investments in research and development. During the years ended December 31, 2005, 2004 and 2003, we spent $23.6 million, $25.7 million and $27.6 million, respectively, on research and development activities.

Discovery

We have a fully integrated discovery organization with expertise in medicinal chemistry, development chemistry, molecular pharmacology, biochemistry, screening, and preclinical drug evaluation. We have invested in state-of-the-art equipment as well as internal and contracted laboratory space for performing synthetic, process, and analytical chemistry, determination of compound structure and biological activity, and evaluation of drug efficacy, pharmacokinetics, pharmacodynamics, and tolerability. We have built the infrastructure to develop, validate, and scale-up biochemical and cellular assays in a number of versatile formats, and to conduct high throughput screening operations on a structurally diverse chemical library that we own and maintain. We continue to identify and synthesize new chemical entities with promising activity, stability and metabolic profiles for further testing in a variety of respiratory/allergy, ophthalmic, and cardiovascular indications. We conduct preclinical development studies to advance promising compounds to pre-IND status and conduct the requisite preclinical studies to support IND filing, if appropriate. Through the use of material transfer agreements or

sponsored research agreements, we routinely collaborate with academic institutions to advance basic and translational research and to augment our internal research capabilities. We primarily use contract research organizations for toxicology, pharmacokinetics, toxicokinetics, and other studies required for IND and NDA regulatory submissions. We have recently built the capability to develop and validate preclinical disease models and to conduct proof-of-concept efficacy experiments for evaluating new drug targets and compounds to make stage-gate decisions in advancing a lead series through the early drug discovery process.

Highly active areas of discovery research are in the areas of orally bio-available inhibitors of $P2Y_{12}$ receptors and compounds that are active in modifying the acto-cytoskeleton as potential treatments for glaucoma. In addition we have an active research program studying the pharmacological effects (such as potency, efficacy, mechanism and duration of action) of various marketed antihistamines on cloned histamine receptors involved in itch, vasodilation, vaso-permeability, and inflammation. We routinely present our scientific research at ophthalmic, respiratory, allergy, cardiovascular, and neurobiology conferences and in peer-reviewed publications.

Development

After a molecule is determined to be an appropriate product candidate based upon our research findings and business strategy, it moves into the development function of our organization, where extensive testing of both the characteristics of the molecule and the effects it has on humans are conducted. The progression of product candidates through the various stages of development is overseen by our Portfolio Review Committee, a group comprised of certain company officers and selected senior staff. Our development function is divided into four functional areas, Pharmaceutical Development, Regulatory Affairs, Clinical Research, and Biostatistics and Data Management. Our Clinical Research function has been organized into two groups; one with an ophthalmic disease focus and a second with a respiratory/allergy and other diseases focus.

When a product candidate is judged as ready for human testing, an IND is filed with the FDA that, in the absence of FDA objections, allows us to embark on human testing in the United States. Other regulatory filings outside of the United States are completed as necessary. Since 1997, we have filed seven INDs for product candidates that were subsequently evaluated in humans. Some of these product candidates have progressed to later phases of development. In addition to internal resources, we collaborate with external contract research organizations that allow us to perform development activities with a limited number of staff.

See "Management's Discussion and Analysis of Financial Conditions and Results of Operations – Research and Development Expenses."

Sales and Marketing

Beginning in the first quarter of 2004, we initiated commercial operations and began co-promoting *Elestat*® and *Restasis*® to a select number of high prescribing eye care professionals and allergists. As a company, we have limited sales and marketing experience, having just completed our second year of sales and marketing activities. We employ 64 territory managers and 6 regional sales directors to provide us with national sales coverage for *Elestat*® and *Restasis*®. We also have a marketing team and a training and operations team to support our commercialization effort. Our small, specialty sales and marketing organization focuses its promotional efforts on ophthalmologists, optometrists and allergists. We believe our focused marketing combined with our specialty sales force can effectively co-promote *Elestat*® and *Restasis*®. Eye care professionals account for the majority of the dry eye disease prescriptions and combined with the allergists, these specialties prescribe approximately half of the ocular allergies prescriptions. Targeting these medical specialties is a sound strategy for advancing *Elestat*®, *Restasis*® and our dry eye disease product candidate, diquafosol.

In the United States, we are co-promoting *Elestat*® and *Restasis*® and intend to co-promote diquafosol if and when that product candidate receives FDA approval. We co-promote *Restasis*® in the United States with Allergan, but we have primary U.S. sales and marketing responsibilities for *Elestat*®. We have not developed

commercial plans for our product candidates beyond *Elestat®*, *Restasis®* and diquafosol as these plans will be dependent in large part on the timing of their commercial launch and our financial resources. We intend to establish corporate partnering, licensing or other arrangements for the marketing and sale of selected product candidates that we develop, especially outside of North America. We do not intend to develop international operations outside of North America. Accordingly, third parties may have significant control or influence over important aspects of the commercialization of our product candidates, including market identification, marketing methods, pricing, composition and magnitude of sales force and promotional activities. We may have limited control over the amount and timing of resources that a third party devotes to our products.

We feel the establishment of our commercial operations provides us with the foundation to leverage opportunities to market and sell other products we are developing, or products that we may in-license or otherwise acquire, and to maximize their commercial value in the United States.

Compliance

We are committed to conducting our business fairly, honestly, ethically and lawfully. We act responsibly and with integrity in our relationships with patients, health care professionals, providers, governments, regulatory entities, customers, suppliers, vendors and stockholders.

We have designated a Corporate Compliance Officer who reports to the Chief Executive Officer and Chairman of the Audit Committee of the Board of Directors. The Corporate Compliance Officer is responsible for evaluating potential compliance risks within the company and designing control procedures. This is achieved by conducting audits consistent with implementation of applicable industry codes, policies and other controls. Areas of control include, but are not limited to, compliance with current Federal and State law, such as the Sarbanes-Oxley Act of 2002, U.S. Foreign Corrupt Practices Act of 1977, NASDAQ and National Association of Securities Dealers listing requirements and Securities and Exchange Commission, FDA, the Department of Health and Human Services' and Office of Inspector General regulations. Codes and policies that have been implemented include, but are not limited to, "Code of Ethics and Conduct Relating to Financial Affairs," "Code of Business Ethics," "Whistleblower Policy" and "Code of Conduct: Promotional Interactions with Health Care Professionals." The Corporate Compliance Officer provides frequent updates to senior management, the Audit Committee of the Board of Directors and to the full Board of Directors.

Manufacturing and Supply

We do not currently engage in, nor do we expect to engage in, the manufacture of bulk active pharmaceutical ingredients, or APIs, for preclinical, clinical or commercial purposes. We rely on a contract manufacturing supply arrangement with a single cGMP compliant manufacturer located in Choshi, Japan, for the development stage production of diquafosol and denufosol. We expect that this vendor will ultimately supply commercial quantities of these compounds for both ophthalmic and respiratory applications. Under our agreements with Allergan, Allergan will be responsible for the manufacture and supply of diquafosol, if approved by the FDA. We have already obtained several cGMP batches of these compounds from our vendor and it has completed the validation of the manufacturing process for diquafosol. The API for our antiplatelet program, INS50589, is manufactured by a cGMP vendor located in Ontario, Canada. It has been agreed that Boehringer Ingelheim, located in Germany, will be responsible for supplying us with active drug substance for our intranasal epinastine development program. Manufacturing facilities in non-U.S. countries are subject to inspection by the FDA as well as manufacturing requirements of the local regulatory authorities. Actions by local authorities for failure to comply with one or more local requirements could affect the status of the site for manufacturing product for the U.S. market either by notice to the FDA of a cGMP issue or indirectly by affecting production and availability of product for export to the United States. Although we have identified potential alternative sources for our product candidates, we presently depend on two vendors as the sole manufacturers of APIs for our current clinical development programs. See "Risk Factors— Reliance on a single party to manufacture and supply either finished product or the bulk active pharmaceuticals ingredients for a product or product candidates could adversely affect us."

In addition to the bulk APIs, our products incorporate pharmacopeial grade excipients such as sodium chloride, sodium hydroxide and hydrochloric acid, all of which are readily available from numerous sources. Many of our clinical trial materials are packaged in form-fill-seal vials, which are manufactured by a single vendor, but similar vials are also available from other commercial filling and packing companies. In addition to form-fill-seal vial packaging, we also administer our product candidates as intravenous infusions. The intravenous infusions have been manufactured by a single vendor using standard glass vials and rubber stoppers. In the case of our intravenous infusion product candidate, INS50589 Antiplatelet, alternate sources of both components and manufacturing sites are available.

We conduct qualification and routine audits of our contract manufacturers. These contract manufacturers are identified in our regulatory agency filings, such as with the FDA, and are subject to regulatory agency inspections. We also attempt to stay informed on the financial condition of contract manufacturers and their status with regulatory agencies. Although we also maintain an inventory of drug product in order to minimize the risk of material shortage, a prolonged interruption in supply could adversely disrupt our manufacturing plans.

The manufacture of our products and product candidates is based, in part, on technology that we believe to be proprietary to our contract manufacturers or our collaborative partners. Such manufacturers may not abide by the limitations or confidentiality restrictions in agreements with us. In addition, any such manufacturer may develop process technology related to the manufacture of our compounds that such supplier owns either independently or jointly with us. This would increase our reliance on such manufacturer or require us to obtain a license from such manufacturer in order to have our products manufactured.

Patents and Proprietary Rights

We believe that the proprietary protection of our product candidates, processes and know-how is important to the success of our business. We aggressively file and prosecute patents covering our proprietary technology and, if warranted, will defend our patents and proprietary technology. As of January 31, 2006, we owned or licensed patent rights consisting of 57 issued U.S. patents, none of which expire before 2011, and numerous pending applications in the United States and corresponding patents and patent applications in foreign jurisdictions. We seek patent protection for our proprietary technology and products in the United States and Canada and in key commercial European and Asia/Pacific countries and other major commercial sectors of the world, as appropriate. We intend to seek trademark protection in the United States and foreign countries, as appropriate. We also rely upon trade secrets, know-how, continuing technological innovation and licensing opportunities to develop and maintain our competitive position.

In March 1995, September 1998, and January 2002, we entered into three separate agreements with UNC granting us exclusive worldwide licenses to develop, make, use and sell products based on UNC patented technology relating to the use of P2Y receptor agonists and antagonists for respiratory therapeutics, such as diquafosol tetrasodium for respiratory diseases; respiratory diagnostics, such as INS316 Diagnostic; and prevention of platelet aggregation, such as INS50589 Antiplatelet. The term of each of the UNC exclusive licenses is based upon the duration of the patents covered by each of these agreements. The U.S. government may have limited rights in some of this UNC patented technology. We are also required to meet due diligence milestones and UNC may terminate the licenses if we fail to do so. A fourth agreement, entered into in March 1995, granted us a non-exclusive worldwide license to use other UNC patented technology as a research tool to identify agonists and antagonists for P2Y receptors.

In November 2004, we entered into an agreement with WARF granting us an exclusive license to develop, make, have made, use, market, distribute, import, offer for sale, and sell products based on WARF patented technology relating to the treatment of glaucoma. The term of the exclusive license from WARF is based upon the duration of the patents covered by this agreement. The U.S. government may have limited rights in some of this patented technology. We are also required to meet due diligence milestones and WARF may terminate the license if we fail to do so.

On February 17, 2006, we entered into a development and license agreement with Boehringer Ingelheim. The agreement grants us certain exclusive rights to develop and market an intranasal dosage form of epinastine, in the United States and Canada, for the treatment or prevention of rhinitis. In general, the exclusive license granted to us will expire and convert into a perpetual, fully paid-up, non-exclusive license on December 31, 2022. Certain other rights and royalty obligations will continue beyond such date.

Additional patent applications have been filed on discoveries made in support of the UNC technologies, from research conducted at UNC or in our own laboratories. Our sponsored research agreements, material transfer agreements, and other collaborations have the potential to result in license agreements with universities, institutions and businesses. We believe that our patents and licensed patents provide a substantial proprietary base that will allow us, and our collaborative partners, to exclude others from conducting our business as described in this report and as encompassed by our issued patents and issued patents licensed to us. We cannot be sure, however, that pending or future applications will issue, that the claims of any patents which do issue will provide any significant protection of our technology or that our directed discovery research will yield compounds and products of therapeutic and commercial value.

Our competitors or potential competitors may have filed for, or have received, United States and foreign patents and may obtain additional patents and proprietary rights relating to compounds, uses and/or processes which may compete with our product candidates. Accordingly, there can be no assurance that our patent applications will result in patents being issued or that, if issued, the claims of the patents will afford protection against competitors with similar technology, nor can we be sure that others will not obtain patents that we would need to license or circumvent in order to practice our inventions.

Competition

Many pharmaceutical companies engage in research and development to commercialize products to treat allergic conjunctivitis, dry eye disease, cystic fibrosis, allergic rhinitis, glaucoma, and other diseases that we are researching. We compete with these companies for funding, access to licenses, personnel, third party collaborators and product development. Most of these companies have substantially greater financial, marketing, sales, distribution and technical resources and more experience in research and development, clinical trials and regulatory matters, than we do.

We are aware of existing treatments that will compete with our products. There are multiple therapies available to treat or prevent allergic conjunctivitis. The primary brands that *Elestat®* competes with are *Patanol®*, by Alcon, Inc.; *Zaditor®*, by Novartis; and *Optivar®* by MedPointe Pharmaceuticals. *Patanol®* currently has the majority of the prescriptions in the allergic conjunctivitis market.

The current prescription and non-prescription treatments for dry eye disease include artificial tear replacement therapy or lubricant eye drops. The FDA approved *Restasis®* in December of 2002 for patients with dry eye disease whose tear production is presumed to be suppressed due to ocular inflammation. In addition to our development program for diquafosol, several other companies are attempting to develop dry eye therapies. We are aware of the following candidates in various phases of clinical development: rimexolone by Alcon, Inc.; OPC-12759 (rebamipide), by Otsuka Pharmaceuticals, licensed to Novartis; ecabet sodium by ISTA Pharmaceuticals, licensed from Senju; ProGraf/FK-506, by Fujisawa Healthcare, Inc.; pimecrolimus by Novartis; NP50301 by Nascent Pharmaceuticals; and Androgen Tears by Allergan.

There are two products approved in the United States specifically for the treatment of complications of cystic fibrosis lung disease: *Pulmozyme®*, by Genentech, Inc., an agent designed to break up thickened airway secretions, and *TOBI®*, by Chiron Corporation, an inhaled antibiotic. At least one clinical trial has been completed that demonstrated clinical benefit with *Zithromax®*, by Pfizer, Inc., an oral antibiotic. Although *Zithromax®* has not been officially approved by the FDA for use in cystic fibrosis, it has been added to the treatment regimen in patients with evidence of airway infection. In addition, Corus Pharma, Inc. is developing

aztreonam via inhalation as an antibiotic therapy for cystic fibrosis. Vertex Pharmaceuticals and Predix Pharmaceuticals have preclinical discovery programs related to cystic fibrosis but no compounds in clinical development.

Plavix®, by Bristol-Myers Squibb/Sanofi Pharmaceuticals Partnership, is an approved platelet aggregation inhibitor that irreversibly inhibits the $P2Y_{12}$ receptor on platelets. *Trasylol*®, by Bayer Pharmaceuticals Corporation, is a protease inhibitor indicated for use in patients having bypass surgery to reduce blood loss and the need for transfusion. There are three additional $P2Y_{12}$ receptor antagonists in clinical development as platelet aggregation inhibitors. Cangrelor, currently being developed by The Medicines Company, has finished Phase 2 clinical testing using intravenous administration. AZD6140, currently being developed by AstraZeneca plc, is in Phase 2 clinical testing and is an oral formulation. Prasugrel, an oral antiplatelet agent, is currently in Phase 3 clinical testing and is being developed by Eli Lilly and Company and Sankyo Pharmaceuticals.

The current prescription nasal treatments for allergic rhinitis include *Flonase*® and *Beconase AQ*®, both by GlaxoSmithKline; *Nasonex*®, by Schering-Plough; *Nasacort AQ*®, by Sonofi-Aventis; *Rinocort Aqua*®, by AstraZeneca; and *Astelin*®, by MedPointe Pharmaceuticals.

The current prescription treatments for glaucoma include *Xalatan*®, by Pfizer; *Alphagan*®*P* and *Lumigan*®, by Allergan; *Cosopt*®, by Merck & Co., Inc. and *Travatan*® by Alcon.

The introduction of new products or the development of new processes by competitors or new information about existing products may result in price reductions or product replacements, even for products protected by patents. However, we believe our competitive position is enhanced by our commitment to research leading to the discovery and development of new products. Other factors that may help us meet competition include the quality and breadth of our technology platform, the skill and expertise of our employees and our ability to recruit and retain highly-qualified employees, our aggressive program of seeking patent protection and our capabilities for early stage research and drug discovery. However, many large pharmaceutical and biotechnology companies have significantly larger intellectual property estates than we do, more substantial capital resources than we have and greater capabilities and experience than we do in preclinical and clinical development, sales, marketing, manufacturing and regulatory affairs.

Governmental Regulation

The research, development, testing, manufacture, promotion, marketing and distribution of human therapeutic and diagnostic products are extensively regulated by governmental authorities in the United States and other countries. In the United States, the FDA regulates drugs and diagnostic products and similar regulatory agencies exist in other countries. The steps ordinarily required before a new drug may be marketed in the United States, which are similar to steps required in most other countries, include:

- Preclinical laboratory tests, preclinical studies in animals and formulation studies and the submission to the FDA of an IND prior to beginning clinical trials for a new drug;
- Adequate and well-controlled clinical trials to establish the safety and efficacy of the drug for each indication;
- The submission of an NDA to the FDA; and
- FDA review and approval of the NDA before any commercial sale or shipment of the drug.

Preclinical tests include laboratory evaluation of product toxicity and formulation, as well as animal studies. The results of preclinical testing are submitted to the FDA as part of an IND. A 30-day waiting period after the filing of each IND is required before the commencement of clinical testing in humans. At any time during this 30-day period or later, the FDA may place a clinical hold and halt proposed or ongoing clinical trials for any one of several conditions that are set out in regulations, and the clinical trial may not resume until the FDA withdraws

its hold on the clinical trials. The IND process may be extremely costly and substantially delay development of our products. Moreover, positive results of preclinical tests will not necessarily indicate positive results in clinical trials.

Clinical trials to support NDAs are typically conducted in three sequential phases, but the phases may overlap. During Phase 1, the initial introduction of the drug into healthy human subjects or patients, the drug is tested to assess metabolism, pharmacokinetics and pharmacological actions and safety, including side effects associated with increasing doses.

Phase 2 usually involves studies in a limited patient population to:

- Assess the efficacy of the drug in specific, targeted indications;
- Assess dosage tolerance and optimal dosage; and
- Identify possible adverse effects and safety risks.

If a compound is found to be potentially effective and to have an acceptable safety profile in Phase 2 evaluations, Phase 3 clinical trials, also called pivotal studies, major studies or advanced clinical trials, are undertaken to further demonstrate clinical efficacy and to further test for safety within an expanded patient population at geographically dispersed clinical trial sites.

After successful completion of the required clinical testing, generally an NDA is submitted. The FDA may request additional information before accepting an NDA for filing, in which case the application must be resubmitted with the additional information. Once the submission has been accepted for filing, the FDA has 180 days to review the application and respond to the applicant. The review process is often significantly extended by FDA requests for additional information or clarification. The FDA may refer the NDA to an appropriate advisory committee for review, evaluation and recommendation as to scientific issues relevant to whether the application should be approved, but the FDA is not bound by the recommendation of an advisory committee.

If FDA evaluations of the NDA and the manufacturing facilities are favorable, the FDA may give us either an approval letter or an approvable letter. An approvable letter will usually contain a number of conditions that must be met, which may include additional testing, in order to secure final approval of the NDA and authorization of commercial marketing of the drug for particular indications; however, the receipt of an approvable letter does not guarantee the final approval of a product. The FDA may refuse to approve the NDA or give us a non-approvable letter, outlining the deficiencies in the submission. If regulatory approval of a product is granted, it will be limited to particular disease states and conditions of use.

We and all of our contract manufacturers are also required to comply with the applicable FDA cGMP regulations to ensure that the product can be consistently manufactured to meet the specifications submitted to the FDA in an NDA. Current good manufacturing practice regulations include requirements relating to quality control and quality assurance as well as the corresponding maintenance of records and documentation. Manufacturing facilities are subject to inspection by the FDA. These facilities must be approved by the FDA before we can use them in commercial manufacturing of our products. Based on an inspection, the FDA determines whether manufacturing facilities are in compliance with applicable regulations and could conclude that our contract manufacturers or we are not in compliance with one or more applicable cGMP requirements and other FDA regulatory requirements.

Outside the United States, our ability to market our products will also depend on our receipt of marketing authorizations from the appropriate regulatory authorities. The requirements governing the conduct of clinical trials and marketing authorization vary widely from country to country. At present, foreign marketing authorizations are applied for at a national level, although within the European Union procedures are available to companies wishing to market a product in more than one member state. If the regulatory authority is satisfied that

adequate evidence of safety, quality and efficacy has been presented, a marketing authorization will be granted. This foreign regulatory approval process, including those in Europe and Japan, involves all of the risks associated with obtaining FDA marketing approval discussed above.

In addition, manufacturing facilities in non-U.S. countries are subject to inspection by the FDA as well as the local requirements of the local regulatory authorities. Actions by local authorities for failure to comply with one or more local requirements could affect production and availability of product in relevant markets.

Health Care Reform Measures and Third Party Reimbursement

The efforts of governments and third party payors to contain or reduce the cost of health care will continue to affect the business and financial condition of drug companies. A number of legislative and regulatory proposals to change the health care system have been considered in recent years. In addition, an increasing emphasis on managed care in the United States has and will continue to increase pressure on drug pricing. Legislative or regulatory proposals or changes in managed care systems may be adopted that may have a negative effect on our business. The announcement and/or adoption of proposals could have an adverse effect on our ability to earn profits and financial condition. Sales of prescription drugs depend significantly on the availability of reimbursement to the consumer from third party payors, such as government and private insurance plans. These third party payors frequently require that drug companies give them predetermined discounts from list prices and they are increasingly challenging the prices for medical products and services. Third party payors may not consider products we may bring to the market to be cost effective and may not reimburse the consumer sufficiently to allow us, and/or our collaborators, to sell our products on a profitable basis.

In both the United States and some foreign jurisdictions, there have been a number of legislative and regulatory changes to the healthcare system that could affect our ability to sell our products profitably. In the United States, new Medicare Part D prescription drug coverage legislation was signed into law in December 2003. The voluntary benefit covers certain outpatient prescription drugs effective January 1, 2006. Beneficiaries who chose to participate select either (i) a qualified prescription drug plan, which is a stand-alone, drug-only insurance benefit offered by a private entity licensed to offer health insurance under state law; or (ii) a Medicare Advantage managed care plan that includes prescription drug coverage along with other Medicare services. Participating drug plans may establish drug formularies that exclude coverage of specific drugs, and payment levels for drugs negotiated with Part D drug plans may be lower than reimbursement levels available through private health plans or other payers. Moreover, beneficiary co-insurance requirements could influence which products are recommended by physicians and selected by patients. There is no assurance that our drugs will be offered by drug plans participating under the new Medicare Part D program, that, if covered, the terms of any such coverage, or that covered drugs will be reimbursed at amounts that reflect current or historical levels. Allergan is responsible for the implementation of the Medicare Part D program as it relates to *Elestat*® and *Restasis*®. Our results of operations could be materially adversely affected by the reimbursement changes emerging in 2006 and in future years from the Medicare prescription drug coverage legislation. To the extent that private insurers such as Blue Cross and Blue Shield or managed care programs follow Medicare coverage and payment developments, the adverse effects of lower Medicare payment may be magnified by private insurers adopting lower payment. New federal or state drug payment changes or healthcare reforms in the United States may be enacted or adopted in the future that could further lower payment for our products.

Employees

As of January 31, 2006, we had 165 full-time and part-time employees. In addition, we utilize interns, outside contractors and consultants as needed. Our future success will depend in large part upon our ability to attract and retain highly qualified personnel. Our employees are not represented by any collective bargaining agreements, and we have never experienced a work stoppage. Employees are required to execute confidentiality and assignment of intellectual property agreements.

Internet Information

Our internet site is located at www.inspirepharm.com. Copies of our reports filed pursuant to Section 13(a) or 15(d) of the Exchange Act, including annual reports on Form 10-K, quarterly reports on Form 10-Q, current reports on Form 8-K and any amendments to those reports may be accessed from our website, free of charge, as soon as reasonably practicable after we electronically file such reports with, or furnish such reports to, the Securities and Exchange Commission. Please note that the information contained on our website is not incorporated by reference into our reports that are filed with the SEC.

We file our annual reports on Form 10-K, quarterly reports on Form 10-Q and current reports on Form 8-K pursuant to Section 13(a) or 15(d) of the Securities Exchange Act of 1934 electronically with the Securities and Exchange Commission, or the SEC. The public may read or copy any materials we file with the SEC at the SEC's Public Reference Room at 100 F Street, NE, Room 1580, Washington DC 20549. The public may obtain information on the operation of the Public Reference Room by calling the SEC at 1-800-SEC-0330. The SEC maintains an Internet site that contains reports, proxy and information statements, and other information regarding issuers that file electronically with the SEC. The address of that site is www.sec.gov.

Item 1A. Risk Factors.

RISK FACTORS

An investment in the shares of our common stock involves a substantial risk of loss. You should carefully read this entire report and should give particular attention to the following risk factors. You should recognize that other significant risks may arise in the future, which we cannot foresee at this time. Also, the risks that we now foresee might affect us to a greater or different degree than expected. There are a number of important factors that could cause our actual results to differ materially from those indicated by any forward-looking statements in this document. These factors include, without limitation, the risk factors listed below and other factors presented throughout this document and any other documents filed by us with the Securities and Exchange Commission.

If the FDA does not conclude that our product candidates meet statutory requirements for safety and efficacy, we will be unable to obtain regulatory approval for marketing in the United States, and if foreign governments do not conclude that our product candidates meet their requirements for marketing, we will be unable to sell those product candidates in those foreign markets.

To achieve profitable operations, we must, alone or with others, successfully identify, develop, introduce and market proprietary products. We have not received marketing approval for any of our product candidates, although we are co-promoting two products with Allergan. We have one product candidate, diquafosol, for which we have received two approvable letters from the FDA. There is no guarantee that the FDA will approve diquafosol and allow Allergan and us to begin selling diquafosol in the United States. It may be necessary to undertake additional Phase 3 clinical trials in support of our diquafosol NDA and there can be no guarantee that any such additional clinical trials would be successful or that the FDA would approve diquafosol even if such additional clinical trials were successful. Also, if additional diquafosol Phase 3 clinical trials are required by the FDA, we may decide not to conduct those clinical trials and we would therefore be unable to obtain FDA approval of diquafosol. Even if we do receive FDA approval for diquafosol, we and Allergan may not be able to successfully commercialize diquafosol in the United States. We have not applied for marketing approval of diquafosol in any other jurisdiction.

In addition to our product candidates in clinical development, we have early stage preclinical product candidates for which a substantial amount of work will be required to advance these product candidates to clinical testing and ultimately to commercial approval. We will have to conduct significant additional development activities, non-clinical and clinical tests and obtain regulatory approval before our product candidates can be commercialized. Product candidates that may appear to be promising at early stages of development may not successfully reach the market for a number of reasons. The results of preclinical and initial clinical testing of our product candidates under development may not necessarily indicate the results that will be obtained from later or more extensive testing. Accordingly, some preclinical candidates may not advance to clinical development. Additionally, companies in the pharmaceutical and biotechnology industries, including us, have suffered significant setbacks in advanced clinical trials, even after obtaining promising results in earlier clinical trials. Our ongoing clinical trials might be delayed or halted for various reasons, including:

- The drug is not effective or physicians think that the drug is not effective;
- The drug effect is not statistically significant compared to placebo;
- Patients experience severe side effects or serious adverse events during treatment;
- Patients die during the clinical trial because their disease is too advanced or because they experience medical problems that may or may not relate to the drug being studied;
- Patients do not enroll in the clinical trials at the rate we expect;
- We decide to modify the drug during testing;

- Our commercial partners, or future commercial partners, delay, amend or change our development plan or strategy;
- We allocate our limited financial and other resources to other clinical programs; and
- Weather events, natural disasters, malicious activities or other unforeseen events may occur.

The introduction of our products in foreign markets will subject us to foreign regulatory clearances, the receipt of which may be unpredictable, uncertain and may impose substantial additional costs and burdens which we or our partners in such foreign markets may be unwilling or unable to fund. As with the FDA, foreign regulatory authorities must be satisfied that adequate evidence of safety, quality and efficacy of the product has been presented before marketing authorization is granted. The foreign regulatory approval process includes all of the risks associated with obtaining FDA marketing approval. Approval by the FDA does not ensure and is not a factor in obtaining approval by other regulatory authorities.

Failure to successfully market and commercialize *Restasis*® and *Elestat*® will negatively impact our revenues.

Allergan launched *Restasis*® in the United States in April 2003 and we began receiving co-promotion revenue from Allergan on the net sales of *Restasis*® beginning in April 2004. Although our agreement with Allergan provides, and we have exercised, the right to co-promote *Restasis*® in the United States, Allergan is primarily responsible for marketing and commercializing *Restasis*®. Accordingly, our revenues on the net sales of *Restasis*® are largely dependent on the actions and success of Allergan, over whom we have no control.

The commercial exclusivity period for *Restasis*® under the Hatch-Waxman Act has expired. However, the manufacture and sale of *Restasis*® is protected under a use patent which expires in August 2009 and a formulation patent which expires in May 2014. If and when we experience generic competition for *Restasis*®, our revenues attributable to *Restasis*® will be significantly impacted.

In February 2004, we launched *Elestat*® in the United States. Our agreement with Allergan provides that we have the responsibility for selling, promoting and marketing *Elestat*® in the United States and paying the associated costs. We expect revenues from *Elestat*® and *Restasis*® to exceed selling, promoting and marketing expenses associated with co-promotion activities for these products during the year ending December 31, 2006; however, there can be no assurances that revenues associated with such products will exceed the related expenses. Our revenues may be impacted from time to time by the number of formularies upon which these products are listed, the discounts and pricing under such formularies, as well as the estimated amount of rebates.

The commercial exclusivity period for *Elestat*® under the Hatch-Waxman Act will expire in October 2008, after which time *Elestat*® could face generic or over-the-counter competition if there is no other intellectual property protection covering *Elestat*®. If and when we experience generic or over-the-counter competition for *Elestat*®, our agreement with Allergan to co-promote *Elestat*® will no longer be in effect, and our revenues attributable to *Elestat*® are expected to cease, which will materially impact our results of operations and cash flows.

In December 2004, Alcon, Inc. received FDA approval of once-daily olopatadine hydrochloride ophthalmic solution. Alcon has not yet launched once-daily olopatadine hydrochloride ophthalmic solution, but *Patanol*® (olopatadine hydrochloride ophthalmic solution) that requires administration twice-a-day currently competes with *Elestat*®. We cannot predict what effect, if any, the introduction of once-daily olopatadine hydrochloride ophthalmic solution will have on our sales of *Elestat*®.

Our present revenues depend solely upon and our future revenues will depend, at least in part, upon the acceptance of *Elestat*® and *Restasis*® by eye-care professionals, allergists and patients. Factors that could affect the acceptance of *Elestat*® and *Restasis*® include:

- Satisfaction with existing alternative therapies;
- Perceived efficacy relative to other available therapies;
- Extent and effectiveness of our sales and marketing efforts;
- Extent and effectiveness of Allergan's sales and marketing efforts;
- Changes in, or the levels of, third-party reimbursement of product costs;
- Coverage and reimbursement under Medicare Part D;
- Cost of treatment;
- Marketing and sales activities of competitors;
- Duration of market exclusivity of *Elestat*® and *Restasis*®;
- Pricing and availability of alternative products, including generic or over-the-counter products;
- Shifts in the medical community to new treatment paradigms or standards of care;
- Relative convenience and ease of administration;
- Prevalence and severity of adverse side effects; and
- Regulatory approval in other jurisdictions.

We cannot predict the potential long-term patient acceptance of, or the effects of competition and managed health care on, sales of either product.

Revenues in future periods could vary significantly and may not cover our operating expenses.

We recognize revenue from product co-promotion based on net sales for *Elestat*® and *Restasis*® as defined in the co-promotion agreements and as reported to us by our collaborative partner, Allergan. Accordingly, our co-promotion revenue is based upon Allergan's revenue recognition policy, other accounting policies and the underlying terms of our co-promotion agreements. Allergan's filings with the Securities and Exchange Commission indicate that Allergan maintains disclosure controls and procedures in accordance with applicable laws, which are designed to provide reasonable assurance that the information required to be reported by Allergan in its Exchange Act filings is reported timely and in accordance with applicable laws, rules and regulations. We are not entitled to review Allergan's disclosure controls and procedures. All of our revenues are currently derived from net sales of *Elestat*® and *Restasis*® as reported to us by Allergan. Management has concluded that our internal control over financial reporting was effective as of December 31, 2005 and these internal controls allow us to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles; however, we are unable to provide complete assurance that Allergan will not revise reported revenue amounts in the future. If these reported revenue amounts were inaccurate, it could have a material impact on our financial statements, including financial statements for previous periods.

We recognize milestone revenue under our collaborative research and development agreements when we have performed services under such agreements or when we or our collaborative partner has met a contractual milestone triggering a payment to us. We did not reach any such milestones in 2004 or 2005, and there can be no assurances that we will reach any during the year ending December 31, 2006 or at any later date. Revisions in the commitment period are made in the period that the facts related to the change first become known.

Additionally, our revenues may fluctuate from period to period due in part to:

- Fluctuations in sales of *Elestat*®, *Restasis*® and other future licensed or co-promoted products due to competition, manufacturing difficulties, reimbursement and pricing under commercial or government plans, seasonality, or other factors that affect the sales of a product;

- Deductions from gross sales relating to estimates of sales returns, credits and allowances, normal trade and cash discounts, managed care sales rebates and other allocated costs as defined in our agreements, all of which are determined by Allergan and are outside our control;
- Duration of market exclusivity of *Elestat*® and *Restasis*®;
- The timing of approvals, if any, for future products;
- The progress toward and the achievement of developmental milestones by us or our partners;
- The initiation of new contractual arrangements with other companies;
- The failure or refusal of a collaborative partner to pay royalties;
- The expiration or invalidation of our patents or licensed intellectual property; or
- Fluctuations in foreign currency exchange rates.

Failure to adequately market and commercialize diquafosol, if approved by the FDA, will limit our revenues.

If approved by the FDA in the United States and other applicable regulatory authorities outside the United States, the commercial success of diquafosol will largely depend on a number of factors, including the timing and scope of Allergan's launch into the United States and other major pharmaceutical markets, acceptance by patients and eye care professionals and allergists, the effectiveness of Allergan's sales and marketing efforts, a knowledgeable sales force, adequate market penetration, reimbursement under commercial or government plans, and any competitors, including Allergan's, ability to successfully launch a new dry eye therapy. Accordingly, our revenue on the net sales of diquafosol would be largely dependent on the actions and success of Allergan, over whom we have no control. In the event diquafosol is approved by the FDA, we plan to co-promote diquafosol within the United States; however, Allergan is primarily responsible for launching and marketing diquafosol in the United States and other major worldwide pharmaceutical markets, excluding Asian markets. If diquafosol is not successfully commercialized, our revenues will be limited.

We cannot sell *Elestat*®, *Restasis*® or any of our product candidates if governmental approvals are not obtained and maintained.

Pharmaceutical companies are subject to significant regulation by a number of national, state and local agencies, including the FDA. Failure to comply with applicable regulatory requirements could, among other things, result in fines, suspensions of regulatory approvals of products, product recalls, delays in product distribution, delays in marketing activities and sales, and civil or criminal sanctions.

The manufacturing and marketing of drugs, including our products, are subject to continuing FDA and foreign regulatory review, and later discovery of previously unknown problems with a product, manufacturing process or facility may result in restrictions, including withdrawal of the product from the market. The FDA is permitted to revisit and change its prior determinations and based on new information it may change its position with regard to the safety or effectiveness of our products. The FDA is authorized to impose post-marketing requirements such as:

- Testing and surveillance to monitor the product and its continued compliance with regulatory requirements;
- Submitting products for inspection and, if any inspection reveals that the product is not in compliance, the prohibition of the sale of all products from the same lot;
- Suspending manufacturing;
- Recalling products;

- Withdrawing marketing approval;
- Seizing violative products; and
- Seeking to enjoin the manufacture or distribution, or both, of an approved product that is found to be adulterated or misbranded.

Even before any formal regulatory action, we, or our collaborative partners, could voluntarily decide to cease distribution and sale or recall any of our products if concerns about safety or effectiveness develop, or if economic conditions support such action.

In its regulation of advertising, the FDA may issue correspondence to pharmaceutical companies alleging that its advertising or promotional materials are false, misleading or deceptive. The FDA has the power to impose a wide array of sanctions on companies for such advertising practices and if we were to receive correspondence from the FDA alleging these practices we might be required to:

- Incur substantial expenses, including fines, penalties, legal fees and costs to conform to the FDA's limits on such promotion;
- Change our methods of marketing and selling products;
- Take FDA-mandated corrective action, which could include placing advertisements or sending letters to physicians rescinding previous advertisements or promotion; or
- Disrupt the distribution of products and stop sales until we are in compliance with the FDA's position.

In recent years, various legislative proposals have been offered in Congress and in some state legislatures that include major changes in the health care system. These proposals have included price or patient reimbursement constraints on medicines and restrictions on access to certain products. We cannot predict the outcome of such initiatives and it is difficult to predict the future impact of the broad and expanding legislative and regulatory requirements affecting us.

We have been named as a defendant in litigation that could result in substantial damages and costs and divert management's attention and resources.

On February 15, 2005, a purported class action complaint was filed in the United States District Court for the Middle District of North Carolina by Mirco Investors, LLC on behalf of itself and all other similarly situated purchasers against us and certain of our senior officers. The complaint alleges violations of sections 10(b) and 20(a) of the Securities Exchange Act of 1934, and Securities and Exchange Commission Rule 10b-5, and focuses on statements that are claimed to be false and misleading regarding a Phase 3 clinical trial of our dry eye product candidate, diquafosol. The plaintiffs seek unspecified damages on behalf of a purported class of purchasers of our securities during the period from June 2, 2004 through February 8, 2005. Four additional proposed stockholder class actions were filed in the same court, making substantially the same allegations against the same parties as defendants and seeking certification of the same class of purchasers. These individual lawsuits have now been consolidated into a single civil action, and a lead plaintiff appointed. We anticipate that an amended consolidated complaint may be filed in March 2006. We intend to defend the litigation vigorously. No assurance can be made that we will be successful in our defense of the pending claims. If we are not successful in our defense of the claims, we could be forced to, among other ramifications, make significant payments to resolve the claims and such payments could have a material adverse effect on our business, future results of operations, financial position and/or cash flows if not covered by our insurance carriers or if damages exceed the limits of our insurance. Furthermore, regardless of our success in defending against the litigation, the litigation itself may result in substantial costs, use of resources and divert the attention of management and other employees which could adversely affect our business.

The investigation by the U.S. Securities and Exchange Commission could have a material adverse effect on our business.

On August 30, 2005, the Securities and Exchange Commission notified us that it is conducting a formal, nonpublic investigation, which we believe relates to trading in our securities surrounding our February 9, 2005 announcement of the results of a Phase 3 clinical trial of our dry eye product candidate, diquafosol, as well as our disclosures regarding this Phase 3 clinical trial. We are continuing to cooperate with the Securities and Exchange Commission's ongoing investigation. We are unable to predict the outcome of the investigation and no assurance can be made that the investigation will be concluded favorably. In the event of an adverse outcome, our business future results of operations, financial position and/or cash flows could be materially affected. Furthermore, regardless of the outcome of the investigation, the investigation itself may result in substantial uninsured costs, use of resources and divert the attention of management and other employees which could adversely affect our business.

Recent Medicare prescription drug coverage legislation and future legislative or regulatory reform of the healthcare system may affect our or our partner's ability to sell products profitably.

In both the United States and some foreign jurisdictions, there have been a number of legislative and regulatory changes to the healthcare system that could affect our ability to sell our products profitably. In the United States, new Medicare Part D prescription drug coverage legislation was signed into law in December 2003. The voluntary benefit covers certain outpatient prescription drugs effective January 1, 2006. Beneficiaries who chose to participate select either (i) a qualified prescription drug plan, which is a stand-alone, drug-only insurance benefit offered by a private entity licensed to offer health insurance under state law; or (ii) a Medicare Advantage managed care plan that includes prescription drug coverage along with other Medicare services. Participating drug plans may establish drug formularies that exclude coverage of specific drugs, and payment levels for drugs negotiated with Part D drug plans may be lower than reimbursement levels available through private health plans or other payers. Moreover, beneficiary co-insurance requirements could influence which products are recommended by physicians and selected by patients. There is no assurance that our drugs will be offered by drug plans participating under the new Medicare Part D program, that, if covered, the terms of any such coverage, or that covered drugs will be reimbursed at amounts that reflect current or historical levels. Allergan is responsible for the implementation of the Medicare Part D program as it relates to *Elestat*® and *Restasis*®. Our results of operations could be materially adversely affected by the reimbursement changes emerging in 2006 and in future years from the Medicare prescription drug coverage legislation. To the extent that private insurers such as Blue Cross and Blue Shield or managed care programs follow Medicare coverage and payment developments, the adverse effects of lower Medicare payment may be magnified by private insurers adopting lower payment. New federal or state drug payment changes or healthcare reforms in the United States may be enacted or adopted in the future that could further lower payment for our products.

Future implementation of certain government initiatives could create risks for our business.

The Medicare Prescription Drug, Improvement and Modernization Act of 2003, or MMA, established a new voluntary outpatient prescription drug benefit under Part D of the Social Security Act. The program, which went into effect January 1, 2006, is administered by the Centers for Medicare & Medicaid Services, or CMS, within the Department of Health and Human Services, or HHS. CMS has issued extensive regulations and other subregulatory guidance documents implementing the new benefit. Moreover, the HHS Office of Inspector General has issued regulations and other guidance in connection with the program. Allergan has contracted with Part D plan sponsors to cover our drugs under the Part D benefit. The federal government can be expected to continue to issue guidance and regulation regarding the obligations of Part D sponsors and their subcontractors. The receipt of federal funds through the Part D program may require us to comply with these new policies as well as other established laws and regulations governing the federal government's payment for health care goods and services. There are many uncertainties about the financial and regulatory risks of participating in the Medicare Part D program, and we can give no assurance that these risks will not be material to our business in future periods.

Failure to adequately control compliance with all applicable regulations may adversely affect our business.

There are extensive state, federal and foreign regulations applicable to public pharmaceutical companies engaged in the discovery, development and commercialization of medicinal products. There are laws that govern areas including financial controls, clinical trials, testing, manufacturing, labeling, safety, packaging, shipping, distribution and promotion of pharmaceuticals. While we have implemented corporate quality, ethics and compliance programs based on current best practices, we cannot guarantee against all possible transgressions. The potential ramifications are far-reaching if there are areas identified as out of compliance by regulatory agencies including, but not limited to, significant financial penalties, manufacturing and clinical trial consent decrees, commercialization restrictions or other restrictions and litigation.

Since our clinical candidates utilize new or different mechanisms of action and in some cases there may be no regulatory precedents, conducting clinical trials and obtaining regulatory approval may be difficult, expensive and prolonged, which would delay any marketing of our products.

To complete successful clinical trials, our candidates must demonstrate safety and provide substantial evidence of efficacy, which the FDA evaluates based on the statistical significance of a candidate meeting predetermined clinical endpoints. The design of clinical trials to establish meaningful endpoints is done in collaboration with the FDA prior to the commencement of clinical trials. We establish these endpoints based on guidance from the FDA, including FDA guidance documents applicable to establishing the efficacy, safety and tolerability measures required for approval of products. However, since many of our product candidates utilize new or different mechanisms of action, the FDA may not have established guidelines for the design of our clinical trials and may take longer than average to consider our product candidates for approval. The FDA could change its view on clinical trial design and establishment of appropriate standards for efficacy, safety and tolerability and require a change in clinical trial design, additional data or even further clinical trials before granting approval of our product candidates. We could encounter delays and increased expenses in our clinical trials if the FDA determines that the endpoints established for a clinical trial do not adequately predict a clinical benefit.

We have one product candidate, diquafosol, for which we have received two approvable letters from the FDA. There is no guarantee that the FDA will approve diquafosol and allow Allergan and us to begin selling diquafosol in the United States. It may be necessary to undertake additional Phase 3 clinical trials in support of our diquafosol NDA and there can be no guarantee that any such additional clinical trials would be successful or that the FDA would approve diquafosol even if such additional clinical trials were successful. Also, if additional diquafosol Phase 3 clinical trials are required by the FDA, we may decide not to conduct those clinical trials and we would therefore be unable to obtain FDA approval of diquafosol.

We cannot predict or guarantee the outcome or timing of our Phase 3 program for denufosol for cystic fibrosis. A significant amount of work will be required to advance denufosol through clinical testing, including satisfactory completion of additional clinical trials and toxicology and carcinogenicity studies. There can be no assurance that we, either alone or with the support of any other third party, will be able to recruit sufficient patients for any clinical trial. We may later decide to change the focus of a Phase 3 program. The Phase 3 clinical trials for denufosol for cystic fibrosis may not be successful or unexpected safety concerns may emerge that would negatively change the risk/benefit profile for this product candidate. Even if such clinical trials are successful, we cannot predict when, or if, the FDA or other regulatory authorities will approve denufosol and allow its commercialization.

After initial regulatory approval, the FDA continues to monitor and regulate a marketed product and its manufacturer. The FDA may require us or our partners to conduct long-term safety studies after approval. Discovery of previously unknown problems through adverse event reporting may result in restrictions on the product, including withdrawal from the market. The FDA could seize a product that is adulterated or misbranded and seek to enjoin further manufacture. The FDA could withdraw approval to market a product. Additionally, we and our officers and directors could be subject to civil and criminal penalties as a result of such problems.

Estimated development costs are difficult to project and may change frequently prior to regulatory approval.

While all new compounds require standard regulated phases of testing, the actual type and scope of testing can vary significantly among different product candidates which may result in significant disparities in total costs required to complete the respective development programs.

The number and type of studies that may be required by the FDA, or other regulatory authorities, for a particular compound are based on the compound's clinical profile compared to existing therapies for the targeted patient population. Factors that affect the costs of a clinical trial include:

- The number of patients required to participate in clinical trials to demonstrate statistical significance for a drug's safety and efficacy and the number and geographical location of clinical trial sites necessary to enroll such patients;
- The time required to enroll the targeted number of patients in clinical trials, which may vary depending on the size and availability of the targeted patient population and the perceived benefit to the clinical trial participants; and
- The number and type of required laboratory tests supporting clinical trials.

Other activities required before submitting an NDA include regulatory preparation for submission, biostatistical analyses, scale-up synthesis, and validation of commercial product. In addition, prior to product launch, production of a certain amount of commercial grade drug product inventory meeting FDA cGMP standards is required, and the manufacturing facility must pass an inspection conducted by the FDA to determine whether the product can be consistently manufactured to meet cGMP requirements.

Also, ongoing development programs and associated costs are subject to frequent, significant and unpredictable changes due to a number of factors, including:

- Data collected in preclinical or clinical trials may prompt significant changes, delays or enhancements to an ongoing development program;
- Commercial partners and the underlying contractual agreements may require additional or more involved clinical or preclinical activities;
- The FDA, or other regulatory authorities, may direct the sponsor to change or enhance its ongoing development program based on developments in the testing of similar compounds or related compounds;
- Unexpected regulatory requirements or interim reviews by regulatory agencies may cause delays or changes to development programs; and
- Anticipated manufacturing costs may change significantly due to required changes in manufacturing processes, variances from anticipated manufacturing process yields or changes in the cost and/or availability of starting materials, and other costs to ensure the manufacturing facility is in compliance with cGMP requirements and is capable of consistently producing the drug candidate in accordance with established specifications submitted to the FDA.

If we are not able to obtain sufficient additional funding to meet our expanding capital requirements, we may be forced to reduce or eliminate research programs and product development.

We have used substantial amounts of cash to fund our research and development activities. Our operating expenses were approximately $58.8 million and approximately $56.6 million in the fiscal years ended December 31, 2005 and 2004, respectively. We anticipate that our operating expenses in 2006 will increase from our 2005 operating expenses. Our cash, cash equivalents and investments totaled approximately $122.3 million

on December 31, 2005. We expect that our capital and operating expenditures will continue to exceed our revenue over the next several years as we conduct our research and development activities, clinical trials and commercial activities. Many factors will influence our future capital needs, including:

- The number, breadth and progress of our research and development programs;
- The size and scope of our marketing programs;
- Our ability to attract collaborators for our products and establish and maintain those relationships;
- Achievement of milestones under our existing collaborations with Allergan and Santen, and any future collaborative programs;
- Progress by our collaborators;
- The level of activities relating to commercialization of our products;
- Competing technological and market developments;
- The costs involved in defending any litigation claims against us;
- The costs involved in responding to SEC investigations;
- The costs involved in enforcing patent claims and other intellectual property rights; and
- The costs and timing of regulatory approvals.

In addition, our capital requirements will depend upon:

- The receipt of revenue from Allergan on net sales of *Elestat*® and *Restasis*®;
- The receipt of milestone payments from collaborative agreements;
- Our ability to obtain approval from the FDA for our first product candidate, diquafosol;
- Upon any such approval, our ability together with the ability of our marketing partner, Allergan, to generate sufficient sales of diquafosol;
- Future potential revenue from Santen; and
- Payments from future collaborators.

In the event that we do not receive timely regulatory approvals, we may need substantial additional funds to fully develop, manufacture, market and sell all of our other potential products and support our co-promotion efforts. We may seek such additional funding through public or private equity offerings and debt financings. Additional financing may not be available when needed. If available, such financing may not be on terms favorable to us or our stockholders. Stockholders' ownership will be diluted if we raise additional capital by issuing equity securities. If we raise funds through collaborations and licensing arrangements, we may have to give up rights to our technologies or product candidates which are involved in these future collaborations and arrangements or grant licenses on unfavorable terms. If adequate funds are not available, we would have to scale back or terminate research programs and product development and we may not be able to successfully commercialize any product candidate.

Clinical trials may take longer to complete and cost more than we expect, which would adversely affect our ability to commercialize product candidates and achieve profitability.

Clinical trials are lengthy and expensive. They require appropriate identification of optimal treatment regimens and relevant patient population, adequate supplies of drug product, and sufficient patient enrollment. Patient enrollment is a function of many factors, including:

- The size and availability of the relevant patient population;

- The nature of the protocol;
- The proximity of patients to clinical sites;
- The eligibility criteria for the clinical trial; and
- The perceived benefit of participating in a clinical trial.

Delays in patient enrollment can result in increased costs and longer development times. For example, enrollment in our denufosol Phase 2 clinical trials for retinal detachment and macular edema progressed at a significantly slower rate than originally anticipated and we discontinued enrollment in these clinical trials. In addition, the timing of our Phase 3 program for denufosol for the treatment of cystic fibrosis will be impacted by a number of variables, including clinical development decisions regarding identifying the optimal treatment regimens, patient population, competition for clinical trial participants, approval of other products during our clinical trials, number and length of clinical trials, parallel versus sequential timing of our clinical trials, the exclusion criteria for the clinical trials and use of non standard therapies such as hypertonic saline. These cystic fibrosis clinical trials will present some unique challenges due to the early-intervention approach we are taking with regards to the clinical trials. This will require studying mild patients and usually younger patients who do not typically participate in clinical trials since new products are generally focused on the sicker patient population. In addition, due to the age group of these mild patients, many will be in school and will be required to take the medication three times a day. Even if we successfully complete clinical trials, we may not be able to submit any required regulatory submissions in a timely manner and we may not receive regulatory approval for the product candidate. In addition, if the FDA or foreign regulatory authorities require additional clinical trials, we could face increased costs and significant development delays.

From time to time, we conduct clinical trials in different countries around the world and are subject to the risks and uncertainties of doing business internationally. Disruptions in communication and transportation, changes in governmental policies, civil unrest and currency exchange rates may affect the time and costs required to complete clinical trials in other countries.

Changes in regulatory policy or new regulations could also result in delays or rejection of our applications for approval of our product candidates. Product candidates designated as "fast track" products by the FDA may not continue to qualify for expedited review. Even if some of our product candidates receive "fast track" designation, the FDA may not approve them at all or any sooner than other product candidates that do not qualify for expedited review.

Our common stock price has been volatile and your investment in our stock may decline in value.

The market price of our common stock has been volatile. These fluctuations create a greater risk of capital losses for our stockholders as compared to less volatile stocks. Factors that have caused volatility and could cause additional volatility in the market price of our common stock include among others:

- Announcements regarding our NDA or foreign regulatory equivalent submissions;
- Announcements made by us concerning results of our clinical trials with diquafosol, denufosol for the treatment of cystic fibrosis, INS50589 Antiplatelet and any other product candidates;
- Market acceptance and market share of products we co-promote;
- Duration of market exclusivity of *Elestat*® and *Restasis*®;
- Volatility in other securities including pharmaceutical and biotechnology securities;
- Changes in government regulations;
- Regulatory actions and/or investigations, including our ongoing SEC investigation;

- Changes in the development priorities of our collaborators that result in changes to, or termination of, our agreements with such collaborators, including our agreements with Allergan and Santen;
- Developments concerning proprietary rights including patents by us or our competitors;
- Variations in our operating results;
- Litigation;
- Terrorist attacks; and
- Military actions.

Extreme price and volume fluctuations occur in the stock market from time to time that can particularly affect the prices of biotechnology companies. These extreme fluctuations are sometimes unrelated to the actual performance of the affected companies.

If we continue to incur operating losses for a period longer than anticipated, or in an amount greater than anticipated, we may be unable to continue our operations.

We have experienced significant losses since inception. We incurred net losses of $31.8 million for the year ended December 31, 2005 and $44.1 million for the year ended December 31, 2004. As of December 31, 2005, our accumulated deficit was approximately $203.0 million. We expect to incur significant operating losses over the next several years and expect that cumulative losses may increase in the near-term due to expanded research and development efforts, preclinical studies, clinical trials and commercialization efforts. We expect that losses will fluctuate from quarter to quarter and that such fluctuations may be substantial. Such fluctuations will be affected by the following:

- Timing of regulatory approvals and commercial sales of our product candidates and any co-promotion products;
- The level of patient demand for our products and any licensed products;
- Timing of payments to and from licensors and corporate partners;
- Timing of investments in new technologies and commercial capability;
- Commercialization activities to support co-promotion efforts; and
- The costs involved in defending any litigation claims against, or government investigations of, us.

To achieve and sustain profitable operations, we must, alone or with others, develop successfully, obtain regulatory approval for, manufacture, introduce, market and sell our products. The time frame necessary to achieve market success is long and uncertain. We may not generate sufficient product revenues to become profitable or to sustain profitability. If the time required to achieve profitability is longer than we anticipate, we may not be able to continue our business.

If we fail to reach milestones or to make annual minimum payments or otherwise breach our obligations under our license agreements, our licensors may terminate our agreements with them.

We hold licenses for diquafosol tetrasodium for respiratory diseases and a $P2Y_{12}$ receptor program for cardiovascular uses from UNC. In addition, we also have a license agreement for glaucoma technologies with WARF, and a development and license agreement with Boehringer Ingelheim which grants us certain exclusive rights to develop and market an intranasal dosage form of epinastine, in the United States and Canada, for the treatment or prevention of rhinitis. If we fail to meet performance milestones relating to the timing of regulatory filings or fail to pay the minimum annual payments under our respective licenses, our licensors may terminate the applicable license. In addition, if any licensor were to re-license some or all of the technologies currently covered by our licenses, competitors could develop products that compete with ours.

It may be necessary in the future for us to obtain additional licenses to avoid infringement of third party patents. Additionally, we may enter into license arrangements with other third parties as we build our product portfolio. We do not know the terms on which such licenses may be available, if at all.

Reliance on a single party to manufacture and supply either finished product or the bulk active pharmaceutical ingredients for a product or product candidates could adversely affect us.

Under our agreements with Allergan, Allergan is responsible for the manufacture and supply of *Elestat®*, *Restasis®*, and diquafosol, if approved by the FDA. It is our understanding that Allergan relies upon an arrangement with a single third party for the manufacture and supply of APIs for *Elestat®*, *Restasis®*, and will do so for diquafosol, if it is approved by the FDA. Allergan then completes the manufacturing process to yield finished product. In the event such third party was unable to supply Allergan, if such supply was unreasonably delayed, or if Allergan was unable to complete the manufacturing cycle, sales of the product could be adversely impacted, which would result in a reduction in any revenue from product co-promotion received under our agreements with Allergan. In addition, if Allergan or the third party manufacturer do not maintain cGMP compliance, the FDA could require corrective actions or take enforcement actions that could affect production and availability of the product thus adversely affecting sales.

In addition, we have relied upon supply agreements with third parties for the manufacture and supply of the bulk APIs for our product candidates for purposes of preclinical testing and clinical trials. We presently depend upon one vendor as the sole manufacturer of our supply of APIs for diquafosol and denufosol, one vendor as the sole manufacturer for INS50589, and one vendor as the sole manufacturer of epinastine. We intend to contract with these vendors, as necessary, for commercial scale manufacturing of our products where we are responsible for such activities. In the case of diquafosol, we expect Allergan to purchase commercial quantities of bulk APIs from our sole manufacturer, including initial launch quantities should the product candidate receive FDA approval. In addition, if Allergan or the third party manufacturer do not maintain cGMP compliance, the FDA could require corrective actions or take enforcement actions that could affect production and availability of the product thus adversely affecting sales. Although we have identified alternate sources for our product candidates, it would be time consuming and costly to qualify these sources. If our vendors were to terminate our arrangement or fail to meet our supply needs we might be forced to delay our development programs and/or be unable to supply products to the market which could delay or reduce revenues and result in loss of market share.

If we are unable to contract with third parties for the synthesis of APIs required for preclinical testing, for the manufacture of drug products for clinical trials, or for the large-scale manufacture of any approved products, we may be unable to develop or commercialize our drug products.

We have no experience or capabilities to conduct the large-scale manufacture of any of our product candidates. We do not currently expect to engage directly in the manufacturing of drug substance or drug products, but instead intend to contract with third parties to accomplish these tasks. With the exception of Santen, for which we are required to supply bulk APIs, all of our partners are responsible for making their own arrangements for the manufacture of drug products, including arranging for the manufacture of bulk APIs. Our dependence upon third parties for the manufacture of both drug substance and finished drug products that remain unpartnered may adversely affect our ability to develop and deliver such products on a timely and competitive basis. Similarly, our dependence on our partners to arrange for their own supplies of finished drug products may adversely affect our revenues. If we, or our partners, are unable to engage or retain third party manufacturers on commercially acceptable terms, our products may not be commercialized as planned. Our strategy of relying on third parties for manufacturing capabilities presents the following risks:

- The manufacturing processes for most of our APIs have not been validated at the scale required for commercial sales;
- Delays in scale-up to commercial quantities and any change at the site of manufacture could delay clinical trials, regulatory submissions and ultimately the commercialization of our products;

- Manufacturers of our products are subject to the FDA's cGMP regulations, and similar foreign standards that apply, and we do not necessarily have full control over compliance with these regulations by third party manufacturers;
- The FDA must inspect and approve a facility before an NDA is approved and the facility is subject to ongoing post-approval FDA inspections to ensure continued compliance with cGMP regulations;
- If the manufacturing facility does not maintain cGMP compliance after NDA approval, the FDA has the authority to seize product produced under such conditions and may seek to enjoin further manufacture and distribution, as well as other equitable remedies;
- Without satisfactory long-term agreements with manufacturers, we will not be able to develop or commercialize our product candidates as planned or at all;
- We may not have intellectual property rights, or may have to share intellectual property rights, to any improvements in the manufacturing processes or new manufacturing processes for our product candidates; and
- If we are unable to engage or retain an acceptable third party manufacturer for any of our product candidates, we would either have to develop our own manufacturing capabilities or delay the development of such product candidate.

We may not be successful in our efforts to expand our product portfolio.

A key element in our strategy is to develop and commercialize new ophthalmic and respiratory/allergy products. We are seeking to do so through our internal research program and through licensing or otherwise acquiring the rights to potential new drugs and drug targets.

A significant portion of the research that we are conducting involves new and unproven technologies. Research programs to identify new disease targets and product candidates require substantial technical, financial and human resources whether or not we ultimately identify any candidates. Our research programs may initially show promise in identifying potential product candidates, yet fail to yield product candidates for clinical development for a number of reasons, including:

- The research methodology used may not be successful in identifying potential product candidates; or
- Potential product candidates may, upon further study, be shown to have harmful side effects or other characteristics that indicate they are unlikely to be successful drugs.

We may be unable to license or acquire suitable product candidates or products from third parties for a number of reasons. The licensing and acquisition of pharmaceutical products is a competitive area. A number of more established companies are also pursuing strategies to license or acquire products in our core therapeutic areas. These established companies may have a competitive advantage over us due to their size, cash resources and greater clinical development and commercialization capabilities. Other factors that may prevent us from licensing or otherwise acquiring suitable product candidates include the following:

- We may be unable to license or acquire the relevant technology on terms that would allow us to make an appropriate return on the product;
- Companies that perceive us to be their competitors may be unwilling to assign or license their product rights to us; or
- We may be unable to identify suitable products or product candidates within our area of expertise.

If we are unable to develop suitable potential product candidates through internal research programs or by obtaining rights to novel therapeutics from third parties, our business will suffer.

Our dependence on collaborative relationships may lead to delays in product development, lost revenues and disputes over rights to technology.

Our business strategy depends to some extent upon the formation of research collaborations, licensing and/ or marketing arrangements. We currently have a development collaboration with Santen and development and commercialization collaborations with Allergan. The termination of any collaboration may lead to delays in product development and disputes over technology rights and may reduce our ability to enter into collaborations with other potential partners. Allergan and Santen may immediately terminate their agreements with us if we breach the applicable agreement and fail to cure the breach within 60 days of being notified of such breach. If we materially breach our co-promotion agreement with Allergan for *Elestat*®, Allergan has the right to terminate the agreement upon 90 days written notice if we fail to cure the breach within that 90 day period. If we do not maintain the Allergan or Santen collaborations, or establish additional research and development collaborations or licensing arrangements, it will be difficult to develop and commercialize products using our technology. Any future collaborations or licensing arrangements may not be on terms favorable to us.

Our current or any future collaborations or licensing arrangements ultimately may not be successful. Under our current strategy, and for the foreseeable future, we do not expect to develop or market products on our own in all global markets or outside our therapeutic areas of focus. We are currently pursuing the out-licensing of certain rights related to our cystic fibrosis and platelet programs. We may be unsuccessful in out-licensing these programs or we may out-license these programs on terms that are not favorable to us. We will continue to depend on collaborators and contractors for the preclinical study and clinical development of therapeutic products and for manufacturing and marketing of products which result from our technology. Our agreements with collaborators typically allow them some discretion in electing whether to pursue such activities. If any collaborator were to breach or terminate its agreement with us or otherwise fail to conduct collaborative activities in a timely and successful manner, the preclinical or clinical development or commercialization of product candidates or research programs would be delayed or terminated. Any delay or termination in clinical development or commercialization would delay or eliminate potential product revenues relating to our research programs.

Disputes may arise in the future over the ownership of rights to any technology developed with collaborators. These and other possible disagreements between us and our collaborators could lead to delays in the collaborative development or commercialization of therapeutic or diagnostic products. Such disagreement could also result in litigation or require arbitration to resolve.

We may not be able to successfully compete with other biotechnology companies and established pharmaceutical companies.

The biotechnology and pharmaceutical industries are intensely competitive and subject to rapid and significant technological change. Our competitors in the United States and elsewhere are numerous and include, among others, major multinational pharmaceutical and chemical companies, specialized biotechnology firms and universities and other research institutions. Competitors in our core therapeutic areas include: Alcon, Inc.; ISTA Pharmaceuticals, Inc.; MedPointe Pharmaceuticals; Merck & Co, Inc.; Nascent Pharmaceuticals; Novartis; Otsuka America Pharmaceutical, Inc.; Pfizer, Inc.; Senju Pharmaceutical Co. Ltd.; Sucampo Pharmaceuticals, Inc. (ophthalmic); Chiron Corporation; Corus Pharma Inc.; Genaera Corporation; Genentech, Inc.; Lantibio, Inc.; Predix Pharmaceuticals Holdings, Inc.; Vertex Pharmaceuticals Inc. (cystic fibrosis); AstraZeneca plc; Sanofi-Aventis; Bristol-Myers Squibb Company; Eli Lilly and Company; The Medicines Company; and Portola Pharmaceuticals, Inc. (cardiovascular diseases) AstraZeneca; GlaxoSmithKline; MedPointe Pharmaceuticals; Schering-Plough; and Sonofi-Aventis (allergic rhinitis). Most of these competitors have greater resources than we or our collaborative partners, including greater financial resources, larger research and development staffs and more experienced marketing and manufacturing organizations.

In addition, most of our competitors have greater experience than we do in conducting preclinical and clinical trials and obtaining FDA and other regulatory approvals. Accordingly, our competitors may succeed in obtaining FDA or other regulatory approvals for product candidates more rapidly than we do. Companies that

complete clinical trials, obtain required regulatory approvals, and commence commercial sale of their drugs before we do may achieve a significant competitive advantage, including patent and FDA marketing exclusivity rights that would delay our ability to market products. Drugs resulting from our research and development efforts, or from our joint efforts with our collaborative partners, may not compete successfully with competitors' existing products or products under development.

Acquisitions of competing companies and potential competitors by large pharmaceutical companies or others could enhance financial, marketing and other resources available to such competitors. Academic and government institutions have become increasingly aware of the commercial value of their research findings and are more likely to enter into exclusive licensing agreements with commercial enterprises to market commercial products. Many of our competitors have far greater resources than we do and may be better able to afford larger license fees and milestones attractive to those institutions. Our competitors may also develop technologies and drugs that are safer, more effective, or less costly than any we are developing or which would render our technology and future drugs obsolete and non-competitive. In addition, alternative approaches to treating diseases, such as gene therapy, which we have targeted, such as cystic fibrosis, may make our product candidates obsolete.

We will rely substantially on third parties to market, distribute and sell our products and those third parties may not perform.

We have developed a commercialization organization to co-promote *Elestat®, Restasis®*, and diquafosol, if approved, but we are dependent on Allergan, or other experienced third parties, to perform or assist us in the marketing, distribution or sale of these products and our product candidates. In addition, we may not identify acceptable partners or enter into favorable agreements with them for our other product candidates. If third parties do not successfully carry out their contractual duties, meet expected sales goals, or maximize the commercial potential of our products, we may be required to hire or expand our own staff and sales force to compete successfully, which may not be possible. If Allergan or other third parties do not perform, or assist us in performing, these functions, it could have an adverse effect on product revenue and our overall operations.

We have had limited experience in sales, marketing or distribution of products.

We have established a sales force to market and distribute *Elestat®, Restasis®* as well as other potential products. Although the members of our sales force have had experience in sales with other companies, prior to 2004 we never had a sales force and we may undergo difficulties maintaining the sales force. We have incurred substantial expenses in establishing and maintaining the sales force, including substantial additional expenses for the training and management of personnel and the infrastructure to enable the sales force to be effective. We expect to continue to incur substantial expenses in the future. The costs of maintaining our sales force may exceed our product revenues. We compete with many companies that currently have extensive and well-funded marketing and sales operations. Many of these competing companies have had substantially more experience in, and financial resources for sales, marketing and distribution.

Failure to hire and retain key personnel or to identify, appoint and elect qualified directors, may hinder our product development programs and our business efforts.

We depend on the principal members of management and scientific staff, including Christy L. Shaffer, Ph.D., our President and Chief Executive Officer and a director, and Thomas R. Staab, II, our Chief Financial Officer and Treasurer. If these people leave us, we may have difficulty conducting our operations. We have not entered into agreements with any officers or any other members of our management and scientific staff that bind them to a specific period of employment. We also depend upon the skills and guidance of the independent members of our Board of Directors. While our Board of Directors has instituted succession planning steps to identify qualified board candidates to fill open board seats, there can be no assurance that we can identify, appoint and elect qualified candidates to serve as new members of the Board of Directors. We presently have one

vacancy on our Board of Directors. Our future success also will depend in part on our ability to attract, hire and retain additional personnel skilled or experienced in the pharmaceutical industry. There is intense competition for such qualified personnel. We may not be able to continue to attract and retain such personnel.

If our patent protection is inadequate, the development and any possible sales of our product candidates could suffer or competitors could force our products completely out of the market.

Our business and competitive position depends on our ability to continue to develop and protect our products and processes, proprietary methods and technology. Except for patent claims covering new chemical compounds, most of our patents are use patents containing claims covering methods of treating disorders and diseases by administering therapeutic chemical compounds. Use patents, while providing adequate protection for commercial efforts in the United States, may afford a lesser degree of protection in other countries due to their patent laws. Besides our use patents, we have patents and patent applications covering compositions (new chemical compounds), pharmaceutical formulations and processes for large-scale manufacturing. Many of the chemical compounds included in the claims of our use patents and process applications were known in the scientific community prior to our patent applications. None of our composition patents or patent applications cover these previously known chemical compounds, which are in the public domain. As a result, competitors may be able to commercialize products that use the same previously known chemical compounds used by us for the treatment of disorders and diseases not covered by our use patents. Such competitors' activities may reduce our revenues.

If we must defend a patent suit, or if we choose to initiate a suit to have a third party patent declared invalid, we may need to make considerable expenditures of money and management time in litigation. We believe that there is significant litigation in the pharmaceutical and biotechnology industry regarding patent and other intellectual property rights. A patent does not provide the patent holder with freedom to operate in a way that infringes the patent rights of others. While we are not aware of any patent that we are infringing, nor have we been accused of infringement by any other party, other companies may have, or may acquire, patent rights which we might be accused of infringing. A judgment against us in a patent infringement action could cause us to pay monetary damages, require us to obtain licenses, or prevent us from manufacturing or marketing the affected products. In addition, we may need to initiate litigation to enforce our proprietary rights against others. Should we choose to do this, as with the above, we may need to make considerable expenditures of money and management time in litigation. Further, we may have to participate in interference proceedings in the United States Patent and Trademark Office, or USPTO, to determine the priority of invention of any of our technologies.

Our ability to develop sufficient patent rights in our pharmaceutical, biopharmaceutical and biotechnology products to support commercialization efforts is uncertain and involves complex legal and factual questions. For instance, the USPTO examiners may not allow our claims in examining our patent applications. If we have to appeal a decision to the USPTO's Appeals Board for a final determination of patentability we could incur significant legal fees.

Since we rely upon trade secrets and agreements to protect some of our intellectual property, there is a risk that unauthorized parties may obtain and use information that we regard as proprietary.

We rely upon the laws of trade secrets and non-disclosure agreements and other contractual arrangements to protect our proprietary compounds, methods, processes, formulations and other information for which we are not seeking patent protection. We have taken security measures to protect our proprietary technologies, processes, information systems and data, and we continue to explore ways to further enhance security. However, despite these efforts to protect our proprietary rights, unauthorized parties may obtain and use information that we regard as proprietary. Employees, academic collaborators and consultants with whom we have entered confidentiality and/or non-disclosure agreements may improperly disclose our proprietary information. In addition, competitors may, through a variety of proper means, independently develop substantially the equivalent of our proprietary information and technologies, gain access to our trade secrets, or properly design around any of our patented technologies.

If physicians and patients do not accept our product candidates, they will not be commercially successful.

Even if regulatory authorities approve our product candidates, those products may not be commercially successful. Acceptance of and demand for our products will depend largely on the following:

- Acceptance by physicians and patients of our products as safe and effective therapies;
- Reimbursement of drug and treatment costs by government programs and third party payors;
- Effectiveness of Allergan's sales and marketing efforts;
- Marketing and sales activities of competitors;
- Safety, effectiveness and pricing of alternative products; and
- Prevalence and severity of side effects associated with our products.

In addition, to achieve broad market acceptance of our product candidates, in many cases we will need to develop, alone or with others, convenient methods for administering the products. We intend that diquafosol for the treatment of dry eye disease will be applied from a vial containing a single day's dosage of non-preserved medication. Patients may prefer to purchase preserved medication for multiple doses. We have not yet established a plan to develop a multi-dose formulation. Although our partner, Santen, is developing a multi-dose formulation for use in its licensed territories, a multi-dose formulation has not been developed by our other partner, Allergan, for use in the remainder of the world. In addition, denufosol for the treatment of cystic fibrosis is administered by a standard nebulizer three times a day but patients may prefer a smaller, more portable, hand-held device. Similar challenges may exist in identifying and perfecting convenient methods of administration for our other product candidates.

Our operations involve a risk of injury from hazardous materials, which could be very expensive to us.

Our research and development activities involve the controlled use of hazardous materials and chemicals. We cannot completely eliminate the risk of accidental contamination or injury from these materials. If such an accident were to occur, we could be held liable for any damages that result and any such liability could exceed our resources. In addition, we are subject to laws and regulations governing the use, storage, handling and disposal of these materials and waste products. The costs of compliance with these laws and regulations are substantial.

Our commercial insurance and umbrella policies include limited coverage designated for pollutant clean-up and removal and limited general liability coverage per occurrence and in the aggregate. The cost of these policies is significant and there can be no assurance that we will be able to maintain these policies or that coverage amounts will be sufficient to insure potential losses.

Use of our products may result in product liability claims for which we may not have adequate insurance coverage.

Clinical trials or manufacturing, marketing and sale of our potential products may expose us to liability claims from the use of those products. Although we carry clinical trial liability insurance and product liability insurance, we, or our collaborators, may not maintain sufficient insurance. We do not have the financial resources to self-insure and it is unlikely that we will have these financial resources in the foreseeable future. If we are unable to protect against potential product liability claims adequately, we may find it difficult or impossible to continue to co-promote our products, or to commercialize the product candidates we develop. If claims or losses exceed our liability insurance coverage, we may go out of business.

Insurance coverage is increasingly more costly and difficult to obtain or maintain.

While we currently have insurance for our business, property, directors and officers, and our products, insurance is increasingly more costly and narrower in scope, and we may be required to assume more risk in the

future. If we are subject to claims or suffer a loss or damage in excess of our insurance coverage, we will be required to share that risk in excess of our insurance limits. If we are subject to claims or suffer a loss or damage that is outside of our insurance coverage, we may incur significant uninsured costs associated with loss or damage that could have an adverse effect on our operations and financial position. Furthermore, any claims made on our insurance policies may impact our ability to obtain or maintain insurance coverage at reasonable costs or at all.

Future sales by stockholders into the public market may cause our stock price to decline.

Future sales of our common stock by current stockholders into the public market could cause the market price of our stock to fall. As of January 31, 2006, there were 42,210,593 shares of common stock outstanding. Of these outstanding shares of common stock, approximately 21,500,000 shares were sold in public offerings and are freely tradable without restriction under the Securities Act, unless purchased by our affiliates. In addition, we have the ability to issue additional shares of common stock under an active shelf registration statement, which we filed with the Securities and Exchange Commission on April 16, 2004. Up to 10,178,571 shares of our common stock are issued or issuable upon exercise of stock options that have been, or stock options, stock appreciation rights and stock awards that may be, issued pursuant to our Amended and Restated 1995 Stock Plan and our 2005 Equity Compensation Plan. The shares underlying existing stock options and possible future stock options, stock appreciation rights and stock awards have been registered pursuant to registration statements on Form S-8. The remaining shares of common stock outstanding are not registered under the Securities Act and may be resold in the public market only if registered or if there is an exemption from registration, such as Rule 144.

If some or all of such shares are sold into the public market over a short period of time, the value of all publicly traded shares is likely to decline, as the market may not be able to absorb those shares at then-current market prices. Such sales may make it more difficult for us to sell equity securities or equity-related securities in the future at a time and price that our management deems acceptable, or at all.

Further, we may issue additional shares:

- To employees, directors and consultants;
- In connection with corporate alliances;
- In connection with acquisitions; and
- To raise capital.

As of January 31, 2006, there were outstanding options, which were exercisable to purchase 5,254,960 shares of our common stock. This amount combined with the total common stock outstanding at January 31, 2006 is 47,465,553 shares of common stock. As a result of these factors, a substantial number of shares of our common stock could be sold in the public market at any time.

Our Rights Agreement, the provisions of our Change in Control Severance Benefit Plan and our Change in Control Agreements with management, the anti-takeover provisions in our Restated Certificate of Incorporation and Amended and Restated Bylaws, and our right to issue preferred stock, may discourage a third party from making a take-over offer that could be beneficial to us and our stockholders and may make it difficult for stockholders to replace our Board of Directors and effect a change in our management if they desire to do so.

In October 2002, we entered into a Rights Agreement with Computershare Trust Company. The Rights Agreement could discourage, delay or prevent a person or group from acquiring 15% or more of our common stock. The Rights Agreement provides that if a person acquires 15% or more of our common stock without the approval of our Board of Directors, all other stockholders will have the right to purchase securities from us at a price that is less than its fair market value, which would substantially reduce the value of our common stock

owned by the acquiring person. As a result, our Board of Directors has significant discretion to approve or disapprove a person's efforts to acquire 15% or more of our common stock.

Effective as of January 28, 2005, the Compensation Committee of the Board of Directors of Inspire adopted the Company's Change in Control Severance Benefit Plan, or the CIC Plan, which provides severance benefits to certain employees of the Company as of the date on which a Change in Control occurs. Under the CIC Plan and the Change in Control Agreements discussed below, a Change in Control occurs upon a determination by the Board of Directors or upon certain specified events such as merger and consolidation. The CIC Plan covers any regular full-time or part-time employee, other than employees who are parties to employment agreements or who are parties to any severance plan or agreement with the Company (other than the CIC Plan) that provides for the payment of severance benefits in connection with a Change in Control. Under the CIC Plan, if a Change in Control occurs and a participant's employment is involuntarily terminated within two years, the participant will be entitled to certain payments and benefits based on the participant's salary range and years of service with the Company. All executive officers of the Company are parties to individual agreements with the Company regarding a Change in Control and as a result, are not covered by the CIC Plan. Each Change in Control Agreement provides that upon the executive officer's termination of employment following a Change in Control, unless such termination is for "cause," because of death or disability or by the executive officer without "good reason," within 24 months following such Change in Control, the executive officer will be entitled to a lump sum payment equal to a multiple of the sum of (i) the highest annual base salary received by the executive officer in any of the three most recently completed fiscal years prior to the Change in Control and (ii) the higher of the highest annual bonus received by the executive officer in any of the three most recently completed fiscal years preceding the date of the executive officer's termination, the three most recent completed fiscal years preceding the Change in Control, or the maximum of the bonus opportunity range for the executive officer immediately prior to the date of termination. The multiples used to determine the amount of a lump sum payment range from two to three. The Change in Control Agreements also provide for ongoing benefits, the vesting of outstanding stock options, and gross-up payments. The CIC Plan and the Change in Control Agreements would increase the acquisition costs to a purchasing company that triggers the change in control provisions. As a result, the CIC Plan and the Change in Control Agreements may delay or prevent a change in control.

Our Restated Certificate of Incorporation and Amended and Restated Bylaws contain provisions which could delay or prevent a third party from acquiring shares of our common stock or replacing members of our Board of Directors. Our Restated Certificate of Incorporation allows our Board of Directors to issue shares of preferred stock. Our Board of Directors can determine the price, rights, preferences and privileges of those shares without any further vote or action by the stockholders. As a result, our Board of Directors could make it difficult for a third party to acquire a majority of our outstanding voting stock. Since management is appointed by the Board of Directors, any inability to effect a change in the Board of Directors may result in the entrenchment of management.

Our Restated Certificate of Incorporation also provides that the members of the Board will be divided into three classes. Each year the terms of approximately one-third of the directors will expire. Our Amended and Restated Bylaws include director nomination procedures and do not permit our stockholders to call a special meeting of stockholders. Under the Bylaws, only our Chief Executive Officer, President, Chairman of the Board, Vice-Chairman of the Board or a majority of the Board of Directors are able to call special meetings. The staggering of directors' terms of office, the director nomination procedures and the inability of stockholders to call a special meeting may make it difficult for stockholders to remove or replace the Board of Directors should they desire to do so. The director nomination requirements include a provision that requires stockholders give advance notice to our Secretary of any nominations for director or other business to be brought by stockholders at any stockholders' meeting. Our directors may be removed from our Board of Directors only for cause. These provisions may delay or prevent changes of control or management, either by third parties or by stockholders seeking to change control or management.

We are also subject to the anti-takeover provisions of Section 203 of the Delaware General Corporation Law. Under these provisions, if anyone becomes an "interested stockholder," we may not enter a "business

combination" with that person for three years without special approval, which could discourage a third party from making a take-over offer and could delay or prevent a change of control. For purposes of Section 203, "interested stockholder" means, generally, someone owning 15% or more of our outstanding voting stock or an affiliate of ours that owned 15% or more of our outstanding voting stock during the past three years, subject to certain exceptions as described in Section 203.

FORWARD LOOKING STATEMENTS

This annual report on Form 10-K, including the documents that we incorporate by reference, contains forward-looking statements within the meaning of Section 27A of the Securities Act of 1933, as amended, and within the meaning of Section 21E of the Securities Exchange Act of 1934, as amended, that are subject to the "safe harbor" created by those sections. Any statements about our expectations, beliefs, plans, objectives, assumptions or future events or performance are not historical facts and may be forward-looking. These statements are often, but not always, made through the use of words or phrases such as "anticipate," "estimate," "plan," "project," "continuing," "believe," "expect," "future" and "intend" and similar expressions to identify forward-looking statements. There are a number of important factors that could cause our actual results to differ materially from those indicated by any forward-looking statements, including, without limitation, the risk factors listed above and those relating to product development, revenue and earnings expectations, intellectual property rights and litigation, competitive products, results of clinical trials, the need for additional research and testing, delays in manufacturing, funding and the timing and content of decisions made by regulatory authorities, including the FDA and other factors presented throughout this annual report and any other documents filed by us with the Securities and Exchange Commission.

In light of these assumptions, risks and uncertainties, the results and events discussed in the forward-looking statements contained in this annual report on Form 10-K or in any document incorporated by reference might not occur. Stockholders are cautioned not to place undue reliance on the forward-looking statements, which speak only of the date of this report or the date of the document incorporated by reference in this document. We are not under any obligation, and we expressly disclaim any obligation, to update or alter any forward-looking statements, whether as a result of new information, future events or otherwise. All subsequent forward-looking statements attributable to us or to any person acting on our behalf are expressly qualified in their entirety by the cautionary statements contained or referred to in this section.

Item 1B. Unresolved Staff Comments

Not applicable.

Item 2. Properties.

We lease contiguous administrative and laboratory facilities that comprise approximately 51,000 square feet in Durham, North Carolina, which is adjacent to the Research Triangle Park. The various leases underlying our facilities expire in November 2006 and are renewable. We believe our facilities will be adequate to meet our operational needs through November 2006 when our leases expire. In addition, in November 2005, we entered into a 13-month lease of less than 500 square feet for a sales office in Dallas, Texas.

Item 3. Legal Proceedings.

On February 15, 2005, a purported class action complaint was filed in the United States District Court for the Middle District of North Carolina by Mirco Investors, LLC on behalf of itself and all other similarly situated purchasers against us and certain of our senior officers. The complaint alleges violations of sections 10(b) and 20(a) of the Securities Exchange Act of 1934, and Securities and Exchange Commission Rule 10b-5, and focuses on statements that are claimed to be false and misleading regarding a Phase 3 clinical trial of our dry eye product

candidate, diquafosol. The plaintiffs seek unspecified damages on behalf of a purported class of purchasers of our securities during the period from June 2, 2004 through February 8, 2005. Four additional proposed stockholder class actions were filed in the same court, making substantially the same allegations against the same parties as defendants and seeking certification of the same class of purchasers. These individual lawsuits have now been consolidated into a single civil action and a lead plaintiff appointed. We anticipate that an amended consolidated complaint may be filed in March 2006. We intend to defend the litigation vigorously. As with any legal proceeding, we cannot predict with certainty the eventual outcome of these pending lawsuits, nor can a reasonable estimate of the amounts of loss, if any, be made.

On August 30, 2005, the Securities and Exchange Commission notified us that it is conducting a formal, nonpublic investigation, which we believe relates to trading in our securities surrounding the February 9, 2005 announcement of the results of a Phase 3 clinical trial of our dry eye product candidate, diquafosol, as well as our disclosures regarding this Phase 3 clinical trial. We are continuing to cooperate with the Securities and Exchange Commission's ongoing investigation. We cannot predict with certainty the eventual outcome of this investigation, nor can a reasonable estimate of the costs that might result from the SEC's investigation be made.

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

Not applicable.

PART II

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

Our common stock has been traded on the Nasdaq National Market under the symbol "ISPH" since August 3, 2000. The following table sets forth, for the calendar periods indicated, the range of high and low sale prices for our common stock on the Nasdaq National Market:

2004	High	Low
First Quarter	$15.42	$10.76
Second Quarter	$18.74	$12.60
Third Quarter	$17.04	$11.37
Fourth Quarter	$19.19	$14.75

2005	High	Low
First Quarter	$16.81	$ 7.13
Second Quarter	$ 9.09	$ 6.24
Third Quarter	$10.14	$ 7.15
Fourth Quarter	$ 8.35	$ 4.63

As of January 31, 2006, there were 60 record stockholders and over 4,000 beneficial stockholders of our common stock. On January 31, 2006, the last sale price reported on the Nasdaq National Market for our common stock was $4.98 per share.

We have not paid or declared dividends on our common stock since our inception and do not plan to pay dividends on our common stock in the foreseeable future. Any earnings that we may realize will be retained to finance our growth.

Item 6. Selected Financial Data.

The selected statement of operations data and balance sheet data with respect to the years ended December 31, 2005, 2004, 2003, 2002 and 2001 set forth below are derived from our financial statements. The selected financial data set forth below should be read in conjunction with "Management's Discussion and Analysis of Financial Condition and Results of Operations" contained in Item 7 below, and our financial statements and the notes thereto appended to this annual report. Historical results are not necessarily indicative of our future results.

	(in thousands, except per share amounts)				
	Year Ended December 31,				
	2005	2004	2003	2002	2001
Statement of Operations Data:					
Revenue	$ 23,266	$ 11,068	$ 5,200	$ 4,883	$ 7,285
Operating expenses:					
Research and development	23,566	25,698	27,631	25,229	28,193
Selling and marketing	23,223	21,848	2,838	60	124
General and administrative	12,004	9,041	7,002	5,091	5,758
Total operating expenses	58,793	56,587	37,471	30,380	34,075
Loss from operations	(35,527)	(45,519)	(32,271)	(25,497)	(26,790)
Other income, net	3,680	1,450	876	804	3,655
Net loss	$ (31,847)	$ (44,069)	$ (31,395)	$(24,693)	$(23,135)
Net loss per common share—basic and diluted	$ (0.76)	$ (1.25)	$ (1.03)	$ (0.96)	$ (0.90)
Common shares used in computing weighted average common shares outstanding—basic and diluted	42,101	35,261	30,526	25,821	25,702

	(in thousands)				
	December 31,				
	2005	2004	2003	2002	2001
Balance Sheet Data:					
Cash and cash equivalents	$ 65,018	$ 100,320	$ 34,324	$ 27,128	$ 29,959
Investments	57,305	56,476	40,842	4,501	27,895
Total assets	132,446	165,696	79,678	33,564	60,087
Capital lease obligations, including current portion	1,392	1,881	1,084	505	901
Deferred revenue	—	—	—	2,200	4,083
Common stock	42	42	32	26	26
Accumulated deficit	(203,010)	(171,163)	(127,094)	(95,699)	(71,006)
Total stockholders' equity	118,689	149,598	71,052	28,998	52,595

Item 7. Management's Discussion and Analysis of Financial Condition and Results of Operations.

Cautionary Statement

The discussion below contains forward-looking statements regarding our financial condition and our results of operations that are based upon our financial statements, which have been prepared in accordance with accounting principles generally accepted within the United States, as well as projections for the future. The preparation of these financial statements requires our management to make estimates and judgments that affect the reported amounts of assets, liabilities, revenues and expenses, and related disclosure of contingent assets and liabilities. We evaluate our estimates on an ongoing basis. Our estimates are based on historical experience and on various other assumptions that are believed to be reasonable under the circumstances. The results of our estimates form the basis for making judgments about the carrying values of assets and liabilities that are not readily apparent from other sources.

We operate in a highly competitive environment that involves a number of risks, some of which are beyond our control. We are subject to risks common to biopharmaceutical companies, including risks inherent in our research, development and commercialization efforts, preclinical testing, clinical trials, uncertainty of regulatory actions and marketing approvals, reliance on collaborative partners, enforcement of patent and proprietary rights, the need for future capital, competition associated with *Elestat*® and *Restasis*®, potential competition associated with our product candidates, use of hazardous materials and retention of key employees. In order for one of our product candidates to be commercialized, it will be necessary for us to conduct preclinical tests and clinical trials, demonstrate efficacy and safety of the product candidate to the satisfaction of regulatory authorities, obtain marketing approval, enter into manufacturing, distribution and marketing arrangements, obtain market acceptance and, in many cases, obtain adequate reimbursement from government and private insurers. We cannot provide assurance that we will generate significant revenues or achieve and sustain profitability in the future. Statements contained in Management's Discussion and Analysis of Financial Conditions and Results of Operations which are not historical facts are, or may constitute, forward-looking statements. Forward-looking statements involve known and unknown risks that could cause our actual results to differ materially from expected results. These risks are discussed in the section entitled "Risk Factors." Although we believe the expectations reflected in the forward-looking statements are reasonable, we cannot guarantee future results, levels of activity, performance or achievements.

Our operating expenses are difficult to predict and will depend on several factors. Research and development expenses, including expenses for drug synthesis and manufacturing, preclinical testing and clinical research activities, will depend on the ongoing requirements of our drug development programs, availability of capital and direction from regulatory agencies, which are difficult to predict. Management may in some cases be able to control the timing of research and development expenses in part by accelerating or decelerating preclinical testing, other discovery and basic research activities, and clinical trial activities, but many of these expenditures will occur irrespective of whether our product candidates are approved when anticipated or at all. We have incurred and expect to continue to incur significant selling and marketing expenses to commercialize our products. Once again, management may in some cases be able to control the timing and magnitude of these expenses. As a result of these factors, we believe that period to period comparisons are not necessarily meaningful and you should not rely on them as an indication of future performance. Due to all of the foregoing factors, it is possible that our operating results will be below the expectations of market analysts and investors. In such event, the prevailing market price of our common stock could be materially adversely affected.

Overview

We are a biopharmaceutical company dedicated to discovering, developing and commercializing prescription pharmaceutical products in disease areas with significant commercial potential and unmet medical needs. Our goal is to build and commercialize a sustainable pipeline of innovative new treatments based upon our technical and scientific expertise, focusing in the ophthalmic and respiratory/allergy therapeutic areas. Our ophthalmic products and product candidates are currently concentrated in the allergic conjunctivitis, dry eye disease and glaucoma indications. Our respiratory/allergy product candidates are currently concentrated in the

treatment of respiratory complications of cystic fibrosis and seasonal allergic rhinitis. In addition, we also have an antiplatelet product candidate that we are testing in cardiopulmonary bypass procedures but it could be useful in other cardiovascular indications.

We were incorporated in October 1993 and commenced operations in March 1995 following our first substantial financing and licensing of the initial technology from UNC. We are located in Durham, North Carolina, adjacent to the Research Triangle Park.

We co-promote *Elestat*® and *Restasis*® in the United States under agreements with Allergan and we receive co-promotion revenue based upon net sales of these products. In January 2004, we began co-promoting *Restasis*® for the treatment of dry eye disease. In February 2004, we launched *Elestat*® for the treatment of allergic conjunctivitis.

See Part I of this report for a full discussion of our co-promotion agreements with Allergan and other significant collaborative agreements.

In June 2003, we submitted an NDA to the FDA for our dry eye product candidate, diquafosol, and were granted a "Priority Review" designation in July 2003. Since 2003, we have received two approvable letters from the FDA, the last in December 2005. We are working with Allergan to determine a European regulatory filing strategy for diquafosol for the treatment of dry eye disease.

See Part I of this report for a full discussion of our diquafosol program for the treatment of dry eye disease and other product candidates in clinical development.

In the first quarter of 2004, we emerged out of the development stage, having transformed into a commercial organization, and began receiving co-promotion revenue from the commercial product sales of *Elestat*® and *Restasis*®. Previously, we devoted substantially all of our efforts to the discovery and clinical development of our product candidates as well as the establishment of strategic partnerships. Prior to 2004, our revenues consisted of payments under our various corporate partnerships established for the development and commercialization of our products when approved.

We have incurred significant operating losses since our inception and, as of December 31, 2005, we had an accumulated deficit of $203.0 million. We expect to incur losses for the next several years. We have financed our operations through the sale of equity securities, including private sales of preferred stock and public offerings of common stock, and, to a lesser extent, with revenue from corporate partnerships, including co-promotion revenue. Co-promotion revenue from *Elestat*® and *Restasis*® did not exceed our total operating expenses in 2005. We operate in a single business segment and do not have any foreign operations.

Critical Accounting Policies and Estimates

The accompanying discussion and analysis of our financial condition and results of operations are based upon our financial statements and the related disclosures, which have been prepared in accordance with generally accepted accounting principles. The preparation of these financial statements require us to make estimates and judgments that affect the reported amounts of assets, liabilities, revenues, expenses and related disclosure of contingent assets and liabilities. We evaluate our estimates, judgments and the policies underlying these estimates on a periodic basis as situations change, and regularly discuss financial events, policies, and issues with members of our audit committee and our independent registered public accounting firm. In addition, recognition of revenue from product co-promotion is affected by certain estimates and judgments made by Allergan on which we rely in recording this revenue. We routinely evaluate our estimates and policies regarding revenue recognition, taxes, clinical trial, preclinical/toxicology, manufacturing, research and other service liabilities.

We believe the following policies to be the most critical to an understanding of our financial condition and results of operations because they require us to make estimates and judgments about matters that are inherently uncertain.

Revenue Recognition

We recognize revenue from product co-promotion based on net sales for *Elestat*® and *Restasis*®, as defined in the co-promotion agreements, and as reported to us by our collaborative partner, Allergan. Accordingly, our co-promotion revenue is based upon Allergan's revenue recognition policy, other accounting policies and the underlying terms of our co-promotion agreements. Allergan recognizes revenue from product sales when goods are shipped and title and risk of loss transfers to the customer. The co-promotion agreements provide for gross sales to be reduced by estimates of sales returns, credits and allowances, normal trade and cash discounts, managed care sales rebates and other allocated costs as defined in the agreements, all of which are determined by Allergan and are outside our control. We also reduce gross revenues for incentive programs we manage, estimating the proportion of sales that are subject to such incentive programs and reducing revenue appropriately. Under the co-promotion agreement for *Elestat*®, we are obligated to meet predetermined minimum annual net sales performance levels. If the annual minimum is not satisfied, we record revenues using a reduced percentage of net sales based upon our level of achievement of predetermined calendar year net sales target levels. Amounts contractually due from Allergan in excess of recorded co-promotion revenue are recorded as deferred revenue.

We recognize milestone revenue under our collaborative research and development agreements when we have performed services under such agreements or when we or our collaborative partner have met a contractual milestone triggering a payment to us. Non-refundable fees received at the initiation of collaborative agreements for which we have an ongoing research and development commitment are deferred and recognized ratably over the period of ongoing research and clinical development commitment. We are also entitled to receive milestone payments under our collaborative research and development agreements based upon achievement of development milestones by us or our collaborative partners. We recognize milestone payments as revenues ratably over the period of our research and development commitment. The recognition period begins at the date the milestone is achieved and acknowledged by the collaborative partner, which is generally at the date payment is received from the collaborative partner, and ends on the date that we have fulfilled our research and development commitment. This period is based on estimates by management and the progress towards milestones in our collaborative agreements. The estimate is subject to revision as our development efforts progress and we gain knowledge regarding required additional development. Revisions in the commitment period are made in the period that the facts related to the change first become known. This may cause our revenue to fluctuate from period to period. No milestone revenue under these agreements has been recognized for the years ended December 31, 2005 and 2004. In the year ended December 31, 2003, we recognized $5.2 million in revenue from certain contractual milestones.

Taxes

Significant management judgment is required in determining our provision for income taxes, deferred tax assets and liabilities and any valuation allowance recorded against net deferred tax assets. We have recorded a valuation allowance of $90.8 million as of December 31, 2005 against all potential tax assets due to uncertainties in our ability to utilize deferred tax assets, primarily consisting of certain net operating losses carried forward, before they expire. The valuation allowance is based on estimates of taxable income in each of the jurisdictions in which we operate and the period over which our deferred tax assets will be recoverable.

Liabilities

We generally enter into contractual agreements with third party vendors to provide clinical, preclinical/ toxicology, manufacturing, research and other services in the ordinary course of business. Many of these contracts are subject to milestone-based invoicing and services are completed over an extended period of time. We record liabilities under these contractual commitments when we determine an obligation has been incurred, regardless of the timing of the invoice. We monitor all significant research and development, manufacturing, promotion and marketing and other service activities and the progression of work related to these activities. We estimate the underlying obligation for each activity based upon our estimate of the amount of work performed and compare the estimated obligation against the amount that has been invoiced. Because of the nature of certain

contracts and related delay in the contract's invoicing, the obligation to these vendors may be based upon management's estimate of the underlying obligation. We record the larger of our estimated obligation or invoiced amounts for completed service. In all cases, actual results may differ from our estimate.

Stock Option Expense

As of January 1, 2006, we have adopted Statement of Financial Accounting Standards, or SFAS, No. 123(R), which requires us to measure compensation cost for stock option awards at fair value and recognize compensation over the service period for awards expected to vest. We have selected the Black-Scholes option-pricing model as the most appropriate fair-value method for our awards and will recognize compensation cost ratably over the vesting periods of our awards. The estimation of stock awards that will ultimately vest requires judgment, and to the extent actual results or updated estimates differ from our current estimates, such amounts will be recorded as a cumulative adjustment in the period estimates are revised. We consider many factors when estimating expected forfeitures, including types of awards, employee class, and historical experience. Actual results, and future changes in estimates, may differ substantially from our current estimates. Significant management judgment is required in determining future stock price volatility to be used in the valuation of the options. We use a blended volatility calculation utilizing volatility of peer group companies with similar operations and financial structures in addition to our own historical volatility. We will use the modified prospective method in recognizing stock-based compensation expense in future periods.

See "Impact of Recently Issued Accounting Pronouncements" in this section of the report as well as Note 2 "Summary of Significant Accounting Policies and Concentrations of Risk" for additional discussion of the impact of adopting SFAS No. 123(R).

Impact of Inflation

Although it is difficult to predict the impact of inflation on our costs and revenues in connection with our products, we do not anticipate that inflation will materially impact our costs of operation or the profitability of our products when marketed.

Results of Operations

Years Ended December 31, 2005, 2004 and 2003

Revenues

Our revenues for the year ended December 31, 2005 were $23.3 million, compared to $11.1 million in 2004 and $5.2 million in 2003. The increase in 2005 revenue, as compared to 2004, was due to significantly increased co-promotion revenue from net sales of both *Elestat*® and *Restasis*®. This increase is attributable to: 1) a full year of co-promotion activities in 2005 for both products; 2) increased market share for *Elestat*®; and 3) increased acceptance of *Restasis*®, the only approved prescription product indicated for dry eye disease, as well as a scheduled increase of the percentage of net sales of *Restasis*® to which we are entitled (effective April 2005). In 2005, the revenue generated from our commercial organization exceeded our selling and marketing expenses. When compared to 2004, 2005 co-promotion revenue from net sales of *Elestat*® increased 75% and co-promotion revenue from net sales of *Restasis*® increased 337%. The change in revenue in 2004 as compared to 2003 related to our recognition of co-promotion revenue from *Elestat*® and *Restasis*® commercial product sales in 2004 as compared to revenue recognized from milestone payments and the amortization of deferred revenue under certain of our collaborative research and development agreements with strategic partners during 2003. All deferred revenue under these agreements was fully amortized during 2003. No milestone revenue under these agreements has been recognized for the years ended December 31, 2005 and 2004, respectively.

We began realizing co-promotion revenue from *Elestat*® beginning in February 2004. All of our revenue related to *Elestat*® is from net sales in the United States according to the terms of our collaborative agreement with Allergan. *Elestat*® is a seasonal product with product demand mirroring seasonal trends for topical allergic

conjunctivitis products whereby there is usually a large increase in sales during the Spring and a lesser increase during the Summer and Fall. Revenue from net sales of *Elestat®* in the year ended December 31, 2005 was approximately $16.8 million, as compared to approximately $9.6 million in 2004.

Elestat® is the second most prescribed allergic conjunctivitis product in the United States, based upon weekly prescription volume as reported by IMS Health and continues to increase market share in both new prescriptions and total prescriptions. Based upon weekly national prescription data from IMS Health for the week ending December 30, 2005, *Elestat®* has achieved a market share of approximately 19% for both new prescription volume and total prescription volume in our target universe, the top 200 highest prescribing ophthalmologists, optometrists, and allergists in each of our 64 sales territories. Comparatively, for the week ending December 31, 2004, *Elestat®* had a market share of approximately 16% in new prescription volume and approximately 14% in total prescription volume in our target universe. Also, we have recently achieved approximately 20% market share of prescription volume in our target universe for the week ending February 3, 2006, which is two years from our launch of *Elestat®* in the United States. In regards to the total U.S. allergic conjunctivitis market, *Elestat®* represents approximately 10% of 2005 total prescriptions through the week ending December 30, 2005. By comparison, in 2004, *Elestat®* had approximately 7% of 2004 total allergic conjunctivitis prescriptions through the week ending December 31, 2004.

Allergan has secured coverage on formularies of certain commercial and government plans since the launch of *Elestat®*. This coverage allows us to continue to increase prescription market share, but may require price concessions which would ultimately impact the level of co-promotion revenue that we receive from net sales of *Elestat®*. While the market share for *Elestat®*, in terms of prescriptions, has continued to increase, our 2005 revenues were impacted by higher than expected rebates associated with additions to state Medicaid programs.

In regards to co-promotion revenue from net sales of *Elestat®*, we are entitled to an escalating percentage of net sales based upon predetermined calendar year net sales target levels. During a fiscal year, we recognize product co-promotion revenue associated with targeted net sales levels for *Elestat®* achieved during that time period and defer revenue in excess of the sales level achieved. We achieved the annual 2005 net sales target level in the three-month period ended June 30, 2005, and achieved the annual 2004 net sales target level in the three-month period ended September 30, 2004.

We began co-promotion activities related to *Restasis®* in January 2004 and began receiving co-promotion revenue in April 2004. All of our revenue from *Restasis®* is based on worldwide net sales of *Restasis®* according to the terms of our collaborative agreement with Allergan. We recognized approximately $6.5 million of co-promotion revenue from net sales of *Restasis®* during the year ended December 31, 2005, as compared to approximately $1.5 million in 2004. The increase is due to increased physician and patient acceptance of *Restasis®* as well as a scheduled increase to the percentage of net sales of *Restasis®* to which we were entitled, which became effective in April 2005. Allergan had net sales of *Restasis®* of $191 million in 2005, $100 million in 2004 and $38 million in 2003.

Our future revenue will depend on various factors including the continued commercial success of *Elestat®* and *Restasis®*, rebates, discounts and returns for both products, coverage and reimbursement under commercial or government plans, our entitled percentage of U.S. net sales of *Restasis®* which increases each April for the next two years, seasonality of sales of *Elestat®* and duration of market exclusivity of *Elestat®* and *Restasis®*. If Allergan significantly under-estimates or over-estimates rebate amounts, there could be a material effect on our revenue. In addition, our revenue will also depend on whether we enter additional collaboration agreements, achieve milestones under existing or future collaboration agreements and whether we obtain regulatory approvals for our product candidates.

Costs and Expenses

Research and Development Expenses

Research and development expenses for the year ended December 31, 2005 were $23.6 million, compared to $25.7 million in 2004 and $27.6 million in 2003. Research and development expenses include all direct and indirect costs, including salaries for our research and development personnel, consulting fees, clinical trial costs, sponsored research costs, clinical trial insurance, up-front license fees, milestone and royalty payments relating to research and development, and other fees and costs related to the development of product candidates. Research and development expenses vary according to the number of programs in preclinical and clinical development and the stage of development of our clinical programs. Later stage clinical programs tend to cost more than earlier stage programs due to the length of the trial and the number of patients enrolled in later stage clinical trials.

The decrease in research and development expenses in 2005, as compared to 2004, was primarily due to significantly less spending on diquafosol for dry eye disease due to our NDA amendment filing on June 1, 2005. Additionally, we spent less on our denufosol for retinal disease program due to the discontinuation of this program in 2005. These decreases were partially offset by an increase in denufosol for cystic fibrosis expenditures related to conducting six month and twelve month inhalation toxicology studies and Phase 2 clinical trials during 2005 prior to initiation of our Phase 3 program, which will begin in 2006, as well as an increase in expenses related to our corneal wound healing Phase 2 pilot study which was initiated in 2005 but was later discontinued in the third quarter of 2005.

The decrease in 2004 expenses, as compared to 2003, related to significantly decreased spending on our denufosol for upper respiratory disorders program and our INS316 Diagnostic program, which were partially offset by increased spending on key programs in aggressive clinical and preclinical development; including expenses associated with a Phase 3 clinical trial of diquafosol for dry eye disease, a Phase 2 clinical trial and long-term toxicology studies of denufosol for the treatment of cystic fibrosis and a Phase 2 clinical trial of denufosol for retinal disease. During 2003, we lowered the priority of the denufosol for upper respiratory disorders and the INS316 Diagnostic programs and decreased the resources dedicated to them.

Our research and development expenses for the years ended December 31, 2005, 2004 and 2003 and from the respective project's inception are shown below and includes the percentage of overall research and development expenditures for the years listed.

	(In thousands) Year ended December 31,						Cumulative from Inception (October 28, 1993) to	
	2005	%	2004	%	2003	%	December 31, 2005	%
denufosol tetrasodium (INS37217 Respiratory) for cystic fibrosis	$ 9,223	39	$ 4,256	17	$ 3,146	12	$ 22,232	13
INS50589 Antiplatelet	2,746	12	3,384	13	2,751	10	9,363	5
diquafosol tetrasodium (INS365 Ophthalmic) for dry eye disease	1,961	8	6,835	27	5,896	21	37,707	22
denufosol tetrasodium (INS37217 Ophthalmic) for retinal disease	1,465	6	2,893	11	1,365	5	7,847	5
diquafosol tetrasodium (INS365 Ophthalmic) for corneal wound healing [3]	533	2	—	—	—	—	533	—
denufosol tetrasodium (INS37217 Intranasal) for upper respiratory disorders [3]	55	—	480	2	6,723	24	12,694	7
INS316 Diagnostic (uridine 5'-triphosphate) [1] [3]	43	—	746	3	2,873	10	8,866	5
Other discovery and development costs [2]	7,540	33	7,104	27	4,877	18	73,034	43
Total	$23,566	100	$25,698	100	$27,631	100	$172,276	100

(1) In September 2004, Kirin terminated its license for this drug candidate.

(2) Other discovery and development costs represent all unallocated research and development costs or those costs allocated to preclinical programs, discontinued and/or inactive programs. These unallocated costs include personnel costs of our discovery programs, internal and external general research costs and other internal and external costs of other drug discovery and development programs.

(3) As of December 31, 2005, these programs were not in active development.

Our future research and development expenses will depend on the results and magnitude or scope of our clinical, preclinical and discovery activities and requirements imposed by regulatory agencies. In addition, our future research and development expenses will now have a component of stock-based compensation for unvested options as of January 1, 2006, and thus will increase as this expense has not been included in the past. Accordingly, our development expenses may fluctuate significantly from period to period. In addition, if we in-license or out-license rights to product candidates, our development expenses may fluctuate significantly from prior periods.

Selling and Marketing Expenses

Selling and marketing expenses for the year ended December 31, 2005 were $23.2 million, compared to $21.8 million in 2004 and $2.8 million in 2003. The increase in selling and marketing expenses in 2005, as compared to 2004 resulted from a full year of active promotion of *Elestat®* and *Restasis®* and expanded commercial activity as we continue to build the *Elestat®* brand. Following the launch of *Elestat®* and the start of co-promotion activities for both the *Elestat®* and *Restasis®* brands, we continue to adjust the timing and targeting of our advertising, promotional, Phase 4 clinical trials and other commercial activities for *Elestat®* and *Restasis®* based on seasonal trends and other factors. The increase in selling and marketing expenses in 2004, as compared to 2003, resulted from Inspire beginning commercial operations in the first quarter of 2004, including increases in personnel, advertising and promotion expenses and other administrative costs to enable our active co-promotion of *Elestat®* and *Restasis®*.

Our commercial organization focuses its promotional efforts on approximately 8,500 highly prescribing ophthalmologists, optometrists and allergists in our target universe. Our selling and marketing expenses include all direct costs associated with the commercial organization, which include our sales force and marketing programs. Our sales force expenses include salaries, training and educational program costs, product sample costs, fleet management and travel. Our marketing and promotion expenses include product management, promotion, advertising, public relations, Phase 4 clinical trial costs, physician training and continuing medical education and administrative expenses.

Future selling and marketing expenses will depend on the level of our future commercialization activities. We expect selling and marketing expenses will increase in periods that may immediately precede and follow product launches. In addition, our future selling and marketing expenses will now have a component of stock-based compensation for unvested options as of January 1, 2006, and thus will increase as this expense has not been included in the past.

General and Administrative Expenses

General and administrative costs for the year ended December 31, 2005 were $12.0 million, compared to $9.0 million in 2004 and $7.0 million in 2003. Our general and administrative expenses consist primarily of personnel, facility and related costs for general corporate functions, including business development, finance, accounting, legal, human resources, quality/compliance, facilities and information systems.

The increase in 2005 general and administrative expenses, as compared to 2004, was primarily due to increased salary and personnel related expenses, increased legal and administrative expenses associated with our stockholder litigation and SEC investigation, and overall corporate growth. The increase in 2004 general and

administrative expenses was primarily due to expenses necessary to support and maintain a commercial organization, costs associated with Sarbanes-Oxley compliance, as well as overall corporate growth. Future general and administrative expenses will depend on the level of our future research and development and commercialization activities, as well as the level of legal and administrative expenses incurred to resolve our stockholder litigation and SEC investigation. In addition, our future general and administrative expenses will now have a component of stock-based compensation for unvested options as of January 1, 2006, and thus will increase as this expense has not been included in the past. We expect our future professional fees to continue to increase as a result of our stockholder litigation and SEC investigation (See "Litigation" and "SEC Investigation" described elsewhere in this report).

Other Income (Expense)

Other income, net totaled $3.7 million for the year ended December 31, 2005, compared to $1.5 million for 2004 and $876,000 for 2003. Other income fluctuates from year to year based upon fluctuations in the interest income earned on variable cash and investment balances and realized gains and losses on investments offset by interest expense on debt obligations. The increase in 2005 other income, as compared to 2004, was primarily due to an increase in interest income resulting from larger average cash and investment balances during 2005 as a result of stock offerings in the second half of 2004 and of higher yielding investments overall. This increase was partially offset by write-down of available-for-sale investments of approximately $516,000 due to an impairment deemed other-than-temporary. The increase in 2004 other income, as compared to 2003, was primarily the result of a write-down of a strategic investment in 2003 and larger average cash and investment balances as a result of stock offerings that generated net proceeds in excess of $119 million in the second half of 2004. Future other income will depend on our future cash and investment balances, the return and change in fair market value on these investments, as well as levels of debt and the associated interest rates.

Liquidity and Capital Resources

We have financed our operations through the sale of equity securities, including private sales of preferred stock and public offerings of common stock. We currently receive revenue from co-promotion of *Elestat*® and *Restasis*®, but do not expect this revenue to exceed our 2006 operating expenses.

At December 31, 2005, we had net working capital of $99.3 million, a decrease of approximately $35.3 million from $134.6 million at December 31, 2004. The decrease in working capital is principally due to the use of funds for our normal operating expenses, which exceeded the co-promotion revenue we recognized. Our principal sources of liquidity at December 31, 2005 were $65.0 million in cash and cash equivalents and $56.6 million in investments which are considered "available-for-sale," reflecting a $34.5 million decrease of cash, cash equivalents and investment balances from December 31, 2004.

Our working capital requirements may fluctuate in future periods depending on many factors, including: the efficiency of manufacturing processes developed on our behalf by third parties; the number, magnitude, scope and timing of our drug development programs; the costs related to the potential FDA approval of diquafosol and our other product candidates; the cost, timing and outcome of regulatory reviews, regulatory investigations, and changes in regulatory requirements; the costs of obtaining patent protection for our product candidates; the timing and terms of business development activities; the rate of technological advances relevant to our operations; the timing, method and cost of the commercialization of our product candidates; the level of required administrative and legal support; the availability of capital to support product candidate development programs we pursue; the commercial potential of our products and product candidates; outcome of our stockholder litigation and SEC investigation; and any expansion of facility space.

In fiscal year 2006, we expect approximately $31-39 million of revenue and are targeting 2006 operating expenses of $77-86 million. Using the mid-point of our revenue and expense guidance, we expect an average cash burn rate of approximately $4 million per month in 2006. Our expense range includes the expected impact

of non-cash stock option expense as required under SFAS No. 123(R). We intend to continue to offer stock options to attract and retain qualified employees and directors and we will be required to expense this non-cash cost beginning in the first quarter of 2006. Based upon stock options currently outstanding as well as those we expect to issue in 2006, and utilizing the valuation model and assumptions consistent with our 2005 quarterly calculations, we project non-cash stock option expense to be approximately $2 million for fiscal year 2006.

We believe our existing cash, cash equivalents and investments will be adequate to satisfy our anticipated working capital requirements through 2007. In order for us to continue operations after that point, we will need to: (1) obtain product candidate approvals, (2) in-license commercial products, (3) out-license rights to our product candidates, and/or (4) raise additional capital through equity or debt financings or from other sources. We have the ability to sell approximately $13.9 million worth of common stock under an effective shelf registration statement, which we filed with the Securities and Exchange Commission on April 16, 2004. However, additional funding may not be available on favorable terms from any of these sources or at all. Our ability to achieve our operating expense target range is subject to several risks including unanticipated cost overruns, the need to expand the magnitude or scope of existing development programs, the need to change the number or timing of clinical trials, unanticipated regulatory requirements, costs to successfully commercialize our products and product candidates, commercial success of our products and product candidates, unanticipated professional fees or settlements associated with our stockholder litigation or SEC investigation and other factors described under the Risk Factors located elsewhere in this report.

Contractual Commitments

As part of our drug development strategy, we outsource significant amounts of our preclinical and clinical programs and the manufacture of drug substance used in those programs. Accordingly, we have entered into contractual commitments or purchase arrangements with various clinical research organizations, manufacturers of active pharmaceutical ingredients and/or drug product as well as with others. The amount of our financial commitments under these arrangements totaled approximately $6.6 million at December 31, 2005. In addition, we have other contractual commitments outside of drug development under arrangements which totaled approximately $826,000 at December 31, 2005. These amounts may vary dependent upon the results of underlying studies, the completion of studies and/or projects and certain other variable components that may yield a result that differs from management's estimate. Also, at December 31, 2005, we have future contractual commitments to pay $3.3 million of lease obligations for our administrative offices, fleet vehicles, laboratory facilities and equipment. We have also engaged legal counsel to represent us in our SEC investigation and stockholder litigation, but we are not contractually obligated to incur future costs under the applicable engagement letters. However, we do anticipate future costs to be incurred to retain counsel until these proceedings are resolved. Because of the nature of the situation, we are unable to estimate any future commitment in regards to these legal proceedings and have not included any committed costs in our projected contractual commitment disclosures. The terms of our existing license, collaboration and sponsored research agreements may require that we make future cash payments. In the aggregate, these agreements may require payments of up to $13.9 million assuming the achievement of all development milestones and up to an additional $4.0 million assuming the achievement of all sales milestones. Amounts payable by us under these agreements are uncertain and are contingent on a number of factors, including the progress of our discovery and drug development programs, ongoing costs and outcome of our SEC investigation and stockholder litigation, our ability to obtain regulatory approvals, and the commercial success of our approved products. In addition, there is approximately $600,000 of development milestones under existing license agreements related to currently inactive development programs and we believe it is unlikely the milestones will be achieved and payments made. We are also obligated to pay royalties on net sales, if any, of certain product candidates currently in our portfolio. Some of our existing license agreements require minimum annual license preservation fees of up to $10,000. In addition, if we obtain licenses on additional product candidates in the future, or if our collaborative arrangements identify additional product candidates, our license obligations would increase.

Subject to the information and qualifications included in the above paragraph, the table below sets forth our enforceable and legally binding obligations and future commitments and obligations related to all contracts that

we are likely to continue regardless of the fact that the contracts may be terminated. Some of the figures we include in this table are based on management's estimate and assumptions about these obligations, including their duration, the possibility of renewal, anticipated actions by third parties, and other factors. Because these estimates and assumptions are necessarily subjective, the obligations we will actually pay in future periods may vary from those reflected in the table:

	(In thousands) Payment due by Period as of December 31, 2005				
Contractual and Potential Obligations	**Total**	**Less than 1 year**	**1-3 years**	**3-5 years**	**More than 5 years**
Capital Lease Obligations	$ 1,558	$ 641	$ 913	$ 4	$ —
Operating Lease Obligations [1]	1,788	1,156	631	1	—
Purchase Obligations	7,400	7,400	—	—	—
Minimum Annual Payments	115	15	40	50	10
Development Milestone Obligations [2][3]	13,850	50	250	12,550	1,000
Sales Milestone Obligations [3]	4,000	—	—	—	4,000
Total	$28,711	$9,262	$1,834	$12,605	$5,010

(1) Includes estimated payments for cancelable portion of fleet vehicles under a master lease agreement. See Note 11, "Debt, Commitments and Contingencies" for a full discussion.

(2) Includes $1.9 million of "other long-term liabilities" as recorded on our Balance Sheet as of December 31, 2005.

(3) Development and sales milestone obligations represent potential amounts payable by us contingent on a number of factors, including the progress of our discovery and drug development programs, our ability to obtain regulatory approvals, and the commercial success of our approved products.

Litigation

On February 15, 2005, a purported class action complaint was filed in the United States District Court for the Middle District of North Carolina by Mirco Investors, LLC on behalf of itself and all other similarly situated purchasers against us and certain of our senior officers. The complaint alleges violations of sections 10(b) and 20(a) of the Securities Exchange Act of 1934, and Securities and Exchange Commission Rule 10b-5, and focuses on statements that are claimed to be false and misleading regarding a Phase 3 clinical trial of our dry eye product candidate, diquafosol. The plaintiffs seek unspecified damages on behalf of a purported class of purchasers of our securities during the period from June 2, 2004 through February 8, 2005. Four additional proposed stockholder class actions were filed in the same court, making substantially the same allegations against the same parties as defendants and seeking certification of the same class of purchasers. These individual lawsuits have now been consolidated into a single civil action and a lead plaintiff appointed. We anticipate that an amended consolidated complaint may be filed in March 2006. We intend to defend the litigation vigorously. As with any legal proceeding, we cannot predict with certainty the eventual outcome of these pending lawsuits, nor can a reasonable estimate of the amounts of loss, if any, be made. Furthermore, we will have to incur expenses in connection with these lawsuits, which may be substantial. In the event of an adverse outcome, our business, future results of operations, financial position and/or cash flows could be materially affected. Moreover, responding to and defending the pending litigation will result in a diversion of management's attention and resources and an increase in professional fees.

SEC Investigation

On August 30, 2005, the Securities and Exchange Commission notified us that it is conducting a formal, nonpublic investigation, which we believe relates to trading in our securities surrounding the February 9, 2005 announcement of the results of a Phase 3 clinical trial of our dry eye product candidate, diquafosol, as well as our disclosures regarding this Phase 3 clinical trial. We are continuing to cooperate with the Securities and Exchange Commission's ongoing investigation. We cannot predict with certainty the eventual outcome of this investigation, nor can a reasonable estimate of the costs that might result from the SEC's investigation be made.

In the event of an adverse outcome, our business, future results of operations, financial position and/or cash flows could be materially affected. Responding to this investigation will result in a diversion of management's attention and resources and an increase in professional fees.

Impact of Recently Issued Accounting Pronouncements

In November 2005, the Financial Accounting Standards Board, or FASB, issued FASB Staff Position Nos. FAS 115-1 and FAS 124-1, *"The Meaning of Other-Than-Temporary Impairment and Its Application to Certain Investments"* or FSP FAS 115-1 and FAS 124-1. FSP FAS 115-1 and FAS 124-1 address the determination as to when an investment is considered impaired, whether that impairment is other than temporary, and the measurement of an impairment loss. It also includes accounting considerations subsequent to the recognition of an other-than-temporary impairment and requires certain disclosures about unrealized losses that have not been recognized as other-than-temporary impairments. The guidance set forth in FSP FAS 115-1 and FAS 124-1 is effective for reporting periods beginning after December 15, 2005, but earlier adoption is permitted. We have implemented the provisions set forth in FSP FAS 115-1 and FAS 124-1 effective October 1, 2005.

In June 2005, the Emerging Issues Task Force reached consensus on Issue No. 05-6, *"Determining the Amortization Period for Leasehold Improvements Purchased after Lease Inception or Acquired in a Business Combination"* or EITF 05-6. EITF 05-6 provides guidance on determining the amortization period for leasehold improvements acquired in a business combination or acquired subsequent to lease inception. EITF 05-6 was effective as of June 29, 2005 and we comply with the guidance set forth therein.

In May 2005, the FASB issued SFAS No. 154 *"Accounting Changes and Error Corrections"*, or SFAS No. 154, a replacement of Accounting Principles Board, or APB, Opinion No. 20, *"Accounting Changes"* and FASB Statement No. 3, *"Reporting Accounting Changes in Interim Financial Statements."* SFAS No. 154 provides guidance on the accounting for and reporting of changes in accounting principles and error corrections. SFAS No. 154 applies to all voluntary changes in accounting principles and to changes required by an accounting pronouncement in the unusual instance that the pronouncement does not include specific transition provisions. SFAS No. 154 requires retrospective application to prior periods' financial statements of changes in accounting principles, unless it is impracticable to determine either the period-specific effects or the cumulative effect of the change. SFAS No. 154 is effective for accounting changes and corrections of errors made in fiscal years beginning after December 15, 2005 and we comply with the guidance set forth in SFAS No. 154.

In December 2004, the FASB issued SFAS No. 123(R) (revised 2004, or SFAS No. 123(R)), *"Share-Based Payment,"* a revision of FASB Statement No. 123 *"Accounting for Stock-Based Compensation,"* or SFAS No. 123. SFAS No. 123(R) supersedes APB Opinion No. 25, *"Accounting for Stock Issued to Employees,"* or APB No. 25, and amends SFAS No. 95, *"Statement of Cash Flows."* SFAS No. 123(R) requires all share-based payments to employees, including grants of employee stock options, to be recognized in the income statement based on their fair values for all periods that begin after June 15, 2005. In April 2005, the Securities and Exchange Commission delayed implementation of SFAS No. 123(R) until the next fiscal year beginning after June 15, 2005. Under SFAS No. 123(R), pro forma disclosure will no longer be an alternative method for reporting stock-based compensation. SFAS No. 123(R) permits public companies to adopt its requirements using one of two methods:

1. A "modified prospective" method in which compensation cost is recognized beginning with the effective date (a) based on the requirements of SFAS No. 123(R) for all share-based payments granted after the effective date and (b) based on the requirements of SFAS No. 123 for all awards granted to employees prior to the effective date of SFAS No. 123(R) that remain unvested on the effective date; or

2. A "modified retrospective" method which includes the requirements of the modified prospective method described above, but also permits entities to restate either (a) all prior periods presented or (b) prior interim periods of the year of adoption for all amounts previously presented in pro forma disclosures under SFAS No. 123.

We will adopt SFAS No. 123(R) on January 1, 2006, as required, and will be incorporating the "modified prospective" method for future periods. The adoption of SFAS No. 123(R)'s fair value method will have a significant impact on our results of operations and our overall financial position.

In December 2005, our Board of Directors approved the acceleration of vesting of unvested stock options held by directors and employees, including officers, which had an exercise price equal to or greater than $9.42. The decision to accelerate these options was made primarily to reduce compensation expense that would be expected to be recorded in future periods following our adoption of SFAS No. 123(R). In addition, the Board of Directors determined that because these options had exercise prices well in excess of the current market value, they were not fully achieving their original objectives of incentive compensation and employee retention. As a result of the acceleration, we have reduced future compensation expense, before any applicable tax, by approximately $20 million, which expense would have been recorded over the next 4 years.

We estimate that the non-cash stock option expense for fiscal year 2006, based upon the current number of unvested stock options outstanding as of December 31, 2005, as well as those we expect to issue in 2006, and utilizing the valuation model and assumptions consistent with our 2005 quarterly filings, is approximately $2 million. However, actual stock based compensation expense for 2006 may be different depending on the assumptions, methodologies and number of unvested stock options used in the actual calculation under SFAS No. 123(R).

Item 7A. Quantitative and Qualitative Disclosures About Market Risk.

Interest Rate Sensitivity

We are subject to interest rate risk on our investment portfolio. We maintain an investment portfolio consisting of United States government and government agency obligations, money market and mutual fund investments, municipal and corporate notes and bonds and asset or mortgage-backed securities. Our portfolio has a current average maturity of less than 12 months, using the stated maturity or reset maturity dates associated with individual maturities as the basis for the calculation.

Our exposure to market risk for changes in interest rates relates to the increase or decrease in the amount of interest income we can earn on our investment portfolio, changes in the market value of investments due to changes in interest rates, the increase or decrease in realized gains and losses on investments and the amount of interest expense we must pay with respect to various outstanding debt instruments. Our risk associated with fluctuating interest expense is limited to capital leases and other short-term debt obligations. Under our current policies, we do not use interest rate derivative instruments to manage exposure to interest rate changes. We ensure the safety and preservation of invested principal funds by limiting default risk, market risk and reinvestment risk. We reduce default risk by investing in investment grade securities. Our investment portfolio includes only marketable securities and instruments with active secondary or resale markets to help ensure portfolio liquidity and we have implemented guidelines limiting the duration of investments. A hypothetical 100 basis point drop in interest rates along the entire interest rate yield curve would not significantly affect the fair value of our interest sensitive financial instruments. At December 31, 2005, our portfolio of available-for-sale investments consisted of approximately $37.7 million of investments maturing within one year and approximately $18.9 million of investments maturing after one year but within 36 months. In addition, we have $515,000 of our long-term investments that are held in a restricted account that collateralizes a letter of credit with a financial institution. Additionally, we generally have the ability to hold our fixed-income investments to maturity and therefore do not expect that our operating results, financial position or cash flows will be affected by a significant amount due to a sudden change in interest rates.

Strategic Investment Risk

In addition to our normal investment portfolio, we have a strategic investment in Parion Sciences, Inc. valued at $200,000 as of December 31, 2005. This investment represents unregistered preferred stock and is subject to higher investment risk than our normal investment portfolio due to the lack of an active resale market for the investment.

Item 8. Financial Statements and Supplementary Data.

The financial statements required to be filed pursuant to this Item 8 are appended to this Annual Report on Form 10-K. A list of the financial statements filed herewith is found at "Index to Financial Statements" on page F-1.

Item 9. Changes in and Disagreements with Accountants on Accounting and Financial Disclosure.

Not applicable.

Item 9A. Controls and Procedures.

Evaluation of Disclosure Controls and Procedures

Our management is responsible for establishing and maintaining an adequate system of internal control over our financial reporting. The design, monitoring and revision of the system of internal accounting controls involves, among other items, management's judgments with respect to the relative cost and expected benefits of specific control measures. The effectiveness of the control system is supported by the selection, retention and training of qualified personnel and an organizational structure that provides an appropriate division of responsibility and formalized procedures. The system of internal accounting controls is periodically reviewed and modified in response to changing conditions. Internal audit consultants regularly monitor the adequacy and effectiveness of internal accounting controls. In addition to the system of internal accounting controls, management maintains corporate policy guidelines that help monitor proper overall business conduct, possible conflicts of interest, compliance with laws and confidentiality of proprietary information. Our Chief Executive Officer and Chief Financial Officer have reviewed and evaluated the effectiveness of our disclosure controls and procedures as of the end of the period covered by this report. Based on that evaluation, the Chief Executive Officer and Chief Financial Officer have concluded that our current disclosure controls and procedures are effective.

Management's Report on Internal Control Over Financial Reporting

Our management is responsible for establishing and maintaining adequate internal control over our financial reporting as defined in Rules 13a-15(f) and 15d-15(f) of the Securities Exchange Act of 1934, and for performing an assessment of the effectiveness of internal control over financial reporting as of December 31, 2005. Internal control over financial reporting is a process designed to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles. Our system of internal control over financial reporting includes those policies and procedures that (i) pertain to the maintenance of records that, in reasonable detail, accurately and fairly reflect the transactions and dispositions of the assets of the company; (ii) provide reasonable assurance that transactions are recorded as necessary to permit preparation of financial statements in accordance with generally accepted accounting principles, and that receipts and expenditures of the company are being made only in accordance with authorizations of management and directors of the company; and (iii) provide reasonable assurance regarding prevention or timely detection of unauthorized acquisition, use, or disposition of the company's assets that could have a material effect on the financial statements.

Management conducted an evaluation of the effectiveness of our internal control over financial reporting based on the framework in *Internal Control — Integrated Framework* issued by the Committee of Sponsoring Organizations of the Treadway Commission (COSO). Based on this evaluation, management, including our principal executive officer and principal financial officer, concluded that our internal control over financial reporting was effective as of December 31, 2005. Management's assessment of the effectiveness of our internal control over financial reporting as of December 31, 2005 has been audited by PricewaterhouseCoopers LLP, an independent registered public accounting firm, as stated in their report included herein.

Changes in Control Over Financial Reporting

There were no changes in our internal control over financial reporting identified in connection with the evaluation of our internal control that occurred during our last fiscal quarter, which have materially affected, or are reasonably likely to materially affect, our internal control over financial reporting.

Audit Committee Oversight

The Audit Committee of the Board of Directors, consisting solely of independent directors, appoints the independent registered public accounting firm and receives and reviews the reports submitted by them. The Audit Committee meets several times during the year with management, the internal auditors and the independent registered public accounting firm to discuss audit activities, internal controls and financial reporting matters. The internal auditors and the independent registered public accounting firm have full and free access to the Audit Committee.

ITEM 9B. OTHER INFORMATION

Not applicable.

PART III

ITEM 10. DIRECTORS AND EXECUTIVE OFFICERS OF THE REGISTRANT

The information required by this item is incorporated by reference to the sections of our definitive proxy statement to be filed with the SEC pursuant to Regulation 14A in connection with the 2006 Annual Meeting (the "Proxy Statement") to be contained under the headings "Election of Directors", "Executive Officers who are not Nominees," and "Section 16(a) Beneficial Ownership Reporting Compliance."

ITEM 11. EXECUTIVE COMPENSATION

The information required by this item is incorporated by reference to the sections of our Proxy Statement to be contained under the headings "Executive Compensation," "Compensation Committee Report," and "Relative Stock Performance."

ITEM 12. SECURITY OWNERSHIP OF CERTAIN BENEFICIAL OWNERS AND MANAGEMENT AND RELATED STOCKHOLDER MATTERS

The information required by this item is incorporated by reference to the section of our Proxy Statement to be contained under the heading "Security Ownership of Certain Beneficial Owners and Management and Related Stockholder Matters."

ITEM 13. CERTAIN RELATIONSHIPS AND RELATED TRANSACTIONS

To the extent applicable, the information required by this item is incorporated by reference to the sections of our Proxy Statement to be contained under the headings "Executive Compensation."

ITEM 14. PRINCIPAL ACCOUNTANT FEES AND SERVICES

The information required by this item is incorporated by reference to the sections of our Proxy Statement to be contained the heading "Audit and Other fees" and related captions.

ITEM 15. EXHIBITS and FINANCIAL STATEMENTS SCHEDULES

(a) The following documents are included as part of this Annual Report on Form 10-K:

1. Financial Statements:

2. All schedules are omitted as the information required is inapplicable or the information is presented in the financial statements.

3. Exhibits:

Exhibit Number	Description
3.1	Restated Certificate of Incorporation (Incorporated by reference to Exhibit 3.2 to the Company's Quarterly Report on Form 10-Q filed on August 9, 2005).
3.2	Certificate of Designations of Series H Preferred Stock of Inspire Pharmaceuticals, Inc. (Incorporated by reference to Exhibit 3.3 to the Company's Annual Report on Form 10-K filed March 7, 2003).
3.3	Amended and Restated Bylaws (Incorporated by reference to Exhibit 3.3 to the Company's Quarterly Report on Form 10-Q filed on August 9, 2005).
4.1	Specimen Common Stock Certificate. (Incorporated by reference to Exhibit 4.1 to the Company's registration statement on Form S-1 (Registration No. 333-31174) which became effective on August 3, 2000).
4.2	Rights Agreement, dated as of October 21, 2002, between the Company and Computershare Trust Company, which includes the form of Certificate of Designation of Series H Preferred Stock of Inspire Pharmaceuticals, Inc. as Exhibit "A", the form of Rights Certificate as Exhibit "B" and the Summary of Rights to Purchase Preferred Stock as Exhibit "C" (Incorporated by reference to Exhibit 4.1 to the Company's Current Report on Form 8-K filed on October 22, 2002).
10.1†	Inspire Pharmaceuticals, Inc. Amended and Restated 1995 Stock Plan, as amended (Incorporated by reference to Exhibit 10.1 to the Company's Current Report on Form 8-K filed on April 21, 2005).
10.2†	Form of Incentive Stock Option. (Incorporated by reference to Exhibit 10.2 to the Company's registration statement on Form S-1 (Registration No. 333-31174) which became effective on August 3, 2000).
10.3†	Form of Non-statutory Stock Option. (Incorporated by reference to Exhibit 10.3 to the Company's registration statement on Form S-1 (Registration No. 333-31174) which became effective on August 3, 2000).
10.4	Lease between Inspire Pharmaceuticals, Inc. and Imperial Center, Limited Partnership regarding Royal Center I, Durham, North Carolina, dated as of May 17, 1995, as amended. (Incorporated by reference to Exhibit 10.8 to the Company's registration statement on Form S-1 (Registration No. 333-31174) which became effective on August 3, 2000).
10.5	Lease Agreement between Inspire Pharmaceuticals, Inc. and Petula Associates Ltd. regarding Royal Center II, Durham, North Carolina, dated as of December 30, 1997. (Incorporated by reference to Exhibit 10.10 to the Company's registration statement on Form S-1 (Registration No. 333-31174) which became effective on August 3, 2000).

Exhibit Number	Description
10.6*	Development, License and Supply Agreement between Inspire Pharmaceuticals, Inc. and Santen Pharmaceutical Co., Ltd., dated as of December 16, 1998. (Incorporated by reference to Exhibit 10.15 to the Company's registration statement on Form S-1 (Registration No. 333-31174) which became effective on August 3, 2000).
10.7†	Employee Confidentiality, Invention Assignment and Non-Compete Agreement between Inspire Pharmaceuticals, Inc. and Donald Kellerman dated February 3, 2000. (Incorporated by reference to Exhibit 10.24 to the Company's registration statement on Form S-1 (Registration No. 333-31174) which became effective on August 3, 2000).
10.8†	Employee Confidentiality, Invention Assignment and Non-Compete Agreement between Inspire Pharmaceuticals, Inc. and Benjamin R. Yerxa dated February 4, 2000. (Incorporated by reference to Exhibit 10.26 to the Company's registration statement on Form S-1 (Registration No. 333-31174) which became effective on August 3, 2000).
10.9†	Employee Confidentiality, Invention Assignment and Non-Compete Agreement between Inspire Pharmaceuticals, Inc. and Christy L. Shaffer dated February 10, 2000. (Incorporated by reference to Exhibit 10.28 to the Company's registration statement on Form S-1 (Registration No. 333-31174) which became effective on August 3, 2000).
10.10†	Employee Confidentiality, Invention Assignment and Non-Compete Agreement between Inspire Pharmaceuticals, Inc. and Richard M. Evans dated February 10, 2000. (Incorporated by reference to Exhibit 10.30 to the Company's registration statement on Form S-1 (Registration No. 333-31174) which became effective on August 3, 2000).
10.11†	Employee Confidentiality, Invention Assignment and Non-Compete Agreement between Inspire Pharmaceuticals, Inc. and Mary Bennett dated February 27, 2001. (Incorporated by reference to Exhibit 10.1 to the Company's Quarterly Report on Form 10-Q filed on May 15, 2001).
10.12†	Employee Confidentiality, Invention Assignment and Non-Compete Agreement between Inspire Pharmaceuticals, Inc. and Joseph Schachle dated April 3, 2001. (Incorporated by reference to Exhibit 10.2 to the Company's Quarterly Report on Form 10-Q filed on August 10, 2001).
10.13*	License, Development and Marketing Agreement between Inspire Pharmaceuticals, Inc. and Allergan, Inc., dated as of June 22, 2001. (Incorporated by reference to Exhibit 10.1 to the Company's Current Report on Form 8-K filed on June 29, 2001).
10.14*	Study Funding Agreement, dated as of October 3, 2002, between Inspire Pharmaceuticals, Inc. and The Cystic Fibrosis Foundation Therapeutics, Inc. (Incorporated by reference to Exhibit 10.1 to the Company's Current Report on Form 8-K filed on October 4, 2002).
10.15	First Amendment to Lease Agreement between Inspire Pharmaceuticals, Inc. and Royal Center Two IC, LLC for Royal Center Two, Durham, North Carolina, dated as of June 28, 2002. (Incorporated by reference to Exhibit 10.31 to the Company's Annual Report on Form 10-K filed March 7, 2003).
10.16	Third Amendment to Lease Agreement between Inspire Pharmaceuticals, Inc. and Royal Center One IC, LLC for Royal Center One, Durham, North Carolina, dated as of June 28, 2002. (Incorporated by reference to Exhibit 10.32 to the Company's Annual Report on Form 10-K filed March 7, 2003).
10.17	Second Amendment To Lease between Inspire Pharmaceuticals, Inc. and Royal Center IC, LLC dated as of June 6, 2003. (Incorporated by reference to Exhibit 10.1 to the Company's Quarterly Report on Form 10-Q filed on August 11, 2003).
10.18†	Form of Inspire Pharmaceuticals, Inc. Employee Stock Option Agreement. (Incorporated by reference to Exhibit 10.2 to the Company's Quarterly Report on Form 10-Q filed on August 11, 2003).
10.19†	Form of Inspire Pharmaceuticals, Inc. Director Non-Statutory Stock Option Agreement. (Incorporated by reference to Exhibit 10.3 to the Company's Quarterly Report on Form 10-Q filed on August 11, 2003).

Exhibit Number	Description
10.20*	First Amendment to License, Development and Marketing Agreement, dated December 8, 2003, between Inspire Pharmaceuticals, Inc. and Allergan, Inc. and Allergan Sales, LLC and Allergan Pharmaceuticals Holdings (Ireland) Ltd. (Incorporated by reference to Exhibit 10.1 to the Company's Current Report on Form 8-K filed on December 9, 2003).
10.21*	Elestat (Epinastine) Co-Promotion Agreement, entered into as of December 8, 2003, by and between Allergan Sales, LLC and Inspire Pharmaceuticals, Inc. (Incorporated by reference to Exhibit 10.1 to the Company's Current Report on Form 8-K filed on July 1, 2004).
10.22†	Employee Confidentiality, Invention Assignment and Non-Compete Agreement between Inspire Pharmaceuticals, Inc. and Thomas R. Staab, II, dated May 16, 2003. (Incorporated by reference to Exhibit 10.35 to the Company's Annual Report on Form 10-K filed March 12, 2004).
10.23	Master Lease Agreement between GE Capital Fleet Services and Inspire Pharmaceuticals, Inc., dated as of November 18, 2003, and related documentation (Incorporated by reference to Exhibit 10.38 to the Company's Annual Report on Form 10-K filed March 12, 2004).
10.24	Master Security Agreement between General Electric Capital Corporation and Inspire Pharmaceuticals, Inc., dated as of November 12, 2003, and related documentation (Incorporated by reference to Exhibit 10.39 to the Company's Annual Report on Form 10-K filed March 12, 2004).
10.25	Underwriting Agreement by and among Inspire Pharmaceuticals, Inc. and Morgan Stanley & Co. Incorporated, Deutsche Bank Securities Inc., Piper Jaffray & Co. and SG Cowen & Co., LLC dated July 26, 2004 (Incorporated by reference to Exhibit 1.1 to the Company's Current Report on Form 8-K filed July 27, 2004).
10.26	Third Amendment to Lease, dated as of August 4, 2004, between Inspire Pharmaceuticals, Inc. and Royal Center IC, LLC (Incorporated by reference to Exhibit 10.1 to the Company's Current Report on Form 8-K filed on August 12, 2004.)
10.27	Fourth Amendment to Lease, dated as of August 4, 2004, between Inspire Pharmaceuticals, Inc. and Royal Center IC, LLC (Incorporated by reference to Exhibit 10.2 to the Company's Current Report on Form 8-K filed on August 12, 2004.)
10.28†	Employee Confidentiality, Invention Assignment and Non-Compete Agreement between the Company and R. Kim Brazzell, dated August 5, 2004 (Incorporated by reference to Exhibit 10.4 to the Company's Quarterly Report on Form 10-Q filed November 9, 2004).
10.29†	Amended and Restated Director Compensation Policy (Incorporated by reference to Exhibit 10.40 to the Company's Annual Report on Form 10-K filed March 11, 2005).
10.30†	Employee Confidentiality, Invention Assignment and Non-Compete Agreement between Inspire Pharmaceuticals, Inc. and Barry G. Pea, dated October 13, 2004. (Incorporated by reference to Exhibit 10.42 to the Company's Annual Report on Form 10-K filed March 11, 2005).
10.31†	Transition Agreement between Inspire Pharmaceuticals, Inc. and Gregory J. Mossinghoff, dated October 28, 2004 (Incorporated by reference to Exhibit 10.43 to the Company's Annual Report on Form 10-K filed March 11, 2005).
10.32**	Exclusive License Agreement between Inspire Pharmaceuticals, Inc. and the Wisconsin Alumni Research Foundation, effective November 2, 2004. (Incorporated by reference to Exhibit 10.44 to the Company's Annual Report on Form 10-K filed March 11, 2005).
10.33	Underwriting Agreement, dated November 10, 2004, by and between Inspire Pharmaceuticals, Inc. and Deutsche Bank Securities Inc. (Incorporated by reference to Exhibit 1.1 to the Company's Current Report on Form 8-K filed November 12, 2004).
10.34†	Inspire Pharmaceuticals, Inc. Change in Control Severance Benefit Plan (Incorporated by reference to Exhibit 10.1 to the Company's Current Report on Form 8-K filed January 31, 2005).

Exhibit Number	Description
10.35†	Agreement regarding change in control, dated as of March 29, 2004, by and between Inspire Pharmaceuticals, Inc. and Christy L. Shaffer (Incorporated by reference to Exhibit 10.2 to the Company's Current Report on Form 8-K filed January 31, 2005).
10.36†	Agreement regarding change in control, dated as of March 29, 2004, by and between Inspire Pharmaceuticals, Inc. and Mary B. Bennett (Incorporated by reference to Exhibit 10.3 to the Company's Current Report on Form 8-K filed January 31, 2005).
10.37†	Agreement regarding change in control, dated as of March 29, 2004, by and between Inspire Pharmaceuticals, Inc. and Richard M. Evans (Incorporated by reference to Exhibit 10.4 to the Company's Current Report on Form 8-K filed January 31, 2005).
10.38†	Agreement regarding change in control, dated as of March 29, 2004, by and between Inspire Pharmaceuticals, Inc. and Donald J. Kellerman (Incorporated by reference to Exhibit 10.5 to the Company's Current Report on Form 8-K filed January 31, 2005).
10.39†	Agreement regarding change in control, dated as of March 29, 2004, by and between Inspire Pharmaceuticals, Inc. and Joseph K. Schachle (Incorporated by reference to Exhibit 10.6 to the Company's Current Report on Form 8-K filed January 31, 2005).
10.40†	Agreement regarding change in control, dated as of March 29, 2004, by and between Inspire Pharmaceuticals, Inc. and Thomas R. Staab, II (Incorporated by reference to Exhibit 10.7 to the Company's Current Report on Form 8-K filed January 31, 2005).
10.41†	Agreement regarding change in control, dated as of March 29, 2004, by and between Inspire Pharmaceuticals, Inc. and Benjamin R. Yerxa (Incorporated by reference to Exhibit 10.8 to the Company's Current Report on Form 8-K filed January 31, 2005).
10.42†	Agreement regarding change in control, dated as of August 2, 2004, by and between Inspire Pharmaceuticals, Inc. and R. Kim Brazzell (Incorporated by reference to Exhibit 10.9 to the Company's Current Report on Form 8-K filed January 31, 2005).
10.43†	Agreement regarding change in control, dated as of October 11, 2004, by and between Inspire Pharmaceuticals, Inc. and Barry G. Pea (Incorporated by reference to Exhibit 10.10 to the Company's Current Report on Form 8-K filed January 31, 2005).
10.44†	Form of Inspire Pharmaceuticals, Inc. Employee Stock Option Agreement (Incorporated by reference to Exhibit 10.56 to the Company's Annual Report on Form 10-K filed March 11, 2005).
10.45†	Inspire Pharmaceuticals, Inc. 2005 Equity Compensation Plan (Incorporated by reference to Exhibit 10.2 to the Company's Current Report on Form 8-K filed on April 21, 2005).
10.46†	Form of Incentive Stock Option Grant Agreement (Incorporated by reference to Exhibit 10.2 to the Company's Current Report on Form 8-K filed on June 16, 2005).
10.47†	Form of Nonqualified Stock Option Grant Agreement (Incorporated by reference to Exhibit 10.3 to the Company's Current Report on Form 8-K filed on June 16, 2005).
10.48†	Form of Director's Nonqualified Stock Option Grant Agreement (Incorporated by reference to Exhibit 10.4 to the Company's Current Report on Form 8-K filed on June 16, 2005).
10.49†	Form of Stock Appreciation Right Grant Agreement (Incorporated by reference to Exhibit 10.5 to the Company's Current Report on Form 8-K filed on June 16, 2005).
10.50†	Form of Stock Award Grant Agreement (Incorporated by reference to Exhibit 10.6 to the Company's Current Report on Form 8-K filed on June 16, 2005).
23.1	Consent of PricewaterhouseCoopers LLP, independent registered public accounting firm.

Exhibit Number	Description
31.1	Certification of the Chief Executive Officer pursuant to Rule 13a-14(a)/15d-14(a) of the Securities Exchange Act of 1934.
31.2	Certification of the Chief Financial Officer pursuant to Rule 13a-14(a)/15d-14(a) of the Securities Exchange Act of 1934.
32.1	Certification of the Chief Executive Officer pursuant to 18 U.S.C. Section 1350, as adopted pursuant to Section 906 of the Sarbanes-Oxley Act of 2002.
32.2	Certification of the Chief Financial Officer pursuant to 18 U.S.C. Section 1350, as adopted pursuant to Section 906 of the Sarbanes-Oxley Act of 2002.

* Confidential treatment has been granted with respect to a portion of this Exhibit.

** Confidential treatment has been requested with respect to a portion of this Exhibit.

† Denotes a management contract or compensation plan or arrangement required to be filed as an exhibit pursuant to Item 15(c) of this Form 10-K.

SIGNATURES

Pursuant to the requirements of Section 13 of 15(d) the Securities Exchange Act of 1934, the registrant has duly caused this report to be signed on its behalf by the undersigned, thereunto duly authorized.

Inspire Pharmaceuticals, Inc.

By: /s/ CHRISTY L. SHAFFER

Christy L. Shaffer
President & Chief Executive Officer and Director

Date: March 16, 2006

Pursuant to the requirements of the Securities Exchange Act of 1934, this report has been signed by the following persons on behalf of the registrant and in the capacities and on the dates indicated.

Signature	Title	Date
/s/ CHRISTY L. SHAFFER **Christy L. Shaffer**	President & Chief Executive Officer (principal executive officer) and Director	March 16, 2006
/s/ THOMAS R. STAAB, II **Thomas R. Staab, II**	Chief Financial Officer & Treasurer (principal financial officer and principal accounting officer)	March 16, 2006
/s/ KENNETH B. LEE, JR. **Kenneth B. Lee, Jr.**	Chairman of the Board of Directors	March 16, 2006
_____ **Kip A. Frey**	Director	
/s/ RICHARD S. KENT **Richard S. Kent**	Director	March 16, 2006
/s/ ALAN F. HOLMER **Alan F. Holmer**	Director	March 16, 2006
/s/ WILLIAM R. RINGO, JR. **William R. Ringo, Jr.**	Director	March 16, 2006

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INSPIRE PHARMACEUTICALS, INC.

INDEX TO FINANCIAL STATEMENTS

REPORT OF INDEPENDENT REGISTERED PUBLIC ACCOUNTING FIRM

To the Board of Directors and Stockholders
of Inspire Pharmaceuticals, Inc.:

We have completed integrated audits of Inspire Pharmaceuticals, Inc.'s 2005 and 2004 financial statements and of its internal control over financial reporting as of December 31, 2005 and an audit of its 2003 financial statements in accordance with the standards of the Public Company Accounting Oversight Board (United States). Our opinions, based on our audits, are presented below.

Financial statements

In our opinion, the financial statements listed in the index appearing under Item 15(a)1 present fairly, in all material respects, the financial position of Inspire Pharmaceuticals, Inc. at December 31, 2005 and 2004, and the results of its operations and its cash flows for each of the three years in the period ended December 31, 2005 in conformity with accounting principles generally accepted in the United States of America. These financial statements are the responsibility of the Company's management. Our responsibility is to express an opinion on these financial statements based on our audits. We conducted our audits of these statements in accordance with the standards of the Public Company Accounting Oversight Board (United States). Those standards require that we plan and perform the audit to obtain reasonable assurance about whether the financial statements are free of material misstatement. An audit of financial statements includes examining, on a test basis, evidence supporting the amounts and disclosures in the financial statements, assessing the accounting principles used and significant estimates made by management, and evaluating the overall financial statement presentation. We believe that our audits provide a reasonable basis for our opinion.

Internal control over financial reporting

Also, in our opinion, management's assessment, included in Management's Report on Internal Control Over Financial Reporting appearing under Item 9A, that the Company maintained effective internal control over financial reporting as of December 31, 2005 based on criteria established in *Internal Control - Integrated Framework* issued by The Committee of Sponsoring Organizations of the Treadway Commission (COSO), is fairly stated, in all material respects, based on those criteria. Furthermore, in our opinion, the Company maintained, in all material respects, effective internal control over financial reporting as of December 31, 2005, based on criteria established in *Internal Control - Integrated Framework* issued by the COSO. The Company's management is responsible for maintaining effective internal control over financial reporting and for its assessment of the effectiveness of internal control over financial reporting. Our responsibility is to express opinions on management's assessment and on the effectiveness of the Company's internal control over financial reporting based on our audit. We conducted our audit of internal control over financial reporting in accordance with the standards of the Public Company Accounting Oversight Board (United States). Those standards require that we plan and perform the audit to obtain reasonable assurance about whether effective internal control over financial reporting was maintained in all material respects. An audit of internal control over financial reporting includes obtaining an understanding of internal control over financial reporting, evaluating management's assessment, testing and evaluating the design and operating effectiveness of internal control, and performing such other procedures as we consider necessary in the circumstances. We believe that our audit provides a reasonable basis for our opinions.

A company's internal control over financial reporting is a process designed to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles. A company's internal control over financial reporting includes those policies and procedures that (i) pertain to the maintenance of records that, in reasonable detail, accurately and fairly reflect the transactions and dispositions of the assets of the company; (ii) provide reasonable assurance that transactions are recorded as necessary to permit preparation of financial statements in accordance

with generally accepted accounting principles, and that receipts and expenditures of the company are being made only in accordance with authorizations of management and directors of the company; and (iii) provide reasonable assurance regarding prevention or timely detection of unauthorized acquisition, use, or disposition of the company's assets that could have a material effect on the financial statements.

Because of its inherent limitations, internal control over financial reporting may not prevent or detect misstatements. Also, projections of any evaluation of effectiveness to future periods are subject to the risk that controls may become inadequate because of changes in conditions, or that the degree of compliance with the policies or procedures may deteriorate.

/s/ PricewaterhouseCoopers LLP
Raleigh, North Carolina
March 16, 2006

INSPIRE PHARMACEUTICALS, INC.

BALANCE SHEETS
(in thousands, except per share amounts)

	December 31, 2005	December 31, 2004
Assets		
Current assets:		
Cash and cash equivalents	$ 65,018	$ 100,320
Investments	37,697	41,426
Receivables from Allergan	4,898	3,501
Prepaid expenses and other receivables	2,432	1,916
Other assets	207	207
Total current assets	110,252	147,370
Property and equipment, net	2,181	2,678
Investments	19,608	15,050
Other assets	405	598
Total assets	$ 132,446	$ 165,696
Liabilities and Stockholders' Equity		
Current liabilities:		
Accounts payable	$ 3,460	$ 4,367
Accrued expenses	6,990	7,955
Notes payable and capital leases	537	489
Total current liabilities	10,987	12,811
Capital leases - noncurrent	855	1,392
Other long-term liabilities	1,915	1,895
Total liabilities	13,757	16,098
Commitments and contingencies (Notes 7-11)		
Stockholders' equity:		
Preferred stock, $0.001 par value, 2,000 shares authorized; no shares issued and outstanding	—	—
Common stock, $0.001 par value, 60,000 shares authorized; 42,211 and 41,845 shares issued and outstanding, respectively	42	42
Additional paid-in capital	321,984	321,189
Accumulated other comprehensive loss	(327)	(470)
Accumulated deficit	(203,010)	(171,163)
Total stockholders' equity	118,689	149,598
Total liabilities and stockholders' equity	$ 132,446	$ 165,696

The accompanying notes are an integral part of these financial statements.

INSPIRE PHARMACEUTICALS, INC.

STATEMENTS OF OPERATIONS
(in thousands, except per share amounts)

	Year Ended December 31,		
	2005	2004	2003
Revenues:			
Revenues from product co-promotion	$ 23,266	$ 11,068	$ —
Collaborative research agreements	—	—	5,200
Total revenue	23,266	11,068	5,200
Operating expenses:			
Research and development	23,566	25,698	27,631
Selling and marketing	23,223	21,848	2,838
General and administrative	12,004	9,041	7,002
Total operating expenses	58,793	56,587	37,471
Loss from operations	(35,527)	(45,519)	(32,271)
Other income (expense):			
Interest income	4,343	1,765	1,262
Interest expense	(147)	(117)	(46)
Loss on investments	(516)	(198)	(340)
Other income, net	3,680	1,450	876
Net loss	$(31,847)	$(44,069)	$(31,395)
Basic and diluted net loss per common share	$ (0.76)	$ (1.25)	$ (1.03)
Weighted average common shares used in computing basic and diluted net loss per common share	42,101	35,261	30,526

The accompanying notes are an integral part of these financial statements.

INSPIRE PHARMACEUTICALS, INC.

STATEMENTS OF CASH FLOWS
(in thousands)

	Year Ended December 31,		
	2005	2004	2003
Cash flows from operating activities:			
Net loss	$ (31,847)	$ (44,069)	$(31,395)
Adjustments to reconcile net loss to net cash used in operating activities:			
Amortization expense	207	207	399
Depreciation of property and equipment	1,126	907	680
Loss/(gain) on disposal of property and equipment	18	(9)	80
Loss on investments	516	198	340
Changes in operating assets and liabilities:			
Receivables from Allergan	(1,397)	(3,501)	—
Prepaid expenses and other receivables	(516)	(527)	(553)
Other assets	(14)	19	(993)
Accounts payable	(907)	364	3,079
Accrued expenses	(945)	6,311	2,602
Deferred revenue	—	—	(2,200)
Net cash used in operating activities	(33,759)	(40,100)	(27,961)
Cash flows from investing activities:			
Purchase of investments	(158,609)	(72,978)	(74,933)
Proceeds from sale of investments	157,407	56,955	38,487
Increase in restricted deposits	—	—	(515)
Purchase of property and equipment	(648)	—	(1,193)
Proceeds from sale of property and equipment	1	61	5
Net cash used in investing activities	(1,849)	(15,962)	(38,149)
Cash flows from financing activities:			
Issuance of common stock, net	795	122,806	73,330
Proceeds from notes payable	—	—	619
Payments on notes payable and capital lease obligations	(489)	(748)	(643)
Net cash provided by financing activities	306	122,058	73,306
(Decrease)/increase in cash and cash equivalents	(35,302)	65,996	7,196
Cash and cash equivalents, beginning of period	100,320	34,324	27,128
Cash and cash equivalents, end of period	$ 65,018	$100,320	$ 34,324

Supplemental disclosure of non-cash investing and financing activities: The Company made cash payments for interest of $145, $119 and $42 for the years ended December 31, 2005, 2004 and 2003, respectively. The Company acquired property and equipment through the assumption of capital lease obligations amounting to $1,545 and $603 during the years ended December 31, 2004 and 2003, respectively.

The accompanying notes are an integral part of these financial statements.

INSPIRE PHARMACEUTICALS, INC.

STATEMENTS OF STOCKHOLDERS' EQUITY
(in thousands)

	Common Stock		Additional Paid-In Capital	Accumulated Deficit	Deferred Compensation	Accumulated Other Comprehensive (Loss)/income	Stockholders' Equity
	Number of Shares	Amount					
Balance at December 31, 2002	25,855	$ 26	$125,069	$ (95,699)	$(399)	$ 1	$ 28,998
Issuance of common stock	5,992	6	73,324	—	—	—	73,330
Amortization of deferred compensation	—	—	—	—	399	—	399
Unrealized loss on investments	—	—	—	—	—	(280)	(280)
Net loss	—	—	—	(31,395)	—	—	(31,395)
Balance at December 31, 2003	31,847	32	198,393	(127,094)	—	(279)	71,052
Issuance of common stock	9,998	10	122,796	—	—	—	122,806
Unrealized loss on investments	—	—	—	—	—	(191)	(191)
Net loss	—	—	—	(44,069)	—	—	(44,069)
Balance at December 31, 2004	41,845	42	321,189	(171,163)	—	(470)	149,598
Issuance of common stock	366	—	795	—	—	—	795
Unrealized gain on investments	—	—	—	—	—	143	143
Net loss	—	—	—	(31,847)	—	—	(31,847)
Balance at December 31, 2005	42,211	$ 42	$321,984	$(203,010)	$ —	$(327)	$118,689

The accompanying notes are an integral part of these financial statements.

1. Organization

Inspire Pharmaceuticals, Inc. (the "Company", or "Inspire") was incorporated in October 1993 and commenced operations in March 1995 following the Company's first substantial financing and licensing of the initial technology from The University of North Carolina at Chapel Hill ("UNC"). Inspire is located in Durham, North Carolina, adjacent to the Research Triangle Park.

Inspire has incurred losses and negative cash flows from operations since inception. The Company expects it has sufficient liquidity to continue its planned operations through 2007, but also expects that additional capital may be required. Continuation of its operations beyond 2007 will require the Company to: (1) obtain product candidate approvals, (2) in-license commercial products, (3) out-license rights to its product candidates, and/or (4) raise additional capital through equity or debt financings or from other sources. The Company began receiving revenue from its co-promotion of *Elestat*® (epinastine HCl ophthalmic solution) 0.05% and *Restasis*® (cyclosporine ophthalmic emulsion) 0.05% in 2004, but will continue to incur operating losses until co-promotion and/or product revenues reach a level sufficient to support ongoing operations. *Elestat*® and *Restasis*® are trademarks owned by Allergan, Inc. ("Allergan").

2. Summary of Significant Accounting Policies and Concentrations of Risk

Use of Estimates

The preparation of financial statements in conformity with generally accepted accounting principles requires management to make estimates and assumptions that affect the reported amounts of assets and liabilities and disclosure of contingent assets and liabilities at the date of the financial statements and the reported amounts of revenues and expenses during the reporting period. Actual results will differ from those estimates.

Cash, Cash Equivalents, Interest and Other Receivables

The Company considers all highly-liquid investments with a maturity of three months or less at the date of purchase to be cash equivalents. The carrying values of cash, cash equivalents, interest and receivables approximate their fair value due to the short-term nature of these items.

Investments

Investments consist primarily of United States government and government agency obligations, money market and mutual fund investments, municipal notes and bonds and asset or mortgage-backed securities. The Company invests in high-credit quality investments in accordance with its investment policy which minimizes the possibility of loss. Investments with original maturities at date of purchase beyond three months and which mature at or less than twelve months from the balance sheet date are classified as current. The Company has investments in auction rate securities which have long-term stated maturities of 20 to 30 years. However, these securities have characteristics of short-term investments due to a rate-setting mechanism and the ability to liquidate these securities through a Dutch auction process that occurs on predetermined intervals of 90 days or less. Accordingly, the Company classifies auction rate securities with these maturity re-set dates within twelve months of the balance sheet date as short-term as this corresponds to management's intention and the liquid nature of these securities. Generally, investments with a maturity beyond twelve months from the balance sheet date are classified as long-term. Investments are considered to be available-for-sale and are carried at fair value with unrealized gains and losses recognized in other comprehensive income (loss). Realized gains and losses are determined using the specific identification method and transactions are recorded on a settlement date basis. Marketable and non-marketable equity investments are evaluated periodically for impairment. If it is determined that a decline of any investment is other than temporary, then the investment would be written down to fair value

and the write-down would be included in the Company's operating results. The Company's investment policy requires it to purchase high-quality marketable securities with a maximum individual maturity of three years and requires an average portfolio maturity of no more than one year.

The Company has an equity investment in Parion Sciences, Inc. ("Parion"), a non-public entity for which its fair value is not readily determinable. For this investment in which the Company does not have significant influence and owns less than 5% of Parion, the investment is carried at cost and is subject to a write-down for impairment whenever events or changes in circumstances indicate that the carrying value may not be recoverable. In 2003, the Company wrote-down the value of its investment in Parion and recognized a loss of $300. As of December 31, 2005, 2004 and 2003, this investment's recorded value was $200.

Property and Equipment

Property and equipment is primarily comprised of furniture, software, laboratory and computer equipment which are recorded at cost and depreciated using the straight-line method over their estimated useful lives which range from three to seven years. Leased property and equipment, which includes certain equipment under capital leases, and leasehold improvements are depreciated over the shorter of the lease period or their estimated useful lives.

The carrying values of property and equipment are periodically reviewed to determine if the facts and circumstances suggest that a potential impairment may have occurred. The review includes a determination of the carrying values of assets based on an analysis of undiscounted cash flows over the remaining depreciation period. If the review indicates that carrying values may not be recoverable, the Company will reduce the carrying values to the estimated fair value.

Restricted Deposits

Restricted deposits consist of cash and cash equivalents which collateralize a letter of credit that is required under the terms of a vehicle fleet financing agreement. Restricted deposits are classified as current or long-term based upon the expected release date of such restriction. The carrying amount of these restricted deposits approximates fair value. At December 31, 2005 and 2004, the Company had $515 of restricted deposits recorded as long-term investments.

Intangible Assets

Costs associated with obtaining and maintaining patents on the Company's product candidates and license initiation and preservation fees, including milestone payments by the Company to its licensors, are evaluated based on the stage of development of the related product candidate and whether the underlying product candidate has an alternative use. Costs of these types incurred for product candidates not yet approved by the U.S. Food and Drug Administration ("FDA") and for which no alternative future use exists are recorded as expense. In the event a product candidate has been approved by the FDA or an alternative future use exists for a product candidate, patent and license costs are capitalized and amortized over the expected life of the related product candidate. License milestone payments to the Company's licensors are recognized when the underlying requirement is met.

Other Assets

During December 2003, the Company recorded a deferred charge associated with an up-front milestone payment made in conjunction with the co-promotion agreement for *Elestat*® executed in December 2003. This

asset is amortized ratably on a straight-line basis through October 2008, the expected commercial exclusivity period for *Elestat®* in the United States. At December 31, 2005 and 2004, the Company had $586 and $793 of deferred charges associated with the up-front milestone, respectively, and $414 in accumulated amortization at December 31, 2005.

Revenue Recognition

The Company recognizes revenue from product co-promotion based on net sales for *Elestat®* and *Restasis®*, as defined in the co-promotion agreements, and as reported to Inspire by its collaborative partner, Allergan. Accordingly, the Company's co-promotion revenue is based upon Allergan's revenue recognition policy, other accounting policies and the underlying terms of the co-promotion agreements. Allergan recognizes revenue from product sales when goods are shipped and title and risk of loss transfers to the customer. The co-promotion agreements provide for gross sales to be reduced by estimates of sales returns, credits and allowances, normal trade and cash discounts, managed care sales rebates and other allocated costs as defined in the agreements, all of which are determined by Allergan and are outside the Company's control. The Company also reduces gross revenues for incentive programs it manages, estimating the proportion of sales that are subject to such incentive programs and reducing revenue appropriately. Under the co-promotion agreement for *Elestat®*, the Company is obligated to meet predetermined minimum annual net sales performance levels. If the annual minimum is not satisfied, the Company records revenues using a reduced percentage of net sales based upon its level of achievement of predetermined calendar year net sales target levels. Amounts contractually due from Allergan in excess of recorded co-promotion revenue are recorded as deferred revenue.

The Company recognizes milestone revenue under its collaborative research and development agreements when Inspire has performed services under such agreements or when Inspire or its collaborative partner has met a contractual milestone triggering a payment to the Company. Non-refundable fees received at the initiation of collaborative agreements for which the Company has an ongoing research and development commitment are deferred and recognized ratably over the period of ongoing research and clinical development commitment. The Company is also entitled to receive milestone payments under its collaborative research and development agreements based upon achievement of development milestones by Inspire or its collaborative partners. The Company recognizes milestone payments as revenues ratably over the period of its research and development commitment. The recognition period begins at the date the milestone is achieved and acknowledged by the collaborative partner, which is generally at the date payment is received from the collaborative partner, and ends on the date that the Company has fulfilled its research and development commitment. This period is based on estimates by management and the progress towards milestones in the Company's collaborative agreements. The estimate is subject to revision as the Company's development efforts progress and the Company gains knowledge regarding required additional development. Revisions in the commitment period are made in the period that the facts related to the change first become known. This may cause the Company's revenue to fluctuate from period to period. No milestone revenue under these agreements has been recognized for the years ended December 31, 2005 and 2004. In the year ended December 31, 2003, the Company recognized $5,200 in revenue from certain contractual milestones.

Research and Development

Research and development expenses include all direct costs and indirect development costs related to the development of the Company's portfolio of product candidates. These expenses include: salaries for research and development personnel, consulting fees, clinical trial costs, sponsored research costs, clinical trial insurance, license and milestone fees and other fees and costs related to the development of product candidates. These costs have been charged to operating expense as incurred. License milestone payments to the Company's licensors are recognized when the underlying requirement is met.

(in thousands, except per share amounts)

Income Taxes

The Company accounts for income taxes using the liability method which requires the recognition of deferred tax assets or liabilities for the temporary differences between financial reporting and tax bases of the Company's assets and liabilities and for tax carryforwards at enacted statutory tax rates in effect for the years in which the differences are expected to reverse. The effect on deferred taxes of a change in tax rates is recognized in income in the period that includes the enactment date. In addition, valuation allowances are established when necessary to reduce deferred tax assets to the amounts expected to be realized. If it is "more likely than not" that some portion, or all of a deferred tax asset will not be realized, a valuation allowance is recorded.

Stock-Based Compensation

The Company accounts for stock option issuances to employees and directors in accordance with the provisions of Accounting Principles Board ("APB") Opinion No. 25 "*Accounting for Stock Issued to Employees*" ("APB No. 25"). The Company does not record compensation expense on options granted to employees with exercise prices equal to fair market value at date of grant. If stock options are granted with an exercise price below the estimated fair value of the Company's common stock, the difference is recorded as deferred compensation. Deferred compensation is amortized on a straight-line basis over the service period of the related stock option. The Company did not recognize any deferred compensation during the years ended December 31, 2005 and 2004. The Company recognized $399 of stock-based compensation expense related to amortization of deferred compensation during the year ended December 31, 2003.

Statement of Financial Accounting Standards ("SFAS") No. 123, "*Accounting for Stock – Based Compensation*," ("SFAS No. 123"), as amended by SFAS No. 148, "*Accounting for Stock-Based Compensation – Transaction and Disclosure*" requires the Company to disclose pro forma information regarding option grants and warrants issued to its employees. In December 2004, the Financial Accounting Standards Board ("FASB") issued SFAS No. 123(R) "*Share-Based Payment*," which requires all share-based payments to employees, including any grants of employee stock options, to be recognized in the income statement based on their fair value for interim or annual reporting periods that begin after June 15, 2005. In April 2005, the SEC delayed implementation of SFAS No. 123(R) until the next fiscal year beginning after June 15, 2005. (See "Recent Accounting Pronouncements" below).

The Company has adopted the disclosure requirements of SFAS No. 123, which requires compensation expense be disclosed based on the fair value of the options granted at the date of the grant. For purposes of pro forma disclosures, the estimated fair value of equity instruments is amortized to expense over their respective vesting period. If the Company had elected to recognize compensation expense based on the fair value of stock-based instruments at the grant date, as prescribed by SFAS No. 123, its pro forma net loss and net loss per common share would have been as follows:

	Year Ended December 31,		
	2005	2004	2003
Net loss - as reported	$(31,847)	$(44,069)	$(31,395)
Compensation expense included in reported net loss	—	—	399
Pro forma adjustment for compensation expense	(29,177)	(9,670)	(5,764)
Net loss —pro forma	$(61,024)	$(53,739)	$(36,760)
Net loss per common share—as reported	$ (0.76)	$ (1.25)	$ (1.03)
Net loss per common share—pro forma	$ (1.45)	$ (1.52)	$ (1.20)

(in thousands, except per share amounts)

In December 2005, the Company's Board of Directors approved the acceleration of vesting of unvested stock options held by directors and employees, including officers, which had an exercise price equal to or greater than $9.42. See Note 8, "Stock Option Plans and Warrants" for a full discussion of the accelerated vesting of certain options. Included in the SFAS No. 123 disclosure reflected in the pro forma table above is approximately $20 million of additional compensation expense in the year ended December 31, 2005 related to the options that were accelerated.

To determine the impact of SFAS No. 123, the fair value of each option grant is estimated on the date of the grant using the Black-Scholes valuation model and the following assumptions:

	Year Ended December 31,		
	2005	2004	2003
Expected dividend yield	0%	0%	0%
Expected stock price volatility	79%	110%	120%
Risk free interest rate	4.02%	3.33%	3.19%
Expected life of options (years)	4.8	5.2	5.0

For the years ended December 31, 2004 and 2003, expected volatility for purposes of determining the fair value of the options granted in those years was based on the Company's historical volatility rate. Beginning with the first quarter of 2005, the Company reevaluated and subsequently adjusted its expected volatility assumptions. The Company has determined that the commercial activities initiated in the second half of 2003 to support the co-promotion of *Elestat*® and *Restasis*® significantly changed the risk profile of the Company. The Company now uses a blended volatility calculation utilizing volatility of peer group companies with similar operations and financial structures in addition to the Company's own historical volatility. The Company believes this blended volatility rate better reflects the expected volatility of its stock over the expected life of the options.

Also in 2005, the Company adopted and began granting options under the 2005 Equity Compensation Plan (the "2005 Plan"). (See Note 8, "Stock Option Plans and Warrants"). Due to lack of historical data with regards to exercise activity under the new 2005 Plan, the Company has adopted a simplified method of calculating the expected life of options for grants made to its employees in accordance with the guidance set forth in the SEC Staff Accounting Bulletin No. 107 ("SAB 107"). For options issued to directors under the new 2005 Plan, the Company uses the contractual term of seven years as the expected life of options. The Company will continue with these assumptions in determining expected life of options under the new 2005 Plan until such time that there is available and adequate historical data. For options issued under the 1995 Plan, the Company utilizes the historical data available regarding employee and director exercise activity to calculate an expected life of the options.

Net Loss Per Common Share

Basic net loss per common share is computed by dividing net loss by the weighted average number of common shares outstanding. Diluted net loss per common share is computed by dividing net loss by the weighted average number of common shares outstanding and dilutive potential common shares then outstanding. Dilutive potential common shares consist of shares issuable upon the exercise of stock options and warrants. The calculation of diluted earnings per share for the years ended December 31, 2005, 2004 and 2003 does not include 695, 1,426 and 1,624, respectively, of potential common shares, as their impact would be antidilutive.

(in thousands, except per share amounts)

Accumulated Other Comprehensive Loss

Accumulated other comprehensive loss is comprised of unrealized gains and losses on marketable securities and is disclosed as a component of stockholders' equity. At December 31, 2005, 2004 and 2003, the Company had $327, $470 and $279 of unrealized loss on its investments, respectively.

Comprehensive loss consists of the following components for the years ended December 31,:

	2005	2004	2003
Net loss	$(31,847)	$(44,069)	$(31,395)
Adjustment for realized losses in net loss	516	198	40
Change in unrealized losses on investments	(373)	(389)	(320)
Total comprehensive loss	$(31,704)	$(44,260)	$(31,675)

Advertising

The Company engages in general and direct-response advertising when promoting and marketing *Elestat®*. These advertising costs are expensed as the costs are incurred. Advertising and product promotion expenses were $4,748, $4,666 and $247 for the years ended December 31, 2005, 2004 and 2003, respectively.

Significant Customers and Risk

All revenues recognized and recorded in 2005, 2004 and 2003 were from one collaborative partner. The Company is entitled to receive co-promotion revenue on "Net Sales" of *Elestat®* and *Restasis®* under the terms of its collaborative agreements with Allergan, and accordingly, all trade receivables are concentrated with Allergan. Due to the nature of these agreements, Allergan has significant influence over the commercial success of these products.

Credit Risk

Cash equivalents and investments are financial instruments which potentially subject the Company to concentration of risk to the extent recorded on the balance sheet. Management of the Company believes it has established guidelines for investment of its excess cash relative to diversification and maturities that maintain safety and liquidity. To minimize the exposure due to adverse shifts in interest rates, the Company currently maintains a portfolio of investments with an average maturity of 12 months or less at December 31, 2005. The Company keeps all of its cash deposits in financial institutions in the United States.

Risks from Third Party Manufacturing Concentration

The Company relies on single source manufacturers for each of its product candidates. In addition, Allergan relies on single source manufacturers for the active pharmaceutical ingredients in *Elestat®* and *Restasis®*, products co-promoted by the Company. Accordingly, delays in the manufacture of any product or product candidate could adversely impact the marketing of the Company's products or the development of the Company's product candidates. Furthermore, Allergan is responsible for the manufacture of both *Elestat®* and *Restasis®*. Therefore, the Company has no control over the manufacture of products for which it will receive revenue and over the overall product supply chain.

Reclassifications

Certain prior year amounts have been reclassified to conform with the current year presentation.

Recent Accounting Pronouncements

In November 2005, the FASB issued FASB Staff Position Nos. FAS 115-1 and FAS 124-1, *"The Meaning of Other-Than-Temporary Impairment and Its Application to Certain Investments"* ("FSP FAS 115-1 and FAS 124-1"). FSP FAS 115-1 and FAS 124-1 address the determination as to when an investment is considered impaired, whether that impairment is other than temporary, and the measurement of an impairment loss. It also includes accounting considerations subsequent to the recognition of an other-than-temporary impairment and requires certain disclosures about unrealized losses that have not been recognized as other-than-temporary impairments. The guidance set forth in FSP FAS 115-1 and FAS 124-1 is effective for reporting periods beginning after December 15, 2005 and the Company has implemented the provisions set forth in FSP FAS 115-1 and FAS 124-1.

In June 2005, the Emerging Issues Task Force reached consensus on Issue No. 05-6, *"Determining the Amortization Period for Leasehold Improvements Purchased after Lease Inception or Acquired in a Business Combination"* ("EITF 05-6"). EITF 05-6 provides guidance on determining the amortization period for leasehold improvements acquired in a business combination or acquired subsequent to lease inception. EITF 05-6 was effective as of June 29, 2005 and the Company complies with the guidance set forth therein.

In May 2005, the FASB issued SFAS No. 154 *"Accounting Changes and Error Corrections"* ("SFAS No. 154"), a replacement of APB Opinion No. 20, *"Accounting Changes"* and FASB Statement No. 3, *"Reporting Accounting Changes in Interim Financial Statements."* SFAS No. 154 provides guidance on the accounting for and reporting of changes in accounting principles and error corrections. SFAS No. 154 applies to all voluntary changes in accounting principles and to changes required by an accounting pronouncement in the unusual instance that the pronouncement does not include specific transition provisions. SFAS No. 154 requires retrospective application to prior periods' financial statements of changes in accounting principles, unless it is impracticable to determine either the period-specific effects or the cumulative effect of the change. SFAS No. 154 is effective for accounting changes and corrections of errors made in fiscal years beginning after December 15, 2005 and the Company complies with the guidance set forth in SFAS No. 154.

In December 2004, the FASB issued SFAS No. 123(R) (revised 2004, or "SFAS No. 123(R)"), *"Share-Based Payment,"* a revision of FASB Statement No. 123 *"Accounting for Stock-Based Compensation."* SFAS No. 123(R) supersedes APB No. 25, and amends SFAS No. 95, *"Statement of Cash Flows."* SFAS No. 123(R) requires all share-based payments to employees, including grants of employee stock options, to be recognized in the income statement based on their fair values for all periods that begin after June 15, 2005. In April 2005, the SEC delayed implementation of SFAS No. 123(R) until the next fiscal year beginning after June 15, 2005. Under SFAS No. 123(R), pro forma disclosure will no longer be an alternative method for reporting stock-based compensation. See "Stock-Based Compensation" above for historic pro forma disclosure. SFAS No. 123(R) permits public companies to adopt its requirements using one of two methods:

1. A "modified prospective" method in which compensation cost is recognized beginning with the effective date (a) based on the requirements of SFAS No. 123(R) for all share-based payments granted after the effective date and (b) based on the requirements of SFAS No. 123 for all awards granted to employees prior to the effective date of SFAS No. 123(R) that remain unvested on the effective date; or

2. A "modified retrospective" method which includes the requirements of the modified prospective method described above, but also permits entities to restate either (a) all prior periods presented or (b) prior interim periods of the year of adoption for all amounts previously presented in pro forma disclosures under SFAS No. 123.

(in thousands, except per share amounts)

The Company will adopt SFAS No. 123(R) on January 1, 2006, as required, and will be incorporating the "modified prospective" method for future periods. The adoption of SFAS No. 123(R)'s fair value method will have a significant impact on the Company's results of operations and its overall financial position. The Company estimates the non-cash stock option expense for 2006, based upon the current number of unvested stock options outstanding as of December 31, 2005 and an estimate of options to be granted during 2006, and calculated using assumptions and a valuation model consistent with previous 2005 quarterly filings as defined in Note 2, "Stock-Based Compensation", is approximately $2 million. However, actual stock based compensation expense for 2006 may be materially different depending on the assumptions, methodologies and number of unvested stock options used in the actual calculation under SFAS No. 123(R).

3. Investments

A summary of the fair market value of investments by classification is as follows:

	December 31,	
	2005	2004
United States Government and agencies	$16,921	$27,432
Auction rate securities	13,600	16,500
Corporate bonds	26,069	11,829
Restricted deposits	515	515
Preferred stock	200	200
	$57,305	$56,476

Maturities of debt securities at fair market value are as follows:

	December 31,	
	2005	2004
Less than one year	$37,943	$41,426
Greater than one year	18,647	14,335
	$56,590	$55,761

The following table shows the gross unrealized losses and fair value of the Company's investments with unrealized losses that are not deemed to be other-than-temporarily impaired, aggregated by length of time that the individual securities have been in a continuous unrealized loss position as of December 31, 2005.

	Less than 12 months		12 months or greater		Total	
	Fair Value	Unrealized Loss	Fair Value	Unrealized Loss	Fair Value	Unrealized Loss
United States Government and agencies	$11,516	$ 77	$ 5,405	$ 95	$16,921	$172
Corporate bonds	13,513	106	8,569	56	22,082	162
Total	$25,029	$183	$13,974	$151	$39,003	$334

The unrealized losses on the Company's investments in U.S. Treasury obligations and direct obligations of U.S. government agencies were caused by an increase in interest rates since acquisition. The unrealized losses on the Company's investments in corporate bonds is primarily due to an increase in interest rates and to a lesser

(in thousands, except per share amounts)

extent, changes in credit rating. The contractual terms of these investments do not permit the issuer to settle the securities at a price less than the amortized cost of the investment. Because the Company has the ability and intent to hold those investments until a recovery of fair value, which may be at maturity, the Company does not consider those investments to be other-than-temporarily impaired at December 31, 2005. Gross realized losses, including impairments, on the Company's "available-for-sale" securities were $516, $198 and $40 for the years ended December 31, 2005, 2004 and 2003, respectively.

4. Property and Equipment

Property and equipment consist of the following:

	Useful Life (Years)	December 31, 2005	December 31, 2004
Equipment	5	$ 4,073	$ 3,807
Leasehold improvements	Lesser of lease term or 5 years	1,452	1,296
Computer hardware	3	1,046	931
Software	5	872	894
Furniture and fixtures	7	771	763
		8,214	7,691
Less—accumulated depreciation		(6,033)	(5,013)
Property and equipment, net		$ 2,181	$ 2,678

Depreciation expense was $1,126, $907 and $680 for the years ended December 31, 2005, 2004 and 2003, respectively. The Company leases certain assets under capital lease agreements. The net book value of assets under capital leases at December 31, 2005 and 2004 was approximately $1,006 and $1,621, respectively. Accumulated amortization for assets under capital leases at December 31, 2005 and 2004 was $1,200 and $583, respectively.

5. Accrued Expenses

Accrued expenses are comprised of the following:

	December 31, 2005	December 31, 2004
Compensation and benefits	$3,164	$4,088
Development costs	1,626	1,555
Selling and marketing costs	883	945
Professional fees	751	235
Duties and taxes	324	225
Other	242	907
	$6,990	$7,955

The carrying value of accrued expenses approximates fair value because of their short-term maturity.

(in thousands, except per share amounts)

6. Income Taxes

The Company had no federal, state or foreign income tax expense for the years ended December 31, 2005, 2004 and 2003.

Significant components of the Company's deferred tax assets and liabilities consist of the following:

	December 31, 2005	December 31, 2004
Current deferred tax assets:		
Accrued expenses	$ 738	$ 731
Compensation related items	267	224
Noncurrent deferred tax assets:		
Domestic net operating loss carryforwards	70,150	59,417
Research and development credits	15,622	10,704
Property, equipment and intangible assets	1,802	1,817
Stock-based compensation	1,688	1,688
Contributions	289	286
Investments	275	—
Total deferred tax assets	90,831	74,867
Valuation allowance for deferred assets	(90,831)	(74,867)
Deferred tax assets	$ —	$ —

At December 31, 2005 and 2004, the Company has provided a full valuation allowance against its net deferred tax assets since realization of these benefits could not be reasonably assured. The valuation allowance has increased $15,964, $19,314 and $13,290 for the years ended December 31, 2005, 2004 and 2003, respectively. The increase in the valuation allowance of $15,964 during the year ended December 31, 2005 resulted primarily from the generation of additional net operating loss carryforwards.

As of December 31, 2005, the Company had federal and state net operating loss carryforwards of $180,583 and $192,185, respectively. The net operating loss carryforwards expire in various amounts starting in 2008 and 2010 for federal and state tax purposes, respectively. The utilization of the federal net operating loss carryforwards may be subject to limitation under the rules regarding a change in stock ownership as determined by the Internal Revenue Code. If the Company's utilization of its net operating loss carryforwards is limited and the Company has taxable income which exceeds the permissible yearly net operating loss carryforward, the Company would incur a federal income tax liability even though its net operating loss carryforwards exceed its taxable income. Additionally, as of December 31, 2005 and 2004, the Company has federal research and development and orphan drug credit carryforwards of $15,622 and $10,704, respectively. The credit carryforwards expire in varying amounts starting in 2010.

(in thousands, except per share amounts)

Taxes computed at the statutory federal income tax rate of 34% are reconciled to the provision for income taxes as follows:

	Year Ended December 31,		
	2005	2004	2003
United States Federal tax at statutory rate	$(10,828)	$(14,984)	$(10,674)
State taxes (net of Federal benefit)	(1,483)	(2,075)	(1,439)
Change in valuation reserve	15,964	19,314	13,290
Research and development credit	(4,918)	(2,184)	(2,044)
Nondeductible expenses due to credits	80	140	335
Other nondeductible expenses	1,185	(211)	532
Provision for income taxes	$ —	$ —	$ —

7. Stockholders' Equity

Sales of Common Stock

On August 2, 2000, the Company's Registration Statement on Form S-1, as amended, registering 6,325 shares of common stock, was declared effective by the Securities and Exchange Commission and permitted the Company to sell shares of common stock in its Initial Public Offering ("IPO"). On August 8, 2000, the Company sold 5,500 shares of common stock at the IPO for $12.00 per share which resulted in proceeds to the Company of $66,000. On September 5, 2000, the Company sold an additional 825 shares of common stock pursuant to the exercise by the underwriters of their over-allotment option with respect to such shares, generating additional gross proceeds of $9,900. Total stock issuance costs related to the IPO and exercise of the over-allotment option were $6,713.

In March 2003, the Company sold 5,750 shares of common stock, including the underwriters' over-allotment allocation, in a public offering at a price of $13.50 per share. The proceeds from the offering, net of applicable issuance costs and expenses, totaled approximately $72,600.

In July 2004, the Company sold 6,900 shares of common stock, including the underwriters' over-allotment allocation, in a public offering at a price of $12.00 per share. The proceeds from the offering, net of applicable issuance costs and expenses, totaled approximately $77,100. In November 2004, the Company sold 2,530 shares of common stock, including the underwriter's over-allotment allocation, in a public offering at a price of $17.10 per share. The proceeds from the offering, net of applicable issuance costs and expenses, totaled approximately $42,300.

The holders of common stock shall be entitled to receive dividends from time to time as may be declared by the Board of Directors, but a common stock dividend has never been declared, nor is a dividend payment expected in the near-term. The holders of shares of common stock are entitled to one vote for each share held with respect to all matters voted on by the stockholders of the Company.

Rights Agreement

In October 2002, the Company entered into a Rights Agreement with Computershare Trust Company. The Rights Agreement provides for a dividend of one preferred stock purchase right for each outstanding share of the Company's common stock. Each right entitles a stockholder, after the rights become exercisable, to buy 1/1,000th of a share of Inspire's Series H Preferred Stock at an exercise price of $50. Each right will become

exercisable following the tenth day after an acquiring person or group acquires, or announces its intention to acquire, 15% or more of the common stock. The Company will be entitled to redeem the rights at $0.001 per right at any time on or before the close of business on the tenth day following acquisition by a person or group of 15% or more of the common stock. Under the Rights Agreement, if a person acquires 15% or more of the common stock without the approval of the Company's Board of Directors, all other stockholders will have the right to purchase securities from Inspire at a price that is less than its fair market value, which would substantially reduce the value of the common stock owned by the acquiring person. As a result, the rights will cause substantial dilution to a person or group that attempts to acquire the Company on terms not approved by the Company's Board of Directors, except pursuant to an offer conditioned on a substantial number of Rights being acquired. The rights should not interfere with any merger or other business combination approved by the Board of Directors since the rights may be redeemed by the Company at the redemption price of $0.001 prior to the occurrence of a distribution date.

8. Stock Option Plans and Warrants

The Company has two stock-based compensation plans:

During 1995, the Company adopted the 1995 Stock Plan, which provided for the grant of up to 1,006 options to directors, officers, employees and consultants. In April 1999, the Plan was amended and restated, and is now the Amended and Restated 1995 Stock Plan, as amended (the "1995 Plan"). The option pool was increased to 5,229 shares on September 28, 2001, to 6,429 shares on December 14, 2001 and to 7,179 on June 10, 2004. As of December 31, 2005, non-qualified stock options and restricted stock may be granted under the 1995 Plan. The Board of Directors, or an appropriate committee of the Board of Directors, shall determine the terms, including exercise price and vesting schedule, of all options at grant date.

In June 2005, the Company adopted the 2005 Plan, which provided for the grant of up to 3,000 options to directors, officers, employees and consultants. Under the 2005 Plan, both incentive and non-qualified stock options, as well as stock appreciation rights and restricted stock, may be granted. The Board of Directors, or an appropriate committee of the Board of Directors, shall determine the terms, including exercise price and vesting schedule, of all grants at grant date, provided that for incentive stock options, such exercise price shall not be less than the fair market value of the Company's stock on the date of grant.

The maximum term for any option grant under the 1995 Plan and the 2005 Plan are ten and seven years, respectively, from the date of the grant. Options granted under both plans generally vest 25% upon completion of one full year from date of grant and on a monthly basis over the following three years. The vesting period typically begins on the date of hire for new employees and on the date of grant for existing employees. At December 31, 2005, there were 620 and 1,844 options available for grant under the 1995 Plan and 2005 Plan, respectively.

In December 2005, the Company's Board of Directors approved the acceleration of vesting of unvested stock options held by directors and employees, including officers, which had an exercise price equal to or greater than $9.42. As a result of the accelerated vesting, options to purchase approximately 2,100 shares of common stock, including 687 shares held by executive officers, which otherwise would have vested on a monthly basis through 2009, became immediately exercisable. The weighted average exercise price of the options subject to the acceleration was $13.02. The decision to accelerate these options was made primarily to reduce compensation expense that would be expected to be recorded in future periods following the Company's adoption of SFAS No. 123(R). In addition, the Board of Directors determined that because these options had exercise prices well in excess of the current market value, they were not fully achieving their original objectives of incentive compensation and employee retention.

(in thousands, except per share amounts)

The following table summarizes the stock option activity for both the 1995 Plan and 2005 Plan:

	Number of Shares	Weighted Average Exercise Price (per share)
Options outstanding, December 31, 2002	3,125	$ 5.99
Granted	1,443	17.39
Exercised	(237)	(2.99)
Forfeited	(118)	(4.96)
Options outstanding, December 31, 2003	4,213	$ 10.09
Granted	1,227	14.45
Exercised	(308)	(4.47)
Forfeited	(218)	(12.57)
Options outstanding, December 31, 2004	4,914	$ 11.42
Granted	1,306	9.13
Exercised	(365)	(1.55)
Forfeited	(298)	(14.31)
Options outstanding, December 31, 2005	5,557	$ 11.38

The following table summarizes information concerning options outstanding at December 31, 2005:

	Options Outstanding	Weighted Average Exercise Price (per share)	Weighted Average Remaining Contractual Life (in Years)	Options Exercisable
Exercise Price range (per share):				
$ 0.12 - $ 3.96	938	$ 2.28	5.4	854
$ 5.08 - $ 8.95	519	7.73	6.6	287
$ 9.42 - $ 9.42	956	9.42	6.5	956
$ 9.44 - $ 12.80	930	12.11	5.8	930
$ 12.91 - $ 15.82	931	14.32	7.5	931
$ 15.83 - $ 20.30	1,283	18.29	8.0	1,283
	5,557	$11.38	6.7	5,241

The weighted average fair value (per share) of options granted during 2005, 2004 and 2003 using the Black-Scholes option-pricing model was $5.90, $11.79 and $14.59, respectively.

9. Collaboration Agreements

On December 16, 1998, the Company entered into a Development, License and Supply Agreement (the "Santen Agreement") with Santen Pharmaceutical Co., Ltd. ("Santen") to complete the development of diquafosol for the therapeutic treatment of ocular surface diseases. Santen received an exclusive license to develop and commercialize diquafosol in Japan, China, South Korea, the Philippines, Thailand, Vietnam, Taiwan, Singapore, Malaysia and Indonesia in the field. The Company retains the right to manufacture and supply diquafosol in bulk drug substance form to Santen.

Under the terms of the Santen agreement, Inspire has received a total of $1,500 in equity and $500 in non-refundable milestone payments. Depending on whether all milestones under the Santen Agreement are met, the Company could receive milestone payments of up to $4,750. As of December 31, 2005, the Company had received $500 of these contingent development milestones. In addition, the Company will receive royalties on net sales of diquafosol by Santen, if any. No milestone payments were received under the Santen Agreement during 2005, 2004 or 2003.

The Santen agreement will terminate when all patents licensed under the agreement have expired. Either Santen or the Company may terminate the agreement if the other materially breaches the agreement. In addition, the Company has the right to terminate the agreement at any time, subject to the coordinating committee's review and arbitration, if the Company determines that Santen has not made reasonably sufficient progress in the development or commercialization of potential products. If Santen breaches the agreement, or if the Company terminates the agreement because Santen has not made sufficient progress, Santen's license will terminate. Santen will provide the Company with all data and information relating to the Company's products, and will assign or permit it to cross-reference all regulatory filings and approvals.

On September 12, 2000, the Company entered into a License Agreement (the "Kirin Agreement") with Kirin Brewery Co., Ltd., Pharmaceutical Division ("Kirin") to complete the development and commercialization of INS316 Diagnostic to aid in the diagnosis of lung cancer. Upon the signing of the Kirin Agreement, the Company received a $2,000 non-refundable up-front license fee which the Company recognized as collaborative research revenue over the term of the Company's research and development commitment. Kirin terminated the agreement in September 2004.

In June 2001, the Company entered into a Joint License, Development and Marketing Agreement with Allergan to develop and commercialize diquafosol. The agreement also provided the Company with a specified royalty on net sales of *Restasis*® and granted the right to co-promote *Restasis*® in the United States. This agreement was amended in December 2003, in connection with the execution of the co-promotion agreement for *Elestat*® to reduce the co-promotion revenue rates due on net sales of *Restasis*®. Under the terms of the amended agreement, Allergan obtained an exclusive license to develop and commercialize diquafosol worldwide, with the exception of Japan and nine other Asian countries covered by Inspire's agreement with Santen. In return, Inspire received an up-front payment of $5,000 in 2001 on execution of the agreement and has received milestone payments of $3,000 in 2002 and $3,000 in 2003. Inspire can also receive up to an additional $28,000 in milestone payments assuming the successful completion of all the remaining milestones. The Company will also receive co-promotion revenue from Allergan on sales of diquafosol, if any, and on worldwide sales of Allergan's *Restasis*®, excluding most larger Asian markets. The Company began receiving co-promotion revenue on net sales of *Restasis*® in April 2004.

The Company is responsible for conducting, in collaboration with Allergan, the Phase 3 clinical trials for diquafosol for dry eye disease needed for potential approval and for filing the U.S. New Drug Application. Allergan is responsible for all other development activities under the agreement, including all development and regulatory activities needed for potential approval outside the United States and in its territories, and for ex-U.S. regulatory submissions, filings, and approvals relating to products. Allergan is responsible for all commercial costs except for the cost of Inspire's sales force in the United States. Allergan is required to use commercially reasonable efforts to conduct development, seek regulatory approvals and market and sell the products. Unless earlier terminated pursuant to other terms of the agreement, the agreement will expire as to each product (*Restasis*® or diquafosol, as the case may be) in each applicable country on the later of (i) the 10th anniversary of the first commercial sale of such product in the applicable country, or (ii) the date on which the sale of such product ceases to be covered by any claim of any applicable Inspire or Allergan patent. The agreement will expire in its entirety upon the expiration of the agreement with respect to all products in all countries in all applicable countries.

In October 2002, the Company entered into a study funding agreement with the Cystic Fibrosis Foundation Therapeutics, Inc. ("CFFT"), whereby the majority of the expenses for one Phase 2 INS37217 Respiratory proof-of-concept clinical trial were funded by the CFFT, but the Company also recorded the corresponding expenses and liabilities as the CFFT incurred these costs. This clinical trial was completed in 2004. If the Company receives FDA approval for INS37217 Respiratory for the treatment of cystic fibrosis, the Company will be obligated to pay a development milestone, and possibly a sales milestone, to the CFFT. The aggregate potential milestones under this agreement are approximately $16,000. As of December 31, 2005, 2004, and 2003, the Company has recorded $1,915, $1,895 and $1,325 of contingent liabilities, respectively, in "Other long-term liabilities" associated with this agreement. If it does not receive FDA approval, the Company will have no financial obligation to the CFFT, including the Phase 2 clinical trial costs the CFFT funded on the Company's behalf.

In December 2003, the Company entered into an agreement with Allergan to co-promote *Elestat*® to ophthalmologists, optometrists and allergists in the United States. *Elestat*® was approved by the FDA in October 2003 for the prevention of itching associated with allergic conjunctivitis. Inspire has the responsibility for selling, promoting and marketing *Elestat*® in the United States and is responsible for paying the associated costs. Allergan records sales of *Elestat*® and is responsible for all other product costs as well as retaining responsibility for all international marketing and selling activities. Allergan also retains the licensing rights relating to promotion of *Elestat*® to U.S. prescribers other than ophthalmologists, optometrists and allergists. However, the Company has a right of first refusal to obtain such rights in the event Allergan decides to engage a third party to undertake such activities. Under the terms of the agreement, Inspire paid Allergan an up-front payment and Allergan pays co-promotion revenue to Inspire on U.S. net sales of *Elestat*®. In the event that a third party is engaged by Allergan to promote *Elestat*® to prescribers outside Inspire's field, Inspire will be paid a proportionate share of U.S. net sales of *Elestat*® based upon filled prescriptions written by ophthalmologists, optometrists and allergists. The Company began receiving co-promotion revenue on sales of *Elestat*® in February 2004. The agreement will be in effect until the earlier of: (i) the approval and launch of the first generic epinastine product; or (ii) the approval and launch of the first over-the-counter epinastine product; in each case after expiration of the patents and market exclusivities for *Elestat*® listed in the FDA's publication "Approved Drug Products with Therapeutic Equivalence Evaluations" (generally known as the "Orange Book"). Either Allergan or Inspire may terminate the agreement in the event of a material breach of the agreement by the other or in the event of the other's insolvency. Allergan can terminate the agreement if the Company fails to meet a defined minimum of net sales in any given year, or upon a change of control where the Company becomes an affiliate of a direct competitor of Allergan's as that term is defined in the agreement. Inspire can terminate the agreement in the event that *Elestat*® is withdrawn from the market for more than ninety days.

10. License Agreements

On March 10, 1995, the Company licensed the rights to the patent for a Method of Treating Lung Disease with Uridine Triphosphates which covers INS316 Diagnostic from UNC. In connection with this license agreement, the Company paid $65 in license initiation fees and issued 298 shares of common stock with an estimated value at the date of issuance of $36 or $0.12 per share and has agreed to potential milestone payments totaling up to $1,000. As of December 31, 2005, the Company has paid $500 of these contingent milestones. During 2004, the INS316 Diagnostic program became inactive. A $10 license preservation payment was made during each of 2005, 2004 and 2003.

On September 1, 1998, the Company licensed the rights to the patents for a Method of Treating Cystic Fibrosis with Dinucleotides, a Method of Treating Bronchitis with Uridine Triphosphates and related compounds, and a Method of Treating Ciliary Dyskinesia with Uridine Triphosphates and related compounds, which cover INS365 Respiratory, from UNC. In connection with this license agreement, the Company paid $15 in license

initiation fees and issued 29 shares of common stock with an estimated value at the date of issuance of $90 or $3.15 per share and has agreed to potential milestone payments totaling $100. During 2002, the INS365 Respiratory program became inactive. The Company has made license preservation payments of $5 in 2005, 2004 and 2003 due to the importance of rights to certain patents covered under the license agreement as they relate to certain of the Company's other active development programs.

In January 2002, the Company licensed the rights to the patent for Composition and Method for Initiating Platelet Aggregation from UNC. In connection with this license agreement, the Company paid $25 in license initiation fees and has agreed to pay milestone payments totaling $50.

If the Company fails to meet performance milestones relating to the timing of regulatory filings or pay the minimum annual payments under its respective UNC licenses, UNC may terminate the applicable license. In connection with the license agreements with UNC, the Company has agreed to pay royalties based on net sales of certain Licensed Products (as defined in the license agreements). The Company enters into sponsored research and development and clinical trial agreements with UNC on an annual basis whereby direct and indirect costs, as defined, are reimbursed by the Company.

On November 2, 2004, the Company executed an exclusive license agreement with the Wisconsin Alumni Research Foundation ("WARF") under which WARF granted the Company an exclusive license under several patents, including three U.S. patents, for use in developing and commercializing new treatments for glaucoma. Under the terms of the agreement, Inspire will design and fund all future research, development, testing, regulatory filings and potential marketing activities related to any product developed from the license. Inspire has paid WARF an upfront licensing payment of $150, and will pay additional contingent payments of up to an aggregate of $1,800 upon the achievement of development milestones, and royalties on sales of any regulatory approved product utilizing the licensed patents. Unless terminated earlier, the agreement will expire on a country-by-country basis upon the expiration of the patents in such country. If the Company fails to pay the minimum annual payments under its license or commits any material breach of any other material covenant, as defined in the agreement, and fails to remedy such breach within 90 days of written notice, WARF may terminate the applicable license.

11. Debt, Commitments and Contingencies

Capital Leases

The Company is obligated under master capital lease agreements for furniture, equipment, and computers, for which the underlying furniture, equipment and computers serve as collateral. The lease terms under these master lease agreements expire 48 months from the date of inception and have interest rates ranging from 8.2% to 9.6%. The carrying value of the Company's capital lease obligations at December 31, 2005 and 2004 approximate their fair value as the interest rates on these obligations approximate rates available in the financial market at such dates.

Operating Leases

The Company has entered into non-cancelable operating leases for its fleet of vehicles, facilities and office equipment that extend through 2008 and are subject to voluntary renewal options. The vehicles are leased under a Master Lease Agreement that allows for individual vehicle leases to be cancelable after one year. The Master Lease Agreement requires the Company to maintain a Standby Letter of Credit in the amount of $515 during the term of the lease. The vehicle Master Lease Agreement also requires that the vehicles under lease serve as collateral for the obligation.

(in thousands, except per share amounts)

Total rent expense for operating leases during 2005, 2004 and 2003 was $1,257, $1,081 and $450, respectively. Future minimum lease payments under capital and non-cancelable operating leases with remaining lease payments as of December 31, 2005 are as follows:

Year Ending December 31,	Capital Leases	Operating Leases
2006	$ 641	$696
2007	641	67
2008	272	22
2009	4	—
Total minimum lease payments	1,558	$785
Less amount representing interest	166	
Present value of net minimum capital lease payments	1,392	
Less current portion of capital lease obligations	537	
Capital lease obligations, excluding current portion	$ 855	

Other Commitments

The Company enters into contractual commitments or purchase arrangements with various clinical research organizations, manufacturers of active pharmaceutical ingredients and/or drug product as well as with others. The amount of these financial commitments which includes both cancelable and non-cancelable arrangements totaled approximately $6,574 at December 31, 2005. In addition, the Company has other contractual commitments outside of drug development under cancelable and non-cancelable arrangements which totaled approximately $826 at December 31, 2005. These amounts may vary depending upon the results of underlying studies, the completion of studies and/or projects and certain other variable components that may yield a result that differs from management's estimate.

Contingencies

As of December 31, 2005, the Company's existing license, collaboration and sponsored research agreements require future cash payments upon the achievement of future milestones. In the aggregate, these agreements require payments of up to $13,850 assuming the achievement of all development milestones and up to $4,000 assuming the achievement of all sales milestones. Amounts payable by the Company under these agreements are uncertain and are contingent on a number of factors, including the progress of its discovery and drug development programs, its ability to obtain regulatory approvals, and the commercial success of its approved products. In addition, there is approximately $600 of development milestones under existing license agreements related to currently inactive development programs and management believes it is unlikely the milestones will be achieved and payments made. The Company is also obligated to pay royalties on net sales, if any, of certain product candidates currently in its portfolio. Some of the Company's license agreements require minimum annual license preservation fees.

Litigation

On February 15, 2005, a purported class action complaint was filed in the United States District Court for the Middle District of North Carolina by Mirco Investors, LLC on behalf of itself and all other similarly situated purchasers against the Company and certain of its senior officers. The complaint alleges violations of sections 10(b) and 20(a) of the Securities Exchange Act of 1934, and Securities and Exchange Commission Rule 10b-5, and focuses on statements that are claimed to be false and misleading regarding a Phase 3 clinical trial of the

(in thousands, except per share amounts)

Company's dry eye product candidate, diquafosol. The plaintiffs seek unspecified damages on behalf of a purported class of purchasers of the Company's securities during the period from June 2, 2004 through February 8, 2005. Four additional proposed stockholder class actions were filed in the same court, making substantially the same allegations against the same parties as defendants and seeking certification of the same class of purchasers. These individual lawsuits have now been consolidated into a single civil action and a lead plaintiff appointed. The Company anticipates that an amended consolidated complaint may be filed in March 2006. The Company intends to defend the litigation vigorously. As with any legal proceeding, the Company cannot predict with certainty the eventual outcome of these pending lawsuits, nor can a reasonable estimate of the amounts of loss, if any, be made.

SEC Investigation

On August 30, 2005, the Securities and Exchange Commission notified the Company that it is conducting a formal, nonpublic investigation, which the Company believes relates to trading in its securities surrounding the February 9, 2005 announcement of the results of a Phase 3 clinical trial of the Company's dry eye product candidate, diquafosol, as well as its disclosures regarding this Phase 3 clinical trial. The Company is continuing to cooperate with the Securities and Exchange Commission's ongoing investigation. The Company cannot predict with certainty the eventual outcome of this investigation, nor can a reasonable estimate of the costs that might result from the SEC's investigation be made.

12. Employee Benefit Plan

The Company has adopted a 401(k) Profit Sharing Plan ("the 401(k) Plan") covering all qualified employees on August 1, 1995. Participants may elect a salary reduction of 1% or more up to the IRS allowed maximum as a tax-deferred contribution to the 401(k) Plan. The 401(k) Plan permits discretionary employer contributions. If employer discretionary contributions are implemented, participants will begin vesting 100% immediately in such contributions. In 2005, 2004 and 2003, the Company elected a safe harbor contribution at 3.0% of annual compensation. These safe harbor contributions total $578, $455 and $231 for the years ended December 31, 2005, 2004 and 2003, respectively.

13. Co-promotion Revenue by Product Line

The Company operates its business as one business segment. The Company derives all of its co-promotion revenue for *Elestat®* from product sales in the United States. Approximately 98% of co-promotion revenue for *Restasis®* came from product sales in the United States in both 2005 and 2004.

	Year ended December 31,		
	2005	2004	2003
Elestat®	$16,790	$ 9,586	$ —
Restasis®	6,476	1,482	—
	$23,266	$11,068	$ —

(in thousands, except per share amounts)

14. Quarterly Financial Data (unaudited)

2005	First	Second	Third	Fourth	Total
Revenue	$ 1,851	$ 9,607	$ 6,562	$ 5,246	$ 23,266
Net loss available to common stockholders	(13,342)	(4,656)	(6,752)	(7,097)	(31,847)
Net loss per common share—basic and diluted	$ (0.32)	$ (0.11)	$ (0.16)	$ (0.17)	$ (0.76)

2004	First	Second	Third	Fourth	Total
Revenue	$ 609	$ 2,948	$ 3,791	$ 3,720	$ 11,068
Net loss available to common stockholders	(12,428)	(9,692)	(10,150)	(11,799)	(44,069)
Net loss per common share—basic and diluted	$ (0.39)	$ (0.30)	$ (0.28)	$ (0.29)	$ (1.25)

15. Subsequent Events

On February 17, 2006, the Company entered into a development and license agreement with Boehringer Ingelheim International GmbH ("Boehringer Ingelheim"). The agreement grants Inspire certain exclusive rights to develop and market an intranasal dosage form of epinastine, in the United States and Canada, for the treatment or prevention of rhinitis.

Under the terms of the agreement, Inspire will have full responsibility for the intranasal epinastine development program and regulatory filings in the United States and Canada. Upon the receipt of appropriate regulatory approvals for an intranasal epinastine product, Inspire will be responsible for the commercialization of such product in the United States and Canada. Boehringer Ingelheim has retained the rights to develop and commercialize intranasal epinastine outside the United States and Canada, based on any future results of Inspire's intranasal epinastine development program.

In addition to funding all development activities under the terms of the agreement, Inspire is required to pay Boehringer Ingelheim (a) an upfront license fee of $2,500, and (b) high single digit royalties on net sales of an intranasal epinastine product in the United States and Canada. If Boehringer Ingelheim commercializes Inspire's intranasal epinastine product outside of the United States and Canada, it will be obligated to pay royalties to Inspire on net sales of the product.

In general, the exclusive license granted to Inspire will expire and convert into a perpetual, fully paid-up, non-exclusive license on December 31, 2022. Certain other rights and royalty obligations will continue beyond such date. For a period of five (5) years following December 31, 2022, Boehringer Ingelheim shall have the right, but not the obligation, to switch a product developed under the agreement from a prescription product to an over-the-counter, or OTC, product. Following such a switch, Boehringer Ingelheim will have the right to commercialize such product in the United States and/or Canada. In connection with such a switch, Boehringer Ingelheim will be required to pay an OTC switch payment and ongoing royalties to Inspire.

Exhibit Index

Exhibit Number	Description
3.1	Restated Certificate of Incorporation (Incorporated by reference to Exhibit 3.2 to the Company's Quarterly Report on Form 10-Q filed on August 9, 2005).
3.2	Certificate of Designations of Series H Preferred Stock of Inspire Pharmaceuticals, Inc. (Incorporated by reference to Exhibit 3.3 to the Company's Annual Report on Form 10-K filed March 7, 2003).
3.3	Amended and Restated Bylaws (Incorporated by reference to Exhibit 3.3 to the Company's Quarterly Report on Form 10-Q filed on August 9, 2005).
4.1	Specimen Common Stock Certificate. (Incorporated by reference to Exhibit 4.1 to the Company's registration statement on Form S-1 (Registration No. 333-31174) which became effective on August 3, 2000).
4.2	Rights Agreement, dated as of October 21, 2002, between the Company and Computershare Trust Company, which includes the form of Certificate of Designation of Series H Preferred Stock of Inspire Pharmaceuticals, Inc. as Exhibit "A", the form of Rights Certificate as Exhibit "B" and the Summary of Rights to Purchase Preferred Stock as Exhibit "C" (Incorporated by reference to Exhibit 4.1 to the Company's Current Report on Form 8-K filed on October 22, 2002).
10.1†	Inspire Pharmaceuticals, Inc. Amended and Restated 1995 Stock Plan, as amended (Incorporated by reference to Exhibit 10.1 to the Company's Current Report on Form 8-K filed on April 21, 2005).
10.2†	Form of Incentive Stock Option. (Incorporated by reference to Exhibit 10.2 to the Company's registration statement on Form S-1 (Registration No. 333-31174) which became effective on August 3, 2000).
10.3†	Form of Non-statutory Stock Option. (Incorporated by reference to Exhibit 10.3 to the Company's registration statement on Form S-1 (Registration No. 333-31174) which became effective on August 3, 2000).
10.4	Lease between Inspire Pharmaceuticals, Inc. and Imperial Center, Limited Partnership regarding Royal Center I, Durham, North Carolina, dated as of May 17, 1995, as amended. (Incorporated by reference to Exhibit 10.8 to the Company's registration statement on Form S-1 (Registration No. 333-31174) which became effective on August 3, 2000).
10.5	Lease Agreement between Inspire Pharmaceuticals, Inc. and Petula Associates Ltd. regarding Royal Center II, Durham, North Carolina, dated as of December 30, 1997. (Incorporated by reference to Exhibit 10.10 to the Company's registration statement on Form S-1 (Registration No. 333-31174) which became effective on August 3, 2000).
10.6*	Development, License and Supply Agreement between Inspire Pharmaceuticals, Inc. and Santen Pharmaceutical Co., Ltd., dated as of December 16, 1998. (Incorporated by reference to Exhibit 10.15 to the Company's registration statement on Form S-1 (Registration No. 333-31174) which became effective on August 3, 2000).
10.7†	Employee Confidentiality, Invention Assignment and Non-Compete Agreement between Inspire Pharmaceuticals, Inc. and Donald Kellerman dated February 3, 2000. (Incorporated by reference to Exhibit 10.24 to the Company's registration statement on Form S-1 (Registration No. 333-31174) which became effective on August 3, 2000).
10.8†	Employee Confidentiality, Invention Assignment and Non-Compete Agreement between Inspire Pharmaceuticals, Inc. and Benjamin R. Yerxa dated February 4, 2000. (Incorporated by reference to Exhibit 10.26 to the Company's registration statement on Form S-1 (Registration No. 333-31174) which became effective on August 3, 2000).
10.9†	Employee Confidentiality, Invention Assignment and Non-Compete Agreement between Inspire Pharmaceuticals, Inc. and Christy L. Shaffer dated February 10, 2000. (Incorporated by reference to Exhibit 10.28 to the Company's registration statement on Form S-1 (Registration No. 333-31174) which became effective on August 3, 2000).

Exhibit Number	Description
10.10†	Employee Confidentiality, Invention Assignment and Non-Compete Agreement between Inspire Pharmaceuticals, Inc. and Richard M. Evans dated February 10, 2000. (Incorporated by reference to Exhibit 10.30 to the Company's registration statement on Form S-1 (Registration No. 333-31174) which became effective on August 3, 2000).
10.11†	Employee Confidentiality, Invention Assignment and Non-Compete Agreement between Inspire Pharmaceuticals, Inc. and Mary Bennett dated February 27, 2001. (Incorporated by reference to Exhibit 10.1 to the Company's Quarterly Report on Form 10-Q filed on May 15, 2001).
10.12†	Employee Confidentiality, Invention Assignment and Non-Compete Agreement between Inspire Pharmaceuticals, Inc. and Joseph Schachle dated April 3, 2001. (Incorporated by reference to Exhibit 10.2 to the Company's Quarterly Report on Form 10-Q filed on August 10, 2001).
10.13*	License, Development and Marketing Agreement between Inspire Pharmaceuticals, Inc. and Allergan, Inc., dated as of June 22, 2001. (Incorporated by reference to Exhibit 10.1 to the Company's Current Report on Form 8-K filed on June 29, 2001).
10.14*	Study Funding Agreement, dated as of October 3, 2002, between Inspire Pharmaceuticals, Inc. and The Cystic Fibrosis Foundation Therapeutics, Inc. (Incorporated by reference to Exhibit 10.1 to the Company's Current Report on Form 8-K filed on October 4, 2002).
10.15	First Amendment to Lease Agreement between Inspire Pharmaceuticals, Inc. and Royal Center Two IC, LLC for Royal Center Two, Durham, North Carolina, dated as of June 28, 2002. (Incorporated by reference to Exhibit 10.31 to the Company's Annual Report on Form 10-K filed March 7, 2003).
10.16	Third Amendment to Lease Agreement between Inspire Pharmaceuticals, Inc. and Royal Center One IC, LLC for Royal Center One, Durham, North Carolina, dated as of June 28, 2002. (Incorporated by reference to Exhibit 10.32 to the Company's Annual Report on Form 10-K filed March 7, 2003).
10.17	Second Amendment To Lease between Inspire Pharmaceuticals, Inc. and Royal Center IC, LLC dated as of June 6, 2003. (Incorporated by reference to Exhibit 10.1 to the Company's Quarterly Report on Form 10-Q filed on August 11, 2003).
10.18†	Form of Inspire Pharmaceuticals, Inc. Employee Stock Option Agreement. (Incorporated by reference to Exhibit 10.2 to the Company's Quarterly Report on Form 10-Q filed on August 11, 2003).
10.19†	Form of Inspire Pharmaceuticals, Inc. Director Non-Statutory Stock Option Agreement. (Incorporated by reference to Exhibit 10.3 to the Company's Quarterly Report on Form 10-Q filed on August 11, 2003).
10.20*	First Amendment to License, Development and Marketing Agreement, dated December 8, 2003, between Inspire Pharmaceuticals, Inc. and Allergan, Inc. and Allergan Sales, LLC and Allergan Pharmaceuticals Holdings (Ireland) Ltd. (Incorporated by reference to Exhibit 10.1 to the Company's Current Report on Form 8-K filed on December 9, 2003).
10.21*	Elestat (Epinastine) Co-Promotion Agreement, entered into as of December 8, 2003, by and between Allergan Sales, LLC and Inspire Pharmaceuticals, Inc. (Incorporated by reference to Exhibit 10.1 to the Company's Current Report on Form 8-K filed on July 1, 2004).
10.22†	Employee Confidentiality, Invention Assignment and Non-Compete Agreement between Inspire Pharmaceuticals, Inc. and Thomas R. Staab, II, dated May 16, 2003. (Incorporated by reference to Exhibit 10.35 to the Company's Annual Report on Form 10-K filed March 12, 2004).
10.23	Master Lease Agreement between GE Capital Fleet Services and Inspire Pharmaceuticals, Inc., dated as of November 18, 2003, and related documentation (Incorporated by reference to Exhibit 10.38 to the Company's Annual Report on Form 10-K filed March 12, 2004).

Exhibit Number	Description
10.24	Master Security Agreement between General Electric Capital Corporation and Inspire Pharmaceuticals, Inc., dated as of November 12, 2003, and related documentation (Incorporated by reference to Exhibit 10.39 to the Company's Annual Report on Form 10-K filed March 12, 2004).
10.25	Underwriting Agreement by and among Inspire Pharmaceuticals, Inc. and Morgan Stanley & Co. Incorporated, Deutsche Bank Securities Inc., Piper Jaffray & Co. and SG Cowen & Co., LLC dated July 26, 2004 (Incorporated by reference to Exhibit 1.1 to the Company's Current Report on Form 8-K filed July 27, 2004).
10.26	Third Amendment to Lease, dated as of August 4, 2004, between Inspire Pharmaceuticals, Inc. and Royal Center IC, LLC (Incorporated by reference to Exhibit 10.1 to the Company's Current Report on Form 8-K filed on August 12, 2004.)
10.27	Fourth Amendment to Lease, dated as of August 4, 2004, between Inspire Pharmaceuticals, Inc. and Royal Center IC, LLC (Incorporated by reference to Exhibit 10.2 to the Company's Current Report on Form 8-K filed on August 12, 2004.)
10.28†	Employee Confidentiality, Invention Assignment and Non-Compete Agreement between the Company and R. Kim Brazzell, dated August 5, 2004 (Incorporated by reference to Exhibit 10.4 to the Company's Quarterly Report on Form 10-Q filed November 9, 2004).
10.29†	Amended and Restated Director Compensation Policy (Incorporated by reference to Exhibit 10.40 to the Company's Annual Report on Form 10-K filed March 11, 2005).
10.30†	Employee Confidentiality, Invention Assignment and Non-Compete Agreement between Inspire Pharmaceuticals, Inc. and Barry G. Pea, dated October 13, 2004. (Incorporated by reference to Exhibit 10.42 to the Company's Annual Report on Form 10-K filed March 11, 2005).
10.31†	Transition Agreement between Inspire Pharmaceuticals, Inc. and Gregory J. Mossinghoff, dated October 28, 2004 (Incorporated by reference to Exhibit 10.43 to the Company's Annual Report on Form 10-K filed March 11, 2005).
10.32**	Exclusive License Agreement between Inspire Pharmaceuticals, Inc. and the Wisconsin Alumni Research Foundation, effective November 2, 2004. (Incorporated by reference to Exhibit 10.44 to the Company's Annual Report on Form 10-K filed March 11, 2005).
10.33	Underwriting Agreement, dated November 10, 2004, by and between Inspire Pharmaceuticals, Inc. and Deutsche Bank Securities Inc. (Incorporated by reference to Exhibit 1.1 to the Company's Current Report on Form 8-K filed November 12, 2004).
10.34†	Inspire Pharmaceuticals, Inc. Change in Control Severance Benefit Plan (Incorporated by reference to Exhibit 10.1 to the Company's Current Report on Form 8-K filed January 31, 2005).
10.35†	Agreement regarding change in control, dated as of March 29, 2004, by and between Inspire Pharmaceuticals, Inc. and Christy L. Shaffer (Incorporated by reference to Exhibit 10.2 to the Company's Current Report on Form 8-K filed January 31, 2005).
10.36†	Agreement regarding change in control, dated as of March 29, 2004, by and between Inspire Pharmaceuticals, Inc. and Mary B. Bennett (Incorporated by reference to Exhibit 10.3 to the Company's Current Report on Form 8-K filed January 31, 2005).
10.37†	Agreement regarding change in control, dated as of March 29, 2004, by and between Inspire Pharmaceuticals, Inc. and Richard M. Evans (Incorporated by reference to Exhibit 10.4 to the Company's Current Report on Form 8-K filed January 31, 2005).
10.38†	Agreement regarding change in control, dated as of March 29, 2004, by and between Inspire Pharmaceuticals, Inc. and Donald J. Kellerman (Incorporated by reference to Exhibit 10.5 to the Company's Current Report on Form 8-K filed January 31, 2005).

Exhibit Number	Description
10.39†	Agreement regarding change in control, dated as of March 29, 2004, by and between Inspire Pharmaceuticals, Inc. and Joseph K. Schachle (Incorporated by reference to Exhibit 10.6 to the Company's Current Report on Form 8-K filed January 31, 2005).
10.40†	Agreement regarding change in control, dated as of March 29, 2004, by and between Inspire Pharmaceuticals, Inc. and Thomas R. Staab, II (Incorporated by reference to Exhibit 10.7 to the Company's Current Report on Form 8-K filed January 31, 2005).
10.41†	Agreement regarding change in control, dated as of March 29, 2004, by and between Inspire Pharmaceuticals, Inc. and Benjamin R. Yerxa (Incorporated by reference to Exhibit 10.8 to the Company's Current Report on Form 8-K filed January 31, 2005).
10.42†	Agreement regarding change in control, dated as of August 2, 2004, by and between Inspire Pharmaceuticals, Inc. and R. Kim Brazzell (Incorporated by reference to Exhibit 10.9 to the Company's Current Report on Form 8-K filed January 31, 2005).
10.43†	Agreement regarding change in control, dated as of October 11, 2004, by and between Inspire Pharmaceuticals, Inc. and Barry G. Pea (Incorporated by reference to Exhibit 10.10 to the Company's Current Report on Form 8-K filed January 31, 2005).
10.44†	Form of Inspire Pharmaceuticals, Inc. Employee Stock Option Agreement (Incorporated by reference to Exhibit 10.56 to the Company's Annual Report on Form 10-K filed March 11, 2005).
10.45†	Inspire Pharmaceuticals, Inc. 2005 Equity Compensation Plan (Incorporated by reference to Exhibit 10.2 to the Company's Current Report on Form 8-K filed on April 21, 2005).
10.46†	Form of Incentive Stock Option Grant Agreement (Incorporated by reference to Exhibit 10.2 to the Company's Current Report on Form 8-K filed on June 16, 2005).
10.47†	Form of Nonqualified Stock Option Grant Agreement (Incorporated by reference to Exhibit 10.3 to the Company's Current Report on Form 8-K filed on June 16, 2005).
10.48†	Form of Director's Nonqualified Stock Option Grant Agreement (Incorporated by reference to Exhibit 10.4 to the Company's Current Report on Form 8-K filed on June 16, 2005).
10.49†	Form of Stock Appreciation Right Grant Agreement (Incorporated by reference to Exhibit 10.5 to the Company's Current Report on Form 8-K filed on June 16, 2005).
10.50†	Form of Stock Award Grant Agreement (Incorporated by reference to Exhibit 10.6 to the Company's Current Report on Form 8-K filed on June 16, 2005).
23.1	Consent of PricewaterhouseCoopers LLP, independent registered public accounting firm.
31.1	Certification of the Chief Executive Officer pursuant to Rule 13a-14(a)/15d-14(a) of the Securities Exchange Act of 1934.
31.2	Certification of the Chief Financial Officer pursuant to Rule 13a-14(a)/15d-14(a) of the Securities Exchange Act of 1934.
32.1	Certification of the Chief Executive Officer pursuant to 18 U.S.C. Section 1350, as adopted pursuant to Section 906 of the Sarbanes-Oxley Act of 2002.
32.2	Certification of the Chief Financial Officer pursuant to 18 U.S.C. Section 1350, as adopted pursuant to Section 906 of the Sarbanes-Oxley Act of 2002.

* Confidential treatment has been granted with respect to a portion of this Exhibit.

** Confidential treatment has been requested with respect to a portion of this Exhibit.

† Denotes a management contract or compensation plan or arrangement required to be filed as an exhibit pursuant to Item 15(c) of this Form 10-K.

Exhibit 23.1

Consent of Independent Registered Public Accounting Firm

We hereby consent to the incorporation by reference in the Registration Statement on Form S-3 (333-114517) and Form S-8 (333-56360) of Inspire Pharmaceuticals, Inc. of our report dated March 16, 2006 relating to the financial statements, management's assessment of the effectiveness of internal control over financial reporting and the effectiveness of internal control over financial reporting, which appears in this Annual Report on Form 10-K.

/s/ PricewaterhouseCoopers LLP

Raleigh, North Carolina
March 16, 2006

Exhibit 31.1

INSPIRE PHARMACEUTICALS, INC.

CERTIFICATIONS

I, Christy L. Shaffer, certify that:

1. I have reviewed this annual report on Form 10-K of Inspire Pharmaceuticals, Inc.;

2. Based on my knowledge, this report does not contain any untrue statement of a material fact or omit to state a material fact necessary to make the statements made, in light of the circumstances under which such statements were made, not misleading with respect to the period covered by this report;

3. Based on my knowledge, the financial statements, and other financial information included in this report, fairly present in all material respects the financial condition, results of operations and cash flows of the registrant as of, and for, the periods presented in this report;

4. The registrant's other certifying officer(s) and I are responsible for establishing and maintaining disclosure controls and procedures (as defined in Exchange Act Rules 13a-15(e) and 15d-15(e)) and internal control over financial reporting (as defined in Exchange Act Rules 13a-15(f) and 15d-15(f)) for the registrant and have:

a) Designed such disclosure controls and procedures, or caused such disclosure controls and procedures to be designed under our supervision, to ensure that material information relating to the registrant, including its consolidated subsidiaries, is made known to us by others within those entities, particularly during the period in which this report is being prepared;

b) Designed such internal control over financial reporting, or caused such internal control over financial reporting to be designed under our supervision, to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles;

c) Evaluated the effectiveness of the registrant's disclosure controls and procedures and presented in this report our conclusions about the effectiveness of the disclosure controls and procedures, as of the end of the period covered by this report based on such evaluation; and

d) Disclosed in this report any change in the registrant's internal control over financial reporting that occurred during the registrant's most recent fiscal quarter (the registrant's fourth fiscal quarter in the case of an annual report) that has materially affected, or is reasonably likely to materially affect, the registrant's internal control over financial reporting; and

5. The registrant's other certifying officer(s) and I have disclosed, based on our most recent evaluation of internal control over financial reporting, to the registrant's auditors and the audit committee of the registrant's board of directors (or persons performing the equivalent functions):

a) All significant deficiencies and material weaknesses in the design or operation of internal control over financial reporting which are reasonably likely to adversely affect the registrant's ability to record, process, summarize and report financial information; and

b) Any fraud, whether or not material, that involves management or other employees who have a significant role in the registrant's internal control over financial reporting.

Date: March 16, 2006

/s/ CHRISTY L. SHAFFER

Christy L. Shaffer
President & Chief Executive Officer
(principal executive officer)

Exhibit 31.2

INSPIRE PHARMACEUTICALS, INC.

CERTIFICATIONS

I, Thomas R. Staab, II, certify that:

1. I have reviewed this annual report on Form 10-K of Inspire Pharmaceuticals, Inc.;

2. Based on my knowledge, this report does not contain any untrue statement of a material fact or omit to state a material fact necessary to make the statements made, in light of the circumstances under which such statements were made, not misleading with respect to the period covered by this report;

3. Based on my knowledge, the financial statements, and other financial information included in this report, fairly present in all material respects the financial condition, results of operations and cash flows of the registrant as of, and for, the periods presented in this report;

4. The registrant's other certifying officer(s) and I are responsible for establishing and maintaining disclosure controls and procedures (as defined in Exchange Act Rules 13a-15(e) and 15d-15(e)) and internal control over financial reporting (as defined in Exchange Act Rules 13a-15(f) and 15d-15(f)) for the registrant and have:

a) Designed such disclosure controls and procedures, or caused such disclosure controls and procedures to be designed under our supervision, to ensure that material information relating to the registrant, including its consolidated subsidiaries, is made known to us by others within those entities, particularly during the period in which this report is being prepared;

b) Designed such internal control over financial reporting, or caused such internal control over financial reporting to be designed under our supervision, to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles;

c) Evaluated the effectiveness of the registrant's disclosure controls and procedures and presented in this report our conclusions about the effectiveness of the disclosure controls and procedures, as of the end of the period covered by this report based on such evaluation; and

d) Disclosed in this report any change in the registrant's internal control over financial reporting that occurred during the registrant's most recent fiscal quarter (the registrant's fourth fiscal quarter in the case of an annual report) that has materially affected, or is reasonably likely to materially affect, the registrant's internal control over financial reporting; and

5. The registrant's other certifying officer(s) and I have disclosed, based on our most recent evaluation of internal control over financial reporting, to the registrant's auditors and the audit committee of the registrant's board of directors (or persons performing the equivalent functions):

a) All significant deficiencies and material weaknesses in the design or operation of internal control over financial reporting which are reasonably likely to adversely affect the registrant's ability to record, process, summarize and report financial information; and

b) Any fraud, whether or not material, that involves management or other employees who have a significant role in the registrant's internal control over financial reporting.

Date: March 16, 2006

/s/ THOMAS R. STAAB, II

Thomas R. Staab, II
Chief Financial Officer
(principal financial officer)

Exhibit 32.1

CERTIFICATION PURSUANT TO
18 U.S.C. SECTION 1350,
AS ADOPTED PURSUANT TO
SECTION 906 OF THE SARBANES-OXLEY ACT OF 2002

In connection with the annual report of Inspire Pharmaceuticals, Inc. (the "Company") on Form 10-K for the year ending December 31, 2004, as filed with the Securities and Exchange Commission (the "Report"), I, Christy L. Shaffer, Chief Executive Officer of the Company, certify, pursuant to 18 U.S.C. Section 1350, as adopted pursuant to Section 906 of the Sarbanes-Oxley Act of 2002, that:

1) The Report fully complies with the requirements of Section 13(a) or 15(d) of the Securities Exchange Act of 1934; and

2) The information contained in the Report fairly presents, in all material respects, the financial condition and results of operations of the Company.

Date: March 16, 2006

/s/ CHRISTY L. SHAFFER

Christy L. Shaffer
President & Chief Executive Officer
(principal executive officer)

Exhibit 32.2

CERTIFICATION PURSUANT TO
18 U.S.C. SECTION 1350,
AS ADOPTED PURSUANT TO
SECTION 906 OF THE SARBANES-OXLEY ACT OF 2002

In connection with the annual report of Inspire Pharmaceuticals, Inc. (the "Company") on Form 10-K for the year ending December 31, 2004, as filed with the Securities and Exchange Commission (the "Report"), I, Thomas R. Staab, II, Chief Financial Officer of the Company, certify, pursuant to 18 U.S.C. Section 1350, as adopted pursuant to Section 906 of the Sarbanes-Oxley Act of 2002, that:

1) The Report fully complies with the requirements of Section 13(a) or 15(d) of the Securities Exchange Act of 1934; and

2) The information contained in the Report fairly presents, in all material respects, the financial condition and results of operations of the Company.

Date: March 16, 2006

/s/ THOMAS R. STAAB, II

Thomas R. Staab, II
Chief Financial Officer
(principal financial officer)

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Corporate Information

Annual Meeting:
The Annual Meeting of Stockholders will be held on Tuesday, June 13, 2006 at 9:00 a.m. E.T. at the North Carolina Biotechnology Center, 15 T.W. Alexander Drive, Research Triangle Park, NC 27709

Corporate Counsel:
Reed Smith LLP
Princeton Forrestal Village
Suite 250
136 Main Street
Princeton, NJ 08543

Corporate Information:
Inspire Pharmaceuticals, Inc.
4222 Emperor Boulevard
Suite 200
Durham, NC 27703
www.inspirepharm.com
919-941-9777
Fax 919-941-9797

Independent Registered Public Accounting Firm:
PricewaterhouseCoopers LLP
150 Fayetteville Street Mall
Suite 2300
Raleigh, NC 27601
919-755-3000

Securities Information:
Exchange: NASDAQ National Market®
Symbol: ISPH

Stockholder Information:
Contact Inspire at 919-941-9777 to obtain stockholder information and a copy of Inspire's Annual Report on Form 10-K, as filed with the Securities and Exchange Commission, free of charge.

Transfer Agent:
Computershare Trust Company
350 Indiana Street
Suite 800
Golden, CO 80401
www.computershare.com
303-262-0600
Fax 303-262-0604

Forward-Looking Statements:
This document contains forward-looking statements that present our expectations and plans regarding future performance, and these statements are subject to significant risks and uncertainties that could affect our future performance, including those relating to product development. Actual results could differ materially from those described herein. Information on various factors that could affect our results is detailed in our reports filed with the Securities and Exchange Commission.

Board of Directors:

Kip A. Frey
Partner, Intersouth Partners
Adjunct Professor, Duke University

Alan F. Holmer
Former President and Chief Executive Officer
Pharmaceutical Research and Manufacturers of America (PhRMA)

Richard S. Kent, M.D.
Chief Executive Officer & President
Serenex, Inc.

Kenneth B. Lee, Jr.
Chairman
Inspire Pharmaceuticals, Inc.
General Partner,
Hatteras BioCapital, L.L.C.

William R. Ringo, Jr.
Former Chief Executive Officer & President
Abgenix, Inc.

Christy L. Shaffer, Ph.D.
President and Chief Executive Officer
Inspire Pharmaceuticals, Inc.

Corporate Officers:

Mary B. Bennett
Executive Vice President
Operations and Communications

R. Kim Brazzell, Ph.D.
Senior Vice President
Ophthalmic Research and Development

Donald J. Kellerman, Pharm.D.
Senior Vice President
Development

Joseph K. Schachle
Senior Vice President
Marketing and Sales

Christy L. Shaffer, Ph.D.
President and Chief Executive Officer

Joseph M. Spagnardi
Senior Vice President
General Counsel and Secretary

Thomas R. Staab, II
Chief Financial Officer and Treasurer

Benjamin R. Yerxa, Ph.D.
Chief, Scientific Operations and Alliances

We Honor

Richard M. Evans, Ph.D.
1960–2006

Dr. Evans was a seasoned pharmaceutical executive and Ph.D. scientist with extensive experience in directing complex drug development and manufacturing processes for innovative products. He joined Inspire as one of the first employees and served as Vice President, Pharmaceutical Development. Dr. Evans held both a Bachelor of Pharmacy degree and a Doctorate in Pharmaceutical Chemistry, in the field of inhalation drug delivery, from the Welsh School of Pharmacy, University of Wales College of Cardiff. During his career, Dr. Evans served as an affiliate assistant professor at several universities and was an active member in a number of international pharmaceutical associations.

"Richard played a critical role in making Inspire the special organization that it is today. During his ten years at the company, he made numerous valuable contributions through his knowledge, hard work, dedication and commitment to Inspire. He did it with compassion for others, a true sense of integrity and a warm smile. While Richard's presence and sense of humor can never be replaced, he will live on in the heart of Inspire. His legacy will provide additional motivation for our team to continue to accomplish great things."

Christy L. Shaffer, Ph.D.
President and CEO of Inspire

designed by curran & connors, inc. / www.curran-connors.com

INSPIRE

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Durham, NC 27703
www.inspirepharm.com
919-941-9777
NASDAQ: ISPH