

INSITE VISION INC



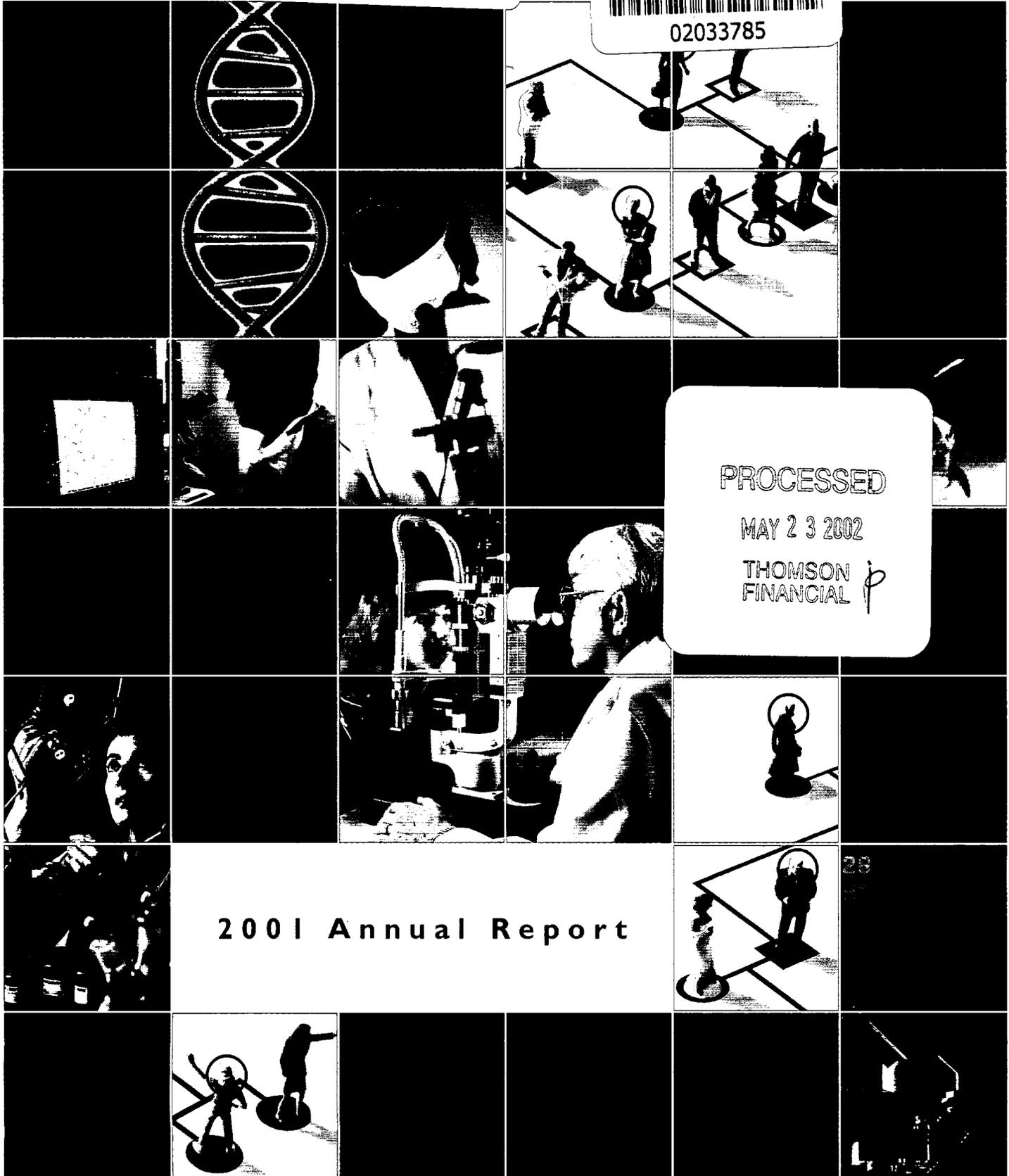
INSITE VISION

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2001 Annual Report

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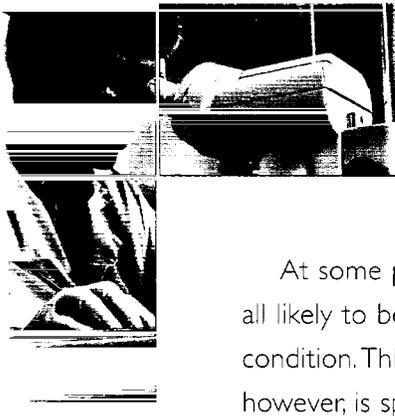
## Corporate Profile

At InSite Vision, our focus is on building a leadership position in ophthalmology by developing innovative diagnostic and prognostic products, and improving treatments by utilizing novel therapeutic agents and drug delivery systems. We have a significant pipeline of products under development based on multiple, patent-protected technologies and we recently began the launch of our first commercial product, our OcuGene™ glaucoma genetic test.

Our strategy includes in-licensing and developing promising compounds with potential applications in the areas of glaucoma, retinal diseases and bacterial infection, and in matching diagnostics with therapeutics for superior and cost-effective outcomes. We intend to seek corporate partnerships to assist with funding late-stage clinical development and product commercialization.

## Product Pipeline

<i>Product</i>	<i>Indication</i>	<i>Clinical Status</i>
<b>AquaSite</b>	Dry eye	Marketed (OTC)
<b>OcuGene</b>	Glaucoma genetic test	Marketed
<b>ISV-900</b>	Glaucoma prognostic/diagnostic	Research
<b>ISV-205</b>	Steroid-induced intraocular pressure elevation, glaucoma	Phase II (b) completed
<b>ISV-401</b>	Bacterial infection including ophthalmia neonatorum	Phase II
<b>ISV-403</b>	Bacterial infection	Preclinical
<b>ISV-014</b>	Retinal drug delivery device for potential treatment of diabetic retinopathy and macular degeneration	Research



## To Our Stockholders...

At some point in our lifetime, we are all likely to be affected by an eye-related condition. This large ophthalmic market, however, is sparse with innovation and relatively few dollars are allocated to new product development. InSite Vision is among the few corporations focused on this market and we believe our rich pipeline of novel products will address this opportunity.

With the introduction of our first commercial product—our Ocugene™ glaucoma genetic test—we reached a significant milestone in bringing our novel products to this attractive market.

### The First Piece... Launching Ocugene

The Ocugene launch marked the first product developed from our ISV-900 ophthalmic genetics program. We are proud at the speed with which we brought this important product to market after we regained the product rights

from Pharmacia Corporation in late 2000, and its companion therapeutic ISV-205 in early 2001.

We selected the American Academy of Ophthalmology (AAO) annual meeting held in November 2001 to introduce the Ocugene test, as that forum provided a prime opportunity to make personal contact with many leading prescribers of glaucoma medications and thought leaders at teaching hospitals. In conjunction with the AAO meeting, we sponsored a special glaucoma and Ocugene symposium featuring panelists from the University of California, San Francisco; Yale University School of Medicine; INSERM (the French equivalent of the U.S. National Institutes of Health); Pennsylvania State University; and a private-practice ophthalmologist.

We also entered an exclusive agreement with the leading provider of genetic diagnostic testing, Quest Diagnostics Incorporated, to provide laboratory services in the U.S. for Ocugene.



## Ocugene

Ocugene is the first glaucoma genetic test available in the U.S. for use by eye care specialists. We believe this genetic test provides clinicians with information for consideration when evaluating current glaucoma patients, their family members or individuals who may be at risk for developing glaucoma. Ocugene is designed to detect a more aggressive form of glaucoma and to assist in identifying people with a higher likelihood of developing the disease.

Ocugene is a simple in-office test. The test kit consists of a pair of swabs used to obtain a sample of the patient's DNA by swabbing the inside of the cheek. These swabs are then sealed in a plastic container provided with the kit and are forwarded to Quest Diagnostics, an analytical laboratory, to assay for gene mutations.

The marketing efforts we are undertaking to commercialize this product include:

- contracting with sales and marketing consultants, and a network of key ophthalmic clinicians, to create product awareness through a variety of avenues, including direct mailings;
- hosting teleconferences with eye care specialists to discuss the use of the Ocugene test;
- launching a special website at <http://www.ocugene.com>, which has information directed both to eye care specialists and to patients at risk for glaucoma; and

- profiling Ocugene in a recent segment of the "Healthy Solutions" television series. A webcast version of this segment can be viewed at [www.ocugene.com](http://www.ocugene.com).

While we are still relatively early in the launch process, the overall response from the eye care community to date has been favorable. Our plans for 2002 include continuing our marketing programs, expanding our contracted sales force and strengthening our management team to further support Ocugene. Additionally, we are aggressively seeking corporate marketing partners for the U.S., Canada, Europe and Japan.

## Eye Diseases

	<p>Three leading causes of visual impairment<sup>1</sup> are:</p> <p><b>Glaucoma</b></p> <ul style="list-style-type: none"> <li>• is the leading cause of preventable blindness in the U.S., affecting about 3 million people in the United States<sup>2</sup>;</li> <li>• can begin without any obvious symptoms; and</li> <li>• can cause visual damage that cannot be reversed.</li> </ul>			
	<p><b>Diabetic Retinopathy</b></p> <ul style="list-style-type: none"> <li>• is responsible for 8% of legal blindness, making it the leading cause of new cases of blindness in adults 20-74 years of age<sup>3</sup>;</li> <li>• is a progressive disease that blurs vision and is often followed by blindness; and</li> <li>• is a major cause of blindness in people with diabetes.</li> </ul>			
	<p><b>Age-related Macular Degeneration (AMD)</b></p> <ul style="list-style-type: none"> <li>• affects as many as 15 million Americans<sup>4</sup>;</li> <li>• is a retinal degenerative disease that causes progressive loss of vision in the central portion of the retina responsible for perceiving fine visual detail; and</li> <li>• most often affects people age 60 and above.</li> </ul>			

<sup>1</sup> source: National Center for Health Statistics

<sup>2</sup> source: Glaucoma Research Foundation

<sup>3</sup> source: American Diabetes Association

<sup>4</sup> source: Macular Degeneration Partnership

# ... Physician Customers and Employees



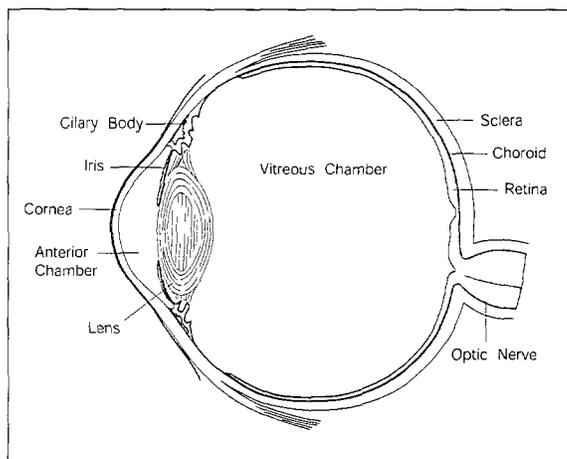
## The Next Piece... New Genetic Tests

Glaucoma is a heterogeneous disease linked to a group of genes. Our intention is to develop genetic tests that incorporate the major genes and mutations associated with glaucoma in order to provide the broadest applicability, from disease management (including severity and progression) to detection (including screening). To this end, we recently licensed the newly discovered Optineurin gene, which is implicated in the onset of primary open-angle glaucoma (POAG), including a subgroup known as normal-tension glaucoma (NTG). Being able to aid in the diagnosis of patients who have, or may develop, glaucoma without the normal marker of elevated intraocular pressure, could have significant benefits for NTG patients who, based on recent study conducted by Dr. Kitazawa in Japan, are estimated to makeup 30% of the U.S. POAG population and 70% of the Japanese POAG population. We plan to begin developing a diagnostic test based on this gene and its mutations.

We have also licensed technology on the genetics of primary congenital glaucoma (PCG). PCG by definition is present at birth, and is caused by the failure of the trabecular meshwork to develop properly. The disease can only be corrected with surgery. Early recognition and appropriate treatment of PCG can significantly improve the child's visual future. We plan to develop a new diagnostic test incorporating this licensed technology.

## The Antibiotic Pieces... ISV-401, ISV-403

We made progress in 2001 on our ISV-401 program for the treatment of bacterial conjunctivitis. ISV-401 is a formulation, in our DuraSite® system, of a broad-spectrum antibiotic not currently used in ophthalmology. DuraSite is our proprietary patented drug-delivery vehicle offering the benefits of controlled time-release of an active ingredient. ISV-401 combines the benefits of DuraSite with an active ingredient that has been shown to be effective against both gram-negative and gram-positive bacteria. We met with the FDA on the program in the second quarter of 2001 and filed an



investigational new drug application (IND) in the third quarter. We also completed our Phase I clinical study, in the third quarter of 2001, and we initiated a Phase II clinical study late in 2001.

In the Phase II study, ISV-401 is being administered in a dosing regimen that is significantly lower than currently approved therapeutics. We plan to initiate Phase III clinical studies in late 2002 and are pursuing partnership discussions.





ISV-403 is our DuraSite formulation of SS734, a fourth-generation fluoroquinolone licensed for ophthalmic use from Japan's SS Pharmaceuticals, Co., Ltd. Late in 2001, additional pre-clinical studies demonstrated that SS734 is effective against ciprofloxacin-resistant staph aureas. When SS734 is formulated in DuraSite, pre-clinical studies indicate that the efficacious dosing frequency was lower than fourth-generation fluoroquinolones under development by other companies.

### **The Glaucoma Therapeutic Piece... ISV-205**

Our ISV-205, being developed as a therapeutic for the treatment of glaucoma, is designed to be used in conjunction with OcuGene, which tests for the presence of TIGR gene mutations. In our findings to date, ISV-205 has demonstrated the ability to lower and maintain intraocular pressure (IOP) in ocular hypertensives who tested positive for the TIGR promoter region mutations. We are currently determining our strategy for product approval and will be planning an end of Phase II meeting with FDA prior to initiating the Phase III program.

### **The Retinal Piece... ISV-014**

ISV-014 is our retinal delivery program that continues to be an intermediate-term opportunity. The device fills a niche that has been identified by retinal specialists and drug delivery pharmacologists for the treatment of retinal diseases with compounds that are too toxic for systemic delivery, molecules too large for topical delivery, and gene therapy. We are pursuing opportunities for licensing or co-development of ISV-014.

We are also evaluating a matrix metalloproteinase inhibitor (MMPI), formulated in DuraSite, for treatment of proliferative diseases such as diabetic retinopathy and macular degeneration. The importance of ocular dosing for these powerful drugs is to decrease their systemic side effects while providing concentrated local delivery to the effected tissues.

### **Putting the Pieces Together in 2002**

In 2002, we are committed to actively move forward with the programs that may provide us with near-term revenue potential, namely OcuGene, the complementary genetics programs and ISV-401. Our intention is to pursue the continued development of the other programs in our pipeline as additional financial resources become available.

We also intend to continue to actively market our story both to the medical and the investment communities, as we work to maximize shareholder value.



On behalf of InSite Vision's Board of Directors and its employees, I would like to take this opportunity to thank you for your continued support.

S. Kumar Chandrasekaran, Ph.D.  
President and Chief Executive Officer

April 5, 2002

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**SECURITIES AND EXCHANGE COMMISSION  
WASHINGTON, D.C. 20549**

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**FORM 10-K**

**FOR 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, 2001

**OR**

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

For the transition period from                    to

Commission file number 0-22332

**INSITE VISION INCORPORATED**

(Exact name of registrant as specified in its charter)

**Delaware**  
(State or other jurisdiction  
of incorporation or organization)

**94-3015807**  
(I.R.S. Employer  
Identification No.)

**965 Atlantic Avenue, Alameda, CA 94501**  
(Address of Principal Executive Offices, including Zip Code)

Registrant's telephone number, including area code: **(510) 865-8800**

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

Title of each class	Name of each exchange on which registered
<b>Common Stock, \$0.01 par value</b>	<b>American Stock Exchange</b>

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

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 the 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.

The aggregate market value of registrant's Common Stock, \$0.01 par value, held by non-affiliates of the Registrant as of March 25, 2002: was approximately \$48,549,934 (based upon the closing sale price of the Common Stock on March 25, 2002). Number of shares of Common Stock, \$0.01 par value, outstanding as of March 25, 2002: 21,968,296. Shares of Common Stock held by each officer and director and by each person who owns 5% or more of the Common Stock have been excluded from such calculation as such persons may be deemed affiliates. This determination of affiliate status is not necessarily a conclusive determination for other purposes.

**DOCUMENTS INCORPORATED BY REFERENCE**

Designated portions of the following document are incorporated by reference into this Report on Form 10-K where indicated: portions of the Proxy Statement for the registrant's 2002 Annual Meeting of Stockholders which will be held on June 3, 2002 are incorporated by reference into Part III.

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**ANNUAL REPORT ON FORM 10-K  
FOR THE FISCAL YEAR ENDED DECEMBER 31, 2001**

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## PART I

### Item 1. BUSINESS

*Except for the historical information contained herein, the discussion in this Annual Report on Form 10-K may contain certain forward-looking statements that involve risks and uncertainties, such as statements of our plans, objectives, expectations and intentions. The cautionary statements made in this document should be read as applicable to all related forward-looking statements wherever they appear in this document. Our actual results could differ materially from those discussed herein. Factors that could cause or contribute to such differences include those discussed below in "Risk Factors," as well as those discussed elsewhere herein. Readers are cautioned not to place undue reliance on these forward-looking statements, which speak as of the date hereof. We undertake no obligation to update any forward-looking statements to reflect events or circumstances after the date hereof or to reflect the occurrence of unanticipated events.*

### THE COMPANY

We are an ophthalmic product development company focused on developing genetically based tools, for the diagnosis, prognosis and management of glaucoma, as well as other ophthalmic pharmaceutical products based on our proprietary DuraSite® eyedrop-based drug delivery technology. In addition, we have retinal programs which include both a therapeutic agent and a retinal drug delivery technology.

We are focusing our commercial efforts and research and development on the following:

- launching our OcuGene™ glaucoma genetic test based on our ISV-900 technology;
- expanding our ISV-900 technology for the diagnosis, prognosis and management of glaucoma;
- ISV-205, a DuraSite formulation for the treatment of glaucoma;
- ISV-401, a DuraSite formulation of a novel antibiotic not currently used in ophthalmology;
- ISV-403, a DuraSite formulation of a fourth generation fluoroquinolone;
- ISV-014, a retinal drug delivery device; and
- treatments for diabetic retinopathy and macular degeneration.

*Glaucoma Genetics.* Our glaucoma genetics program, which is being carried out in collaboration with academic researchers, is focused on discovering genes that are associated with glaucoma, and the mutations on these genes that cause the disease. This genetic information then may be applied to develop new glaucoma diagnostic, prognostic and management tools. The first of these new tools, OcuGene, is still in the launch phase and was first introduced to the medical community at the end of 2001.

A clinical study published in the September 2001 issue of *Clinical Genetics*, showed a correlation between the presence of the TIGR promoter region mutation in individuals with primary open-angle glaucoma, or POAG, and the likelihood of an individual developing a more aggressive form of glaucoma including more visual field damage. Published studies have also shown the correlation of the coding region mutations detected by our OcuGene test and a high probability of developing glaucoma.

To date, our academic collaborators have identified genes associated with POAG (the most prevalent form of the disease in adults), normal tension glaucoma, juvenile glaucoma and primary congenital glaucoma, or PCG. Our academic collaborators for our glaucoma genetics program are with: the University of California, San Francisco, or UCSF; the University of Connecticut Health Center, or UCHC; Institute National de la Sante et de la Recherche Medicale, or INSERM, the French equivalent of US National Institutes of Health; Okayama University in Japan; and other institutions in North America and Europe. This research, other than what has been incorporated into our OcuGene test, still must be converted into commercial products.

*DuraSite-Based Product and Candidates.* Our DuraSite delivery system is a patented eyedrop formulation comprising a cross-linked carboxyl-containing polymer that incorporates the drug to be delivered to the eye. The formulation is instilled in the cul-de-sac of the eye as a small volume eyedrop

and remains in the eye for up to several hours during which time the active drug ingredient is gradually released. This increased residence time is designed to permit lower concentrations of a drug to be administered over a longer period of time, thereby minimizing the inconvenience of frequent dosing and reducing potential related adverse side effects. Eyedrops delivered in the DuraSite system contrast to conventional eyedrops, which typically only last a few minutes in the eye and, thus, require delivery of a highly concentrated burst of drug and frequent administration to sustain therapeutic levels. DuraSite can be customized to deliver a variety of compounds with a broad range of molecular weights and other properties.

We have received patent allowances covering extended viscosity and pH ranges of the DuraSite system. These extended ranges will allow a broader range of compounds to be delivered by the system and the additional patent allowances have patent coverage until 2016.

The first product utilizing our DuraSite technology, AquaSite® dry eye treatment, was launched as an over-the-counter, or OTC, medication in 1992 by CIBA Vision Ophthalmics, or CIBA Vision, to which we have licensed certain co-exclusive rights. In 2000, Global Damon Pharm launched AquaSite in Korea, based on a licensing agreement signed in 1999. In 1999, we also licensed AquaSite to SSP Co., Ltd., or SSP, for sale in Japan. (See “—Collaborative and Licensing Agreements” for additional information on the agreements.) In connection with our DuraSite development efforts, we have licensed marketing rights to certain DuraSite-based product candidates to CIBA Vision and Bausch & Lomb Incorporated, or B&L.

In January 1999, we entered into a license agreement and stock purchase agreement with Pharmacia for certain exclusive worldwide rights to ISV-205 for glaucoma. (See “—Collaborative and Licensing Agreements” for additional information on the agreements.) During 1999, we successfully completed a Phase II trial of ISV-205 and transitioned the lead on the further development of the program to Pharmacia. In May 2001, Pharmacia terminated this license agreement. All global development and commercialization rights that had been granted to Pharmacia were returned to us at the end of a ninety-day termination period.

*Business Strategy.* Our business strategy is to license promising product candidates and technologies from academic institutions and other companies, to conduct preclinical and clinical testing, if necessary, and to partner with pharmaceutical companies to complete clinical development and regulatory filings as needed and to produce and market our products. We also have internally developed DuraSite-based product candidates using either non-proprietary drugs or compounds developed by others for non-ophthalmic indications. As with in-licensed product candidates, we either have or plan to partner with pharmaceutical companies to complete clinical development and commercialization of our own product candidates.

### **Ophthalmic Pharmaceutical Market**

The prevalence of eye disease is ten times greater in persons over the age of 65 than under the age of 65, and the U.S. Census Bureau projects that the U.S. population over age 65 will increase from 34 million in 1997 to approximately 69 million by the year 2030. This aging of the population in the U.S. and other developed countries is a significant factor that we believe will contribute to increased demand for new ophthalmic products.

In addition to changing demographics, we believe that recent improvements in medical technology, such as increasingly sophisticated diagnostic techniques, will allow identification of ocular diseases at an earlier stage, enabling more effective treatments and expanding the range of treatment regimens available to the ophthalmologist. Further, we believe that the emergence of new laser-based procedures to correct certain vision problems has begun to increase the need for comfortable, extended-release drug therapy during the post-surgical ocular healing process.

Glaucoma is the leading cause of preventable blindness affecting two to three million people in the U.S., and 67 million people worldwide, according to the Glaucoma Research Foundation. The prevalence of the disease in first-degree relatives of affected patients has been documented to be as high as seven to ten times that of the general population. Glaucoma also may occur as a complication of conditions such as diabetes, or as a result of extended steroid use.

The world wide ophthalmic antibiotic market was anticipated to reach approximately \$650.0 million in 2001, according to a study by Frost and Sullivan. The study also anticipated sales of fluoroquinolone products to reach \$240.0 million in 2001. The market has been, and will continue to be, impacted by the use of antibiotics in connection with laser-based vision correction procedures.

Age-related macular degeneration, which affects 15 million or more people in the U.S., is the leading cause of severe blindness in Americans age 60 and above, according to the Macular Degeneration Partnership. Laser treatment and the photo-dynamic therapy introduced in 2000, are the only known therapies, but are effective in only a certain portion of affected patients. Even with treatment, the disease usually progresses and eventually leads to vision loss.

Also, approximately 10 to 14 million Americans are diabetic and many of them will develop diabetic retinopathy later in their life. According to the American Diabetes Association, diabetic retinopathy is responsible for 8 percent of the legal blindness in the U.S. and is the leading cause of new cases of blindness in adults 20 to 74 years of age. Laser therapy is effective only in a certain segment of the diabetic population, and has potential side effects such as loss of peripheral vision, retinal detachment, and loss of vision.

## Products and Product Candidates

The following table summarizes the current status of our principal products and product candidates. A more detailed description of each product and product candidate follows the table. There can be no assurance that any of the listed products or product candidates will progress beyond its current state of development, receive necessary regulatory approval or be successfully marketed.

### Products and Product Candidates

<u>Product</u>	<u>Indications</u>	<u>Anticipated Benefits</u>	<u>Status(1)</u>
<b>Glaucoma Genetics</b>			
OcuGene	Glaucoma genetic test	Detect disease susceptibility and determine disease severity	Marketed
ISV - 900	Glaucoma prognostic/diagnostic	Identify new genetic markers to detect disease susceptibility and determine disease severity	Research
<b>Glaucoma Product Candidates</b>			
ISV - 205	Steroid-induced intraocular pressure elevation, glaucoma	Treat/prevent disease progression	Phase II(b) completed
<b>Other Topical Product Candidates and Product</b>			
ISV - 401	Bacterial infection including ophthalmia neonatorum	Broad spectrum antibiotic with reduced dosing frequency	Phase II
ISV - 403	Bacterial infection	Fourth generation fluoroquinolone antibiotic with reduced dosing frequency	Preclinical
ISV - 205	Inflammation and analgesia	Reduced dosing frequency	Preclinical
AquaSite	Dry eye	Reduced dosing frequency and extended duration of action	Marketed (OTC)
<b>Retinal Device</b>			
ISV - 014	Retinal drug delivery device for potential treatment of diabetic retinopathy and macular degeneration	Non-surgical delivery of drugs to the retina	Research

<sup>1)</sup> All products except OcuGene, ISV-900, AquaSite and ISV-014 are expected to be prescription pharmaceuticals. As denoted in the table, "Preclinical" indicates that a specific compound is being tested in preclinical studies in preparation for filing an investigational new drug application, or IND. For a description of preclinical trials, IND, Phase I, Phase II and Phase III clinical trials and New Drug Application, or NDA, see "—Government Regulation."

## **Glaucoma Genetics**

Glaucoma is the leading cause of preventable blindness in the U.S., affecting an estimated two to three million people. The most prevalent form of glaucoma in adults is POAG. Other forms of the disease include PCG, a leading cause of blindness in infants, and juvenile glaucoma that affects children and young adults.

Often called the "sneak thief of sight" because of its lack of symptoms, glaucoma is believed to result when the flow of fluid through the eye is impaired. This may lead to elevated intraocular pressure or IOP, which increases pressure on the optic nerve and can cause irreversible vision loss if left untreated. One form of glaucoma, normal or low tension glaucoma, is associated with individuals who have normal eye pressure. It is estimated that one-third of U.S. glaucoma patients and three-quarters of glaucoma patients in Japan have this form of the disease, based on recent study conducted by Dr. Kitazawa in Japan. These patients cannot be identified with standard glaucoma screening tests that only measure a patient's eye pressure and usually they incur visual field loss before they are diagnosed.

*ISV-900.* There is accumulating evidence that genetic predisposition is a major factor in the development of several forms of glaucoma. (Data has indicated the prevalence of primary open-angle glaucoma or POAG in first-degree relatives of affected patients to be as high as 7 to 10 times that of the general population.) We have formed research collaborations with scientists at institutions located in North America, Europe and Japan both to identify the genes associated with different forms of glaucoma and to build a database of information on how these genes affect the progression of the disease in different populations.

Researchers with whom we collaborate have identified several genes related to POAG including TIGR/MYOC, OPTN, OCLM and APOE, a gene that interacts with TIGR. Additionally, the CYP1B1 gene is related to PCG. We have obtained certain exclusive worldwide licenses for the rights to commercialize research related to the TIGR gene and associated mutations from the Regents of the University of California, the CYP1B1 gene and associated mutations from UCHC, the OCLM gene from Dr. Toshihiko Matsuo of Okayama University and APOE, as it interacts with TIGR, from INSERM.

In December 2001, we entered into an agreement pursuant to which we obtained certain exclusive rights for the Optineuron, or OPTN, gene and associated mutations from UCHC. In early tests, this gene has been linked to POAG, and the normal-tension glaucoma subset. We are in the process of conducting additional research on the Optineuron gene and mutations and we believe we may be able to introduce a test incorporating this gene early in 2003.

We currently hold licenses to patents issued on the TIGR cDNA, TIGR antibodies, methods for the diagnosis of glaucoma using the TIGR technology and methods for the diagnosis of glaucoma using the CYP1B1 technology. Additional patents related to the ISV-900 program are currently pending and if issued will be included in the licenses we hold.

*OcuGene.* Current glaucoma tests are often unable to detect the disease before substantial damage to the optic nerve has occurred. Gene-based tests may make it possible to identify patients at risk and initiate treatment before permanent optic nerve damage and vision loss occurs. Our ISV-900 program is intended to discover the appropriate genetic markers for certain forms of glaucoma and to incorporate those markers into prognostic, diagnostic and management tools. The first version of these tests, OcuGene, has been developed and the product was commercially launched at the end of 2001. We anticipate that as further research identifies new genes, such as Optineuron, and additional mutations, we will bring these to market as additional tests.

## **Glaucoma Product Candidates**

*ISV-205.* Our ISV-205 product candidate contains the drug diclofenac formulated in the DuraSite sustained-release delivery vehicle. Diclofenac is a non-steroidal anti-inflammatory drug or NSAID currently used to treat ocular inflammation. NSAIDs can block steroid-induced IOP elevation by

inhibiting the production of the TIGR protein that appears to affect the fluid balance in the eye. The ISV-205 product candidate delivers to the eye concentrations of diclofenac that have been shown in cell culture systems to inhibit the production of the TIGR protein.

A Phase II clinical study was successfully completed in 1999 to evaluate the efficacy of two concentrations of diclofenac. Analysis of the data from this study indicates that ISV-205 was safe and associated with a 75% reduction in the number of subjects with clinically significant IOP elevation following steroid use.

A second Phase II clinical study was conducted in 233 subjects with ocular hypertension. Genetic information was collected on the subjects using our ISV-900 technology and the subjects were dosed twice daily for six months with ISV-205. Our ISV-900 technology detected the TIGR mt-1 or mt-11 mutations in approximately 70% of the ocular hypertensives participating in the study. In patients with the TIGR mutations, 0.1% formulation of ISV-205 was statistically significantly more effective than placebo in lowering intraocular pressure (IOP) ( $p=0.008$ ). These effects were not seen to the same extent in patients without the TIGR mutations. ISV-205 was similar to placebo in ocular safety and comfort in all patients. We are planning further clinical studies before filing for product approval with the U.S. Food and Drug Administration, or FDA and there is no guarantee that similar clinical results will be achieved.

Other potential indications for ISV-205 may include glaucoma prevention, analgesia and anti-inflammatory indications. Co-exclusive rights, in the U.S., to develop, manufacture, use and sell ISV-205 to treat non-glaucoma indications of inflammation and analgesia, were licensed to CIBA Vision in May 1996.

#### **Other Topical Product Candidates and Marketed Product**

*ISV-401* is an ophthalmic formulation of a broad-spectrum antibiotic that has not previously been used in ophthalmology. The antibiotic has a proven safety and efficacy record in both adult and pediatric populations when used orally. Depending on the indication, current ophthalmic antibiotics must be dosed as often as every 15 to 30 minutes on the first day and then tapered off to a maintenance dose of four times a day for the remainder of the treatment period, which may be up to fourteen days. This may result in patient compliance issues that could be minimized with an improved product. The clinical dosing regimen for this product is significantly lower than the current treatments available.

In September 2001, we conducted a Phase I clinical trial that indicated the formulation was safe and well tolerated. In December 2001, we initiated a Phase II clinical trial using a 1.0% formulation of *ISV-401*, compared to a placebo, to treat bacterial conjunctivitis. We are planning further clinical studies that we anticipate beginning in late 2002 after the Phase II trial is completed and the data has been presented to the FDA.

*ISV-403* is a formulation of a fluoroquinolone in the DuraSite system. Fluoroquinolones are effective against gram-positive and gram-negative bacteria including *Pseudomonas*, and are often used as prophylaxis during ophthalmic surgery. Based on recently conducted preclinical testing, we have determined this is a fourth-generation fluoroquinolone, which has expanded bacterial sensitivities and may be effective against the bacteria that have developed resistance to prior generation fluoroquinolones and other antibiotics. In addition, based on preclinical studies we believe the *ISV-403* formulation may provide for reduced dosing frequency compared to other formulations currently on the market.

*AquaSite*. The first product utilizing our DuraSite technology was introduced to the OTC market in the U.S. in October 1992 by CIBA Vision. We receive a royalty on sales of *AquaSite* by CIBA Vision. The product contains the DuraSite formulation and demulcents for the symptomatic treatment of dry eye. In March 1999, we licensed the product to Global Damon Pharm, a Korean company. The license is royalty-bearing, has a term of 10 years and is exclusive in the Republic of Korea. In August 1999, we entered into a ten year license with SSP for sales and distribution in Japan.

#### **Retinal Device**

Ophthalmic conditions that involve retinal damage include macular degeneration, which affects 15 million or more people in the U.S., and diabetic retinopathy, a common side effect of diabetes.

Approximately 10 million to 14 million people in the U.S. are diabetics. Both macular degeneration and diabetic retinopathy can lead to irreversible vision loss and blindness. Current treatment of retinal diseases, including diabetic retinopathy and macular degeneration, generally involves surgery, laser treatments and photo-dynamic therapy, each of which can lead to loss of vision, retinal detachment, infection and may not slow the progression of the disease. Currently, there is no effective drug therapy for these conditions.

*Retinal Delivery Device.* ISV-014 is one of our technology platforms and consists of a device for the controlled, non-surgical delivery of ophthalmic drugs to the retina and surrounding tissues. During 2001, we continued to enhance the device and performed in vivo experiments delivering products with a variety of molecular sizes to retinal tissues. The combination of this device technology with polymer-based drug platforms may permit long term delivery of therapeutic agents to treat several retinal diseases, including diabetic retinopathy and macular degeneration, most of which cannot be effectively treated at the present time.

The ISV-014 device consists of a handle with a distal platform that is placed against the surface of the eye. A small needle connected to a drug reservoir is extended from the platform into the tissues of the eye. Once in place, a metering mechanism controls the amount and rate that the drug is injected into the tissue. This produces a highly localized depot of drug inside the ocular tissues. By controlling both the distance and direction that the needle protrudes, the device greatly reduces the chance that the needle will penetrate through the sclera of the eye into the underlying tissues, which are easily damaged. We have filed for two patents related to the device and one patent has been allowed. We are currently investigating licensing this technology to a third party.

#### **Collaborative, Licensing and Service Agreements**

As part of our business strategy, we have entered into, and will continue to pursue additional research collaborations, licensing agreements and corporate collaborations. However, there can be no assurance that we will be able to negotiate acceptable collaborative or licensing agreements, or that our existing collaborations will be successful, will be renewed or will not be terminated.

*University of Connecticut Health Center (UCHC).* In July 1997, we exercised our option granted pursuant to a research agreement with UCHC to obtain certain exclusive rights from UCHC for diagnostic uses of the newly discovered gene for PCG. Under the agreement, we will pay a licensing fee and will make royalty payments on future product sales, if any.

In December 2001, we entered into an agreement whereby we exercised our option granted pursuant to a research agreement with UCHC to obtain certain exclusive rights from UCHC for diagnostic uses of the Optineuron gene and associated mutations. Under this agreement, we will pay a licensing fee and will make royalty payments on future product sales, if any.

*Quest Diagnostics Incorporated.* In November 2001, we entered into an exclusive laboratory service agreement with Quest Diagnostics Incorporated, or Quest, for our OcuGene test in the U.S. We will pay Quest for each OcuGene test that they perform. The initial agreement term is for one year and may be extended.

*Pharmacia Corporation.* In December 2000, our November 1999 ISV-900 licensing and credit agreements with Pharmacia were terminated by Pharmacia. All rights to the ISV-900 program granted to Pharmacia were returned to us, and Pharmacia was released from any obligation to fund future research and development, marketing efforts and any corresponding royalties for the program. Additionally, the credit line, which would have become available to us in November 2001, was terminated.

As part of the November 1999 ISV-900 transaction, Pharmacia invested \$2,000,000 in our common stock. The stock purchase agreement also provides for a standstill period of thirty (30) months during which Pharmacia and its subsidiaries will not purchase additional shares of us, other than those provided for under any existing agreements between the companies, without our prior written consent. However,

this standstill period will terminate earlier if certain actions are taken by other parties to acquire more than a 9.99% interest in our stock or if any other party announces their intention to assume control of us, whether by tender offer, merger, proxy contest or otherwise.

On January 28, 1999, we entered into a license agreement and stock purchase agreement that granted Pharmacia certain exclusive rights to ISV-205 for the treatment of glaucoma. The equity investment from Pharmacia described in the stock purchase agreement was made in February 1999. In the license, Pharmacia assumed responsibility for the development of the product upon our completion of, among other activities, Phase II studies we conducted in 1999. In May 2001, Pharmacia terminated the ISV-205 license agreement, and all global development and commercialization rights that had been granted to Pharmacia were returned to us at the end of a ninety-day termination period.

*CIBA Vision Ophthalmics.* In October 1991, we entered into license agreements with CIBA Vision (the "CIBA Vision Agreements"), which granted CIBA Vision certain co-exclusive rights to manufacture, have manufactured, use and sell fluorometholone and tear replenishment products utilizing the DuraSite technology in the U.S. and Canada, ToPreSite®, a product candidate for ocular inflammation/infection, and ISV-205 for non-glaucoma indications.

*Bausch and Lomb.* In July 1996, we entered into a license agreement (the "B&L Agreement") with B&L granting B&L certain exclusive rights to make, use and sell PilaSite® and ISV-208. B&L paid us an up-front license fee of \$500,000 and is obligated to pay royalties on net sales of the licensed products. In addition, B&L made a \$2.0 million investment in us, is sharing the cost of developing ISV-208 and agreed to manufacture other products on our behalf.

In July 1999, we entered into a termination, release and purchase agreement with B&L and the PilaSite license agreement and the manufacturing agreement were terminated and our equipment located at B&L's facility was purchased by B&L. The ISV-208 license and development collaboration remains in effect but no further development activities are being pursued on the program by B&L or us.

*INSTITUTE NATIONAL DE LA SANTE ET DE LA RECHERCHE MEDICALE (INSERM).* In December 1999, we entered into a license agreement with INSERM granting us certain exclusive rights for the diagnostic, prognostic and therapeutic uses of a gene for chronic open angle glaucoma. We paid a licensing fee and will make royalty payments on future product sales, if any.

*UC Regents.* In March 1993, we entered into a license agreement with the UC Regents granting us certain exclusive rights for the development of ISV-205 and, in August 1994, the parties entered into another license agreement granting us certain exclusive rights for the use of a nucleic acid sequence that codes for a protein associated with glaucoma. Under both agreements, we paid initial licensing fees, share sub-licensing fees we receive, if any, and will make royalty payments to the UC Regents on future product sales, if any.

*Columbia Laboratories, Inc.* In February 1992, we entered into a cross-license agreement (the "Columbia Agreement") with Columbia Laboratories, Inc., or Columbia, in which Columbia licensed to us certain exclusive rights to a polymer technology upon which DuraSite is based. This license permits us to make, use and sell products using such polymer technology for non-veterinary ophthalmic indications in the over-the-counter and prescription markets in North America and East Asia (the "Columbia Territory"), and in the prescription market in countries outside the Columbia Territory. In exchange, we granted Columbia a license with certain exclusive rights to sublicense and use certain DuraSite technology in the over-the-counter market outside the Columbia Territory. In addition, we also granted Columbia a license with certain exclusive rights to DuraSite technology in the veterinary field. Under certain circumstances, certain of the licenses in the Columbia Agreement become non-exclusive. Subject to certain rights of early termination, the Columbia Agreement continues in effect until the expiration of all patents covered by the DuraSite technology to which Columbia has certain rights.

*Global Damon Pharm and Kukje Pharma Ind. Co., Ltd.* In March 1999, we entered into a royalty-bearing license agreement with Global Damon Pharm, or Global Damon, a Korean company, to be the exclusive distributor of AquaSite in the Republic of Korea. Concurrently, we entered into a manufacturing agreement with Kukje Pharma Ind. Co., Ltd., or Kukje, a Korean company, to produce the AquaSite to be sold by Global Damon.

*SSP Co., Ltd.* In April 2001, we entered into a royalty-bearing license agreement with SSP Co., Ltd, or SSP, for two fourth-generation fluoroquinolones, one of which is the active ingredient in ISV-403. We have world-wide development and marketing rights except for Japan, which was retained by SSP, and will share the rights with SSP in Asia.

In August 1999, we entered into an exclusive license agreement with SSP to be the exclusive manufacturer and distributor of AquaSite in Japan. We will be the sole supplier to SSP for some of the key ingredients necessary for the manufacture of AquaSite.

*Other.* As part of our basic strategy, we continually discuss entering into agreements with other companies, universities and research institutions concerning the licensing of additional therapeutic agents and drug delivery technologies to complement and expand our family of proprietary ophthalmic products and to develop and market our current products. We intend to continue exploring licensing and collaborative opportunities, though there is no certainty that we can successfully enter into any such agreements.

### **Patents and Proprietary Rights**

Patents and other proprietary rights are important to our business. Our policy is to file patent applications seeking to protect technology, inventions and improvements to our inventions that we consider important to the development of our business. Additionally, we assist UC Regents, UCHC and INSERM in filing patent applications seeking to protect inventions that are the subject of our agreements with those institutions. We also rely upon trade secrets, know-how, continuing technological innovations and licensing opportunities to develop and maintain our competitive position. Our DuraSite drug delivery products are made under patents and applications, including four U.S. patents, owned by Columbia and exclusively licensed to us in the field of human ophthalmic applications. In addition, we have filed a number of patent applications in the U.S. relating to our DuraSite technology, as well as foreign counterparts of certain of these applications in many countries. Of these applications, ten U.S. patents have been issued. In addition, we have obtained two U.S. patents on our unit dose dispenser. We have received six additional U.S. patents directed toward certain uses of lazarooids in ophthalmic applications. Of the patent applications licensed from the UC Regents, eleven patents have issued. Five patents have been issued of the patent applications licensed from UCHC covering the diagnosis of PCG. We have three patent applications on file for our retinal programs and one patent on the device used for delivery of drugs to the retina has been issued. Three patent applications have been filed related to our antibiotic programs with one patent issued. Several other patent applications by us and by the UC Regents, UCHC and INSERM relating to the foregoing and other aspects of our business and potential business are also pending.

The patent positions of pharmaceutical companies, including ours, are uncertain and involve complex legal and factual questions. In addition, the coverage claimed in a patent application can be significantly reduced before a patent is issued. Consequently, we do not know whether any of our pending patent applications will result in the issuance of patents or if any of our patents will provide significant proprietary protection. Since patent applications are maintained in secrecy until patents issue in the U.S., or such patents are published by foreign regulatory authorities, we cannot be certain that we or any licensor was the first to file patent applications for such inventions. Moreover, we might have to participate in interference proceedings declared by the U.S. Patent and Trademark Office to determine priority of invention, which could result in substantial cost to us, even if the eventual outcome were favorable. There can be no assurance that our patents will be held valid or enforceable by a court or that a competitor's technology or product would be found to infringe such patents.

A number of pharmaceutical companies and research and academic institutions have developed technologies, filed patent applications or received patents on various technologies that may be related to our business. Some of these technologies, applications or patents may conflict with our technologies or patent applications. This conflict could limit the scope of the patents, if any, that we may be able to obtain or result in the denial of our patent applications. In addition, if patents that cover our activities have been or are issued to other companies, there can be no assurance that we would be able to obtain licenses to these patents, at all, or at a reasonable cost, or be able to develop or obtain alternative technology.

In addition to patent protection, we also rely upon trade secret protection for our confidential and proprietary information. There can be no assurance that others will not independently develop substantially equivalent proprietary information and techniques or otherwise gain access to our trade secrets, that such trade secrets will not be disclosed or that we can effectively protect our rights to unpatented trade secrets.

We believe our drug delivery technology may expand the ophthalmic pharmaceutical market by permitting the novel use of drugs for ophthalmic indications that are currently used or being developed for non-ophthalmic indications. However, we may be required to obtain licenses from third parties that have rights to these compounds in order to conduct research, to develop or to market products that contain such compounds. There can be no assurance that such licenses will be available on commercially reasonable terms, if at all.

### **Research and Development**

On December 31, 2001, our research and development staff numbered 27 people, of whom 8 have Ph.D.'s. In 2001, our research and development expenses, including third party research we sponsored, were \$7.3 million, of which \$0.7 million was funded by Pharmacia as part of the ISV-205 license. During 2000 and 1999, our research and development expenses were \$6.5 million and \$5.6 million, which included \$4.8 million and \$4.2 million, respectively, funded by Pharmacia as part of the ISV-900 and ISV-205 license agreements.

### **Manufacturing**

We have no experience or facilities for the manufacture of products for commercial processes and we currently have no intention of developing such experience or implementing such facilities. We have a pilot facility, licensed by the State of California, to produce potential products for Phase I and some of our Phase II clinical trials. However, as stated above, we have no large-scale manufacturing capacity and we rely on third parties for supplies and materials necessary for all of our Phase III clinical trials. If we should encounter delays or difficulties in establishing and maintaining our relationship with qualified manufacturers to produce, package and distribute our finished products, then clinical trials, regulatory filings, market introduction and subsequent sales of such products would be adversely affected.

We contract with a third party to assemble the sample collection kits used in our OcuGene glaucoma genetic test. If our assembler should encounter significant delays or we have difficulty maintaining our existing relationship, or in establishing a new one, our sales could be adversely affected.

### **Marketing and Sales**

We have developed a limited marketing and sales organization focused on the launch of OcuGene and we are primarily using external marketing and sales resources that include:

- marketing consultants;
- a network of key ophthalmic clinicians; and
- other resources with ophthalmic expertise.

We are evaluating expansion of the external marketing and sales resources to support the on-going OcuGene efforts. Potential resources being evaluated include:

- contract sales forces;
- co-marketing arrangements in the U.S.; and
- licensing arrangements with companies outside of the U.S.

We do not plan on establishing a dedicated sales force or a marketing organization for our other product candidates.

We have also entered into arrangements, and we plan to enter into arrangements with one or more additional pharmaceutical companies, to market our other products. We may not be able to conclude or maintain such arrangements on acceptable terms, if at all.

*CIBA Vision.* In 1991, we entered into a co-exclusive rights agreement to market the AquaSite product in the U.S. and Canada. Additionally, in May 1996, we granted CIBA Vision a co-exclusive U.S. license for ISV-205 for non-glaucoma indications, and co-exclusive marketing rights within the U.S. to sell and use ToPreSite, a product candidate that currently is not being pursued. CIBA Vision is using our trademark, under license, for AquaSite dry eye treatment and our patents are identified on the AquaSite packaging. We received a one-time licensing fee and are entitled to royalties based on net sales of the products, if any.

*Global Damon and Kukje.* In March 1999, we entered into a royalty-bearing licensing agreement with Global Damon, a Korean company, to be the exclusive distributor of AquaSite in the Republic of Korea. Concurrently, we entered into a manufacturing agreement with Kukje, a Korean company, to produce the AquaSite to be sold by Global Damon.

*SSP Co., Ltd.* In April 2001, we entered into an exclusive licensing agreement with SSP for two fluoroquinolone compounds, one of which is incorporated into our ISV-403 formulation. We have exclusive marketing rights for the world except for Japan, which SSP retained, and shared rights in the rest of Asia. In August 1999, we entered into an exclusive licensing agreement with SSP to be the exclusive manufacturer and distributor of AquaSite in Japan. We will be the sole supplier to SSP for certain key ingredients necessary for the manufacture of AquaSite.

## **Competition**

We have many competitors in the U.S. and abroad. These companies include ophthalmic-oriented companies that market a broad portfolio of products, as well as large integrated pharmaceutical companies that market a limited number of ophthalmic pharmaceuticals in addition to many other pharmaceuticals. Many of these companies have substantially greater financial, technical, marketing and human resources than we do and may succeed in developing technologies and products that are more effective, safer or more commercially accepted than any which we have developed or are developing. These competitors may also succeed in obtaining cost advantages, patent protection or other intellectual property rights that would block our ability to develop our potential products, or in obtaining regulatory approval for the commercialization of their products more rapidly or effectively than us. The ophthalmic prescription pharmaceutical market in the U.S. is dominated by six companies: Allergan Pharmaceuticals, a division of Allergan, Inc.; Alcon Laboratories, Inc., a division of Nestle Company; Bausch and Lomb; CIBA Vision, a division of Novartis Ltd.; Merck, Sharp & Dohme, a division of Merck & Co., Inc.; and Pharmacia Corporation. It is very difficult for smaller companies, such as ours, that do not have well-developed sales and marketing staffs to successfully develop and market products.

We believe there will be increasing competition from new products entering the market that are covered by exclusive marketing rights and, to a lesser degree, from pharmaceuticals that become generic. We are aware of certain products manufactured or under development by competitors that are used for the treatment of certain ophthalmic indications we have targeted for product development. Our competitive position will depend on our ability to develop enhanced or innovative pharmaceuticals, maintain a proprietary position in our technology and products, obtain required governmental approvals on a timely basis, attract and retain key personnel and develop effective products that can be manufactured on a cost-effective basis and marketed successfully.

Over the longer term, our, and our partners', ability to successfully market our current products, and product candidates, expand their usage and bring new products to the marketplace, will depend on many factors, including the effectiveness and safety of the products, and competing products, approved by the FDA and foreign regulatory agencies, the degree of patent protection afforded to particular products, and obtaining approval from managed care and governmental organizations to purchase or reimburse for the purchase of our products.

## Government Regulation

The manufacturing and marketing of our products and our research and development activities are subject to regulation by numerous governmental authorities in the U.S. and other countries. In the U.S., drugs are subject to rigorous FDA regulation. The Federal Food, Drug and Cosmetic Act and regulations promulgated thereunder govern the testing, manufacture, labeling, storage, record keeping, approval, advertising and promotion in the U.S. of our products. In addition to FDA regulations, we are also subject to other federal and state regulations such as the Occupational Safety and Health Act and the Environmental Protection Act. Product development and approval within this regulatory framework take a number of years and involve the expenditure of substantial resources.

While the FDA currently does not regulate genetic tests, it has stated that it has the right to do so, and there can be no assurance that the FDA will not seek to regulate such tests in the future. If the FDA should require that genetic tests receive FDA approval prior to their use, there can be no assurance such approval would be received on a timely basis, if at all. The failure to receive such approval could require us to develop alternative testing methods, which could result in the delay of such tests reaching the market, if at all. Such a delay could materially harm our business.

The steps required before a pharmaceutical agent may be marketed in the U.S. include:

- preclinical laboratory and animal tests;
- submission to the FDA of an IND;
- adequate and well-controlled human clinical trials to establish the safety and efficacy of the drug;
- the submission of an NDA or Product License Application (“PLA”) to the FDA; and
- the FDA approval of the NDA or PLA, prior to any commercial sale or shipment of the drug.

In addition to obtaining FDA approval for each product, each domestic drug manufacturing establishment must be registered with, and approved by, the FDA. Drug product manufacturing establishments located in California also must be licensed by the State of California in compliance with separate regulatory requirements.

Preclinical tests include laboratory evaluation of product chemistry and animal studies to assess the potential safety and efficacy of the product and its formulation. The results of the preclinical tests are submitted to the FDA as part of an IND and, unless the FDA objects, the IND will become effective 30 days following its receipt by the FDA.

Clinical trials involve the administration of the drug to healthy volunteers or to patients under the supervision of a qualified principal investigator. Clinical trials are conducted in accordance with protocols that detail the objectives of the study, the parameters to be used to monitor safety, and the efficacy criteria to be evaluated. Each protocol is submitted to the FDA as part of the IND. Each clinical study is conducted under the auspices of an independent Institutional Review Board that considers, among other things, ethical factors and the rights, welfare and safety of human subjects.

Clinical trials are typically conducted in three sequential phases, but the phases may overlap. In Phase I, the initial introduction of the drug into human subjects, the drug is tested for safety (adverse effects), dosage tolerance, metabolism, distribution, excretion and clinical pharmacology. Phase II involves studies in a limited patient population to (i) determine the efficacy of the drug for specific targeted indications, (ii) determine dosage tolerance and optimal dosage and (iii) identify possible adverse effects and safety risks. When a compound is found to be effective and to have an acceptable safety profile in Phase II evaluations, Phase III trials are undertaken to further evaluate clinical efficacy and to further test for safety within an expanded patient population at multiple clinical study sites. The FDA reviews both the clinical plans and the results of the trials and may discontinue the trials at any time if there are significant safety issues.

The results of the preclinical studies and clinical studies are submitted to the FDA in the form of an NDA or PLA for marketing approval. The testing and approval process is likely to require substantial

time and effort and there can be no assurance that any approval will be granted on a timely basis, if at all. Additional animal studies or clinical trials may be requested during the FDA review period and may delay marketing approval. After FDA approval for the initial indications, further clinical trials are necessary to gain approval for the use of the product for additional indications. The FDA may also require post-marketing testing to monitor for adverse effects, which can involve significant expense.

Among the conditions for manufacture of clinical drug supplies and for NDA or PLA approval is the requirement that the prospective manufacturer's quality control and manufacturing procedures conform to GMP. Prior to approval, manufacturing facilities are subject to FDA and/or other regulatory agency inspection to ensure compliance with GMP. Manufacturing facilities are subject to periodic regulatory inspection to ensure ongoing compliance.

For marketing outside the U.S., we are also subject to foreign regulatory requirements governing human clinical trials and marketing approval for drugs. The requirements governing the conduct of clinical trials, product licensing, pricing and reimbursement vary widely from country to country and in some cases are even more rigorous than in the U.S.

## Scientific and Business Advisors

We have access to a number of academic and industry advisors with expertise in clinical ophthalmology and pharmaceutical development, marketing and sales. Our advisors meet with our management and key scientific employees on an ad hoc basis to provide advice in their respective areas of expertise and further assist us by periodically reviewing with management our preclinical, clinical and marketing activities. We plan to make arrangements with other individuals to join as advisors as appropriate. Although we expect to receive guidance from the advisors, all of the advisors are employed on a full-time basis by other entities, or are primarily engaged in outside business activities, and may have other commitments to, or consulting or advisory contracts with, other entities that may conflict or compete with their obligations to us.

Our advisors are as follows:

<u>Name</u>	<u>Position</u>
Mark Abelson, M.D.	Associate Clinical Professor of Ophthalmology, Department of Ophthalmology, Harvard Medical School
Chandler R. Dawson, M.D.	Emeritus Professor, Department of Ophthalmology, University of California, San Francisco
Barbara L. Handelin, Ph.D.	Advisor and Consultant on Genetics
David G. Hwang, M.D.	Professor of Clinical Ophthalmology, Co-Director, Cornea and Refractive Surgery Service, University of California, San Francisco School of Medicine
Chris A. Johnson, Ph.D.	Director of Diagnostic Research, Discoveries Insight Research Lab, Devers Eye Institute
Steven G. Kramer, M. D., Ph.D.	Chairman, Department of Ophthalmology, Director of Beckman Vision Center and Professor, University of California, San Francisco
Eliot Lazar, M.D.	President, El Con Medical Consulting, Buffalo, New York
Michael Marmor, M. D.	Professor, Department of Ophthalmology, Stanford University School of Medicine
Gary D. Novack, Ph.D.	Founder and President, PharmaLogic Development, Inc.; former Associate Director for Glaucoma Research at Allergan, Inc.
Jon R. Polansky, M. D.	Associate Professor of Ophthalmology, University of California, San Francisco
Mansoor Sarfarazi, Ph.D.	Professor, Department of Surgery, University of Connecticut Health Center
Roger Vogel, M. D.	Medical Director

## Employees

As of December 31, 2001, we employed 39 persons, including 37 full time employees. None of our employees are covered by a collective bargaining agreement. We believe we have good employee relations. We also utilize independent consultants to provide services in certain areas of our scientific and business operations.

## RISK FACTORS

### **It Is Difficult to Evaluate Our Business Because We Are in an Early Stage of Development and Our Technology Is Untested**

We are in an early stage of developing our business. We have only received an insignificant amount of royalties from the sale of one of our products, an over-the-counter dry eye treatment. Before regulatory authorities grant us marketing approval, we need to conduct significant additional research and development and preclinical and clinical testing. All of our products are subject to risks that are inherent to products based upon new technologies. These risks include the risks that our products:

- are found to be unsafe or ineffective;
- fail to receive necessary marketing clearance from regulatory authorities;
- even if safe and effective, are too difficult or expensive to manufacture or market;
- are unmarketable due to the proprietary rights of third parties; or
- are not able to compete with superior, equivalent or more cost-effective products offered by competitors.

Therefore, our research and development activities may not result in any commercially viable products.

### **We Will Require Significant Additional Funding and We May Have Difficulty Raising Additional Funding**

We will require substantial additional funding to develop and conduct testing on our potential products. We will also require additional funding to support our sales and marketing efforts for our OcuGene glaucoma genetic test and if we decide to independently manufacture or market any of our other products. Our future capital requirements depend upon many factors, including:

- the cost of maintaining or expanding a marketing organization for OcuGene and the related promotional activities;
- the progress of our research and development programs;
- our ability to establish additional corporate partnerships to develop, manufacture and market our potential products;
- the progress of preclinical and clinical testing;
- changes in, or termination of, our existing collaboration or licensing arrangements;
- whether we manufacture and market any of our other products ourselves;
- the time and cost involved in obtaining regulatory approvals;
- the cost of filing, prosecuting, defending and enforcing patent claims and other intellectual property rights;
- competing technological and market developments; and
- the purchase of additional capital equipment.

We may seek additional funding through public or private equity or debt financing, collaborative or other arrangements, and from other sources. We may not be able to secure additional funding from these sources, and any funding may not be on terms acceptable to us. In addition, our board of directors has the authority to determine the price and terms of any sale of common stock and the rights, preferences and privileges of any preferred stock or debt or other security that is convertible into or exercisable for the common stock. The terms of any securities issued to future investors may be superior to the rights of our common stockholders, could result in substantial dilution and could adversely affect the market price for our common stock.

Our stockholders will suffer substantial dilution if we raise additional funds by issuing equity securities. However, if we cannot raise additional funding, we may be required to delay, scale back or eliminate one or more of our research, discovery, development or marketing programs, or scale back or cease operations altogether. In addition, the failure to raise additional funding may force us to enter into agreements with third parties on terms which are disadvantageous to us, which may, among other things, require us to relinquish rights to our technologies, products or potential products.

#### **We Have a History of Operating Losses and We Expect to Continue to Have Losses in the Future**

We have incurred significant operating losses since our inception in 1986 and have pursued numerous drug development candidates that did not prove to have commercial potential. As of December 31, 2001, our accumulated deficit was approximately \$97.8 million. We expect to incur net losses for the foreseeable future or until we are able to achieve significant royalties or other revenues from sales of our products.

Attaining significant revenue or profitability depends upon our ability, alone or with third parties, to successfully develop our potential products, conduct clinical trials, obtain required regulatory approvals and successfully manufacture and market our products. We may not ever achieve or be able to maintain significant revenue or profitability.

#### **We Rely on Third Parties to Develop, Market and Sell Our Products, We May Not Be Able to Continue or Enter into Third Party Arrangements, and these Third Parties' Efforts May Not Be Successful**

Following the termination of our ISV-900 agreement with Pharmacia in December 2000, we began to develop a marketing organization focused on the launch of our OcuGene glaucoma genetic test. We do not plan on establishing a dedicated sales force or a marketing organization for our other product candidates and primarily use external marketing and sales resources even for OcuGene. We also rely on third parties for clinical testing or product development. In addition, in May 2001, Pharmacia terminated the January 1999 licensing agreement we had entered into that granted Pharmacia an exclusive worldwide license for ISV-205 for the treatment of glaucoma. We now must enter into another third party collaboration agreement for the development, marketing and sale of our ISV-205 product or develop, market and sell the product ourselves. There can be no assurance that we will be successful in finding a new corporate partner for our ISV-205 program or that any collaboration will be successful, either of which could significantly harm our business. In addition, we have no experience in marketing and selling products and we cannot assure you that we would be successful in marketing ISV-205 ourselves. If we are to successfully develop and commercialize our product candidates, including ISV-205, we will be required to enter into arrangements with one or more third parties that will:

- provide for Phase II and/or Phase III clinical testing;
- obtain or assist us in other activities associated with obtaining regulatory approvals for our product candidates; and
- market and sell our products, if they are approved.

We are marketing and selling our OcuGene glaucoma genetic test mainly using external marketing and sales resources that include:

- marketing consultants;
- a network of key ophthalmic clinicians; and
- other resources with ophthalmic expertise.

We may not be able to enter into arrangements with third parties with ophthalmic or diagnostic industry experience on acceptable terms or at all. If we are not successful in concluding such arrangements on acceptable terms, we may be required to establish our own sales force and significantly expand our marketing organization, despite the fact that we have no experience in sales, marketing or distribution.

Even if we do enter into collaborative relationships, as we have recently experienced with Pharmacia, these relationships can be terminated forcing us to seek alternatives. We may not be able to build a marketing staff or sales force and our sales and marketing efforts may not be cost-effective or successful.

In addition, we currently contract with a third party to assemble the sample collection kits used in our OcuGene glaucoma genetic test. If our assembler should encounter significant delays or we have difficulty maintaining our existing relationship, or in establishing a new one, our sales of this product could be adversely affected.

Our strategy for research, development and commercialization of our products requires us to enter into various arrangements with corporate and academic collaborators, licensors, licensees and others. Furthermore, we are dependent on the diligent efforts and subsequent success of these outside parties in performing their responsibilities.

Because of our reliance on third parties for the development, marketing and sale of our products, any revenues that we receive will be dependent on the efforts of these third parties, such as our corporate collaborators. These partners may terminate their relationships with us and may not diligently or successfully market our products. In addition, marketing consultants and contract sales organizations, such as those deployed by us currently or in the future for OcuGene, may market products that compete with our products and we must rely on their efforts and ability to effectively market and sell our products. We may not be able to conclude arrangements with other companies to support the commercialization of our products on acceptable terms. In addition, our collaborators may take the position that they are free to compete using our technology without compensating or entering into agreements with us. Furthermore, our collaborators may pursue alternative technologies or develop alternative products either on their own or in collaboration with others, including our competitors, as a means for developing treatments for the diseases or disorders targeted by these collaborative programs.

#### **Our Business Depends Upon Our Proprietary Rights, and We May Not Be Able to Adequately Protect, Enforce or Secure Our Intellectual Property Rights**

Our success will depend in large part on our ability to obtain patents, protect trade secrets, obtain and maintain rights to technology developed by others, and operate without infringing upon the proprietary rights of others. A substantial number of patents in the field of ophthalmology and genetics have been issued to pharmaceutical, biotechnology and biopharmaceutical companies. Moreover, competitors may have filed patent applications, may have been issued patents or may obtain additional patents and proprietary rights relating to products or processes competitive with ours. Our patent applications may not be approved. We may not be able to develop additional proprietary products that are patentable. Even if we receive patent issuances, those issued patents may not be able to provide us with adequate protection for our inventions or may be challenged by others. Furthermore, the patents of others may impair our ability to commercialize our products. The patent positions of firms in the pharmaceutical and genetic industries generally are highly uncertain, involve complex legal and factual questions, and have recently been the subject of much litigation. Neither the United States Patent and Trademark Office nor the courts has developed, formulated, or presented a consistent policy regarding the breadth of claims allowed or the degree of protection afforded under pharmaceutical and genetic patents. Despite our efforts to protect our proprietary rights, others may independently develop similar products, duplicate any of our products or design around any of our patents. In addition, third parties from which we have licensed or otherwise obtained technology may attempt to terminate or scale back our rights.

A number of pharmaceutical and biotechnology companies and research and academic institutions have developed technologies, filed patent applications or received patents on various technologies that may be related to our business. Some of these technologies, applications or patents may conflict with our technologies or patent applications. Such conflicts could limit the scope of the patents, if any, we may be able to obtain or result in the denial of our patent applications. In addition, if the United States Patent and Trademark Office or foreign patent agencies have issued or issue patents that cover our activities to other companies, we may not be able to obtain licenses to these patents at all, or at a reasonable cost, or be able to develop or obtain alternative technology. If we do not obtain such licenses, we could encounter delays in or be precluded altogether from introducing products to the market.

We may need to litigate in order to defend against or assert claims of infringement, to enforce patents issued to us or to protect trade secrets or know-how owned or licensed by us. Litigation could result in substantial cost to and diversion of effort by us, which may harm our business. We have also agreed to indemnify our licensees against infringement claims by third parties related to our technology, which could result in additional litigation costs and liability for us. In addition, our efforts to protect or defend our proprietary rights may not be successful or, even if successful, may result in substantial cost to us.

We also depend upon unpatented trade secrets to maintain our competitive position. Others may independently develop substantially equivalent proprietary information and techniques or otherwise gain access to our trade secrets. Our trade secrets may also be disclosed, and we may not be able to effectively protect our rights to unpatented trade secrets. To the extent that we or our consultants or research collaborators use intellectual property owned by others, disputes also may arise as to the rights in related or resulting know-how and inventions.

**If We Engage in Acquisitions, We Will Incur a Variety of Costs, and the Anticipated Benefits of the Acquisition May Never be Realized**

At some point in the future we may pursue acquisitions of companies, product lines, technologies or businesses that our management believes are complementary or otherwise beneficial to us. Any of these acquisitions could have negative effects on our business. Future acquisitions may result in substantial dilution to our stockholders, the incurrence of additional debt and amortization expenses related to goodwill, research and development and other intangible assets. Any of these results could harm our financial condition. In addition, acquisitions would involve several risks for us, including:

- assimilating employees, operations, technologies and products from the acquired companies with our existing employees, operation, technologies and products;
- diverting our management's attention from day-to-day operation of our business;
- entering markets in which we have no or limited direct experience; and
- potentially losing key employees from the acquired companies.

**We Have No Experience in Commercial Manufacturing and Need to Establish Manufacturing Relationships with Third Parties, and If Contract Manufacturing Is Not Available to Us or Does Not Satisfy Regulatory Requirements, We Will Have to Establish Our Own Regulatory Compliant Manufacturing Capability**

We have no experience manufacturing products for commercial purposes. We have a pilot facility licensed by the State of California to manufacture a number of our products for Phase I and Phase II clinical trials but not for late stage clinical trials or commercial purposes. Any delays or difficulties that we may encounter in establishing and maintaining a relationship with qualified manufacturers to produce, package and distribute our finished products may harm our clinical trials, regulatory filings, market introduction and subsequent sales of our products.

We currently contract with a third party to assemble the sample collection kits used in our OcuGene glaucoma genetic test. If our assembler should encounter significant delays or we have difficulty maintaining our existing relationship, or in establishing a new one, our sales of this product could be adversely affected.

Contract manufacturers must adhere to Good Manufacturing Practices regulations that are strictly enforced by the FDA on an ongoing basis through its facilities inspection program. Contract manufacturing facilities must pass a pre-approval plant inspection before the FDA will approve a new drug application. Some of the material manufacturing changes that occur after approval are also subject to FDA review and clearance or approval. The FDA or other regulatory agencies may not approve the process or the facilities by which any of our products may be manufactured. Our dependence on third parties to manufacture our products may harm our ability to develop and deliver products on a timely and competitive basis. Should we be required to manufacture products ourselves, we:

- will be required to expend significant amounts of capital to install a manufacturing capability;
- will be subject to the regulatory requirements described above;
- will be subject to similar risks regarding delays or difficulties encountered in manufacturing any such products; and
- will require substantial additional capital.

Therefore, we may not be able to manufacture any products successfully or in a cost-effective manner.

**We Have No Experience in Performing the Analytical Procedures Related to Genetic Testing and Have Established an Exclusive Commercial Agreement with a Third Party to Perform These Procedures For Our OcuGene Glaucoma Genetic Test. If We Are Unable to Maintain this Arrangement, and Are Unable to Establish New Arrangements with Third Parties, We Will Have to Establish Our Own Regulatory Compliant Analytical Process for Genetic Testing**

We have no experience in the analytical procedures related to genetic testing. We have entered into an agreement with Quest under which Quest will exclusively perform OcuGene genetic analytical procedures at a commercial scale in the United States. Accordingly, we are reliant on Quest for all of our OcuGene analytical procedures. If we are unable to maintain this arrangement, we would have to contract with another clinical laboratory or would have to establish our own facilities. We cannot assure you that we will be able to contract with another laboratory to perform these services on a commercially reasonable basis, or at all.

Clinical laboratories must adhere to Good Laboratory Practice regulations that are strictly enforced by the FDA on an ongoing basis through its facilities inspection program. Should we be required to perform the analytical procedures for genetic testing ourselves, we:

- will be required to expend significant amounts of capital to install an analytical capability;
- will be subject to the regulatory requirements described above; and
- will require substantial additional capital.

We cannot assure you we will be able to successfully enter into another genetic testing arrangement or perform these analytical procedures ourselves on a cost-efficient basis, or at all.

**We Rely on a Sole Source for Some of the Raw Materials in Our Products, and the Raw Materials We Need May Not be Available to Us**

We are dependent upon our development partner for the active drug incorporated into our ISV-616 product candidate. ISV-616 is a DuraSite-based formulation of a compound that may inhibit the growth of new blood vessels. This compound may be a treatment for such retinal diseases as diabetic retinopathy or macular degeneration. We are performing limited formulation and pre-clinical testing of ISV-616 in collaboration with the pharmaceutical company that developed the compound. The further development of this product will be dependent upon reaching appropriate agreement with our development partner on future supply of the compound and other development terms.

In addition, certain of the raw materials we use in formulating our DuraSite drug delivery system, and other components of our product candidates, are available from only one source. Any significant interruption in the supply of these raw materials could delay our clinical trials, product development or product sales and could harm our business.

**Our Products Are Subject to Government Regulations and Approval Which May Delay or Prevent the Marketing of Potential Products and Impose Costly Procedures Upon Our Activities**

The FDA and comparable agencies in state and local jurisdictions and in foreign countries impose substantial requirements upon preclinical and clinical testing, manufacturing and marketing of pharma-

ceutical products. Lengthy and detailed preclinical and clinical testing, validation of manufacturing and quality control processes, and other costly and time-consuming procedures are required. Satisfaction of these requirements typically takes several years and the time needed to satisfy them may vary substantially, based on the type, complexity and novelty of the pharmaceutical product. The effect of government regulation may be to delay or to prevent marketing of potential products for a considerable period of time and to impose costly procedures upon our activities. The FDA or any other regulatory agency may not grant approval for any products we develop on a timely basis, or at all. Success in preclinical or early stage clinical trials does not assure success in later stage clinical trials. Data obtained from preclinical and clinical activities are susceptible to varying interpretations that could delay, limit or prevent regulatory approval. If regulatory approval of a product is granted, such approval may impose limitations on the indicated uses for which a product may be marketed. Further, even after we have obtained regulatory approval, later discovery of previously unknown problems with a product may result in restrictions on the product, including withdrawal of the product from the market. Moreover, the FDA has recently reduced previous restrictions on the marketing, sale and prescription of products for indications other than those specifically approved by the FDA. Accordingly, even if we receive FDA approval of a product for certain indicated uses, our competitors, including our collaborators, could market products for such indications even if such products have not been specifically approved for such indications. Delay in obtaining or failure to obtain regulatory approvals would make it difficult or impossible to market our products and would harm our business.

The FDA's policies may change and additional government regulations may be promulgated which could prevent or delay regulatory approval of our potential products. Moreover, increased attention to the containment of health care costs in the United States could result in new government regulations that could harm our business. Adverse governmental regulation might arise from future legislative or administrative action, either in the United States or abroad. See “—Uncertainties regarding healthcare reform and third-party reimbursement may impair our ability to raise capital, form collaborations and sell our products.”

#### **We Compete in Highly Competitive Markets and Our Competitors' Financial, Technical, Marketing, Manufacturing and Human Resources May Surpass or Limit Our Ability to Develop and/or Market Our Products and Technologies**

Our success depends upon developing and maintaining a competitive advantage in the development of products and technologies in our areas of focus. We have many competitors in the United States and abroad, including pharmaceutical, biotechnology and other companies with varying resources and degrees of concentration in the ophthalmic market. Our competitors may have existing products or products under development which may be technically superior to ours or which may be less costly or more acceptable to the market. Competition from these companies is intense and is expected to increase as new products enter the market and new technologies become available. Many of our competitors have substantially greater financial, technical, marketing, manufacturing and human resources than we do. In addition, they may also succeed in developing technologies and products that are more effective, safer, less expensive or otherwise more commercially acceptable than any that we have or will develop. Our competitors may obtain cost advantages, patent protection or other intellectual property rights that would block or limit our ability to develop our potential products. Our competitors may also obtain regulatory approval for commercialization of their products more effectively or rapidly than we will. If we decide to manufacture and market our products by ourselves, we will be competing in areas in which we have limited or no experience such as manufacturing efficiency and marketing capabilities. See “—We have no experience in commercial manufacturing and need to establish manufacturing relationships with third parties, and if contract manufacturing is not available to us or does not satisfy regulatory requirements, we will have to establish our own regulatory compliant manufacturing capability.”

#### **We Are Dependent Upon Key Employees and We May Not Be Able to Retain or Attract New Key Employees**

We are highly dependent on Dr. Chandrasekaran and other principal members of our scientific and management staff. The loss of services from these key personnel might significantly delay the achievement

of planned development objectives. Furthermore, a critical factor to our success is recruiting and retaining qualified personnel. Competition for skilled individuals in the biotechnology business is highly intense, and we may not be able to continue to attract and retain personnel necessary for the development of our business. The loss of key personnel or the failure to recruit additional personnel or to develop needed expertise could harm our business.

#### **Our Insurance Coverage May Not Adequately Cover Our Potential Product Liability Exposure**

We are exposed to potential product liability risks inherent in the development, testing, manufacturing, marketing and sale of human therapeutic products. Product liability insurance for the pharmaceutical industry is extremely expensive. Our present product liability insurance coverage may not be adequate. In addition, our existing coverage will not be adequate as we further develop, manufacture and market our products, and adequate insurance coverage against potential claims may not be available in sufficient amounts or at a reasonable cost.

#### **Uncertainties Regarding Healthcare Reform and Third-Party Reimbursement May Impair Our Ability to Raise Capital, Form Collaborations and Sell Our Products**

The continuing efforts of governmental and third party payers to contain or reduce the costs of healthcare through various means may harm our business. For example, in some foreign markets the pricing or profitability of health care products is subject to government control. In the United States, there have been, and we expect there will continue to be, a number of federal and state proposals to implement similar government control. The implementation or even the announcement of any of these legislative or regulatory proposals or reforms could harm our business by impeding our ability to achieve profitability, raise capital or form collaborations.

In addition, the availability of reimbursement from third party payers determines, in large part, the demand for healthcare products in the United States and elsewhere. Examples of such third party payers are government and private insurance plans. Significant uncertainty exists as to the reimbursement status of newly approved healthcare products, and third party payers are increasingly challenging the prices charged for medical products and services. If we succeed in bringing one or more products to the market, reimbursement from third party payers may not be available or may not be sufficient to allow us to sell our products on a competitive or profitable basis.

#### **Our Use of Hazardous Materials May Pose Environmental Risks and Liabilities Which May Cause Us to Incur Significant Costs**

Our research, development and manufacturing processes involve the controlled use of small amounts of radioactive and other hazardous materials. We are subject to federal, state and local laws, regulations and policies governing the use, manufacture, storage, handling and disposal of radioactive and other hazardous materials and waste products. Although we believe that our safety procedures for handling and disposing of these materials comply with the standards prescribed by current laws and regulations, we cannot completely eliminate the risk of accidental contamination or injury from these materials. In the event of such an accident, we could be held liable for any damages that result, and any such liability could exceed our resources. Moreover, we may be required to incur significant costs to comply with environmental laws and regulations, especially to the extent that we manufacture our own products.

#### **Management and Principal Stockholders May Be Able to Exert Significant Control On Matters Requiring Approval by Our Stockholders**

As of December 31, 2001, our management and principal stockholders together beneficially owned approximately 25% of our outstanding shares of common stock. As a result, these stockholders, acting together, may be able to effectively control all matters requiring approval by our stockholders, including the election of a majority of our directors and the approval of business combinations.

**The Market Prices For Securities of Biopharmaceutical and Biotechnology Companies such as Ours May Be Highly Volatile Due to Reasons that Are Related and Unrelated to the Operating Performance and Progress of Our Company**

The market prices for securities of biopharmaceutical and biotechnology companies, including ours, have been highly volatile. The market has from time to time experienced significant price and volume fluctuations that are unrelated to the operating performance of particular companies. In addition, future announcements, such as the results of testing and clinical trials, the status of our relationships with third-party collaborators, technological innovations or new therapeutic products, governmental regulation, developments in patent or other proprietary rights, litigation or public concern as to the safety of products developed by us or others and general market conditions, concerning us, our competitors or other biopharmaceutical companies, may have a significant effect on the market price of our common stock. Further, the standstill we have in place with Pharmacia in connection with our November 1999 ISV-900 transaction expires on May 11, 2002. As a result, we will no longer have any control over Pharmacia's future purchases or sales of our common stock, which could increase the volatility in the market price for our common stock. We have not paid any cash dividends on our common stock, and we do not anticipate paying any dividends in the foreseeable future.

In addition, on September 11, 2001, terrorist attacks destroyed the World Trade Center in New York City and damaged the Pentagon in Washington, D.C. The impact of these events, as well as any future events occurring in connection with these events, including U.S. military retaliation or additional terrorist acts, on financial markets is not yet fully known but has included, and could continue to include, among other things, increased price and volume volatility and/or economic recession. These events, as well as fluctuations in our operating results and market conditions for biopharmaceutical and biotechnology stocks in general, could have a significant effect on the volatility of the market price for our common stock and on the future price of our common stock.

**We Have Adopted and Are Subject to Anti-Takeover Provisions That Could Delay or Prevent an Acquisition of Our Company**

Provisions of our certificate of incorporation and bylaws may constrain or discourage a third party from acquiring or attempting to acquire control of us. Such provisions could limit the price that investors might be willing to pay in the future for shares of our common stock. Our board of directors has the authority to issue up to 5,000,000 shares of preferred stock. The board of directors has the authority to determine the price, rights, preferences, privileges and restrictions of the remaining unissued shares of preferred stock without any further vote or action by the stockholders. The rights of the holders of common stock will be subject to, and may be adversely affected by, the rights of the holders of any preferred stock that may be issued in the future. The issuance of preferred stock, while providing desirable flexibility in connection with possible acquisitions and other corporate purposes, could have the effect of making it more difficult for a third party to acquire a majority of our outstanding voting stock. Provisions of Delaware law applicable to us could also delay or make more difficult a merger, tender offer or proxy contest involving us, including Section 203 of the Delaware General Corporation Law, which prohibits a Delaware corporation from engaging in any business combination with any interested stockholder for a period of three years unless conditions set forth in the Delaware General Corporation Law are met.

## EXECUTIVE OFFICERS AND OTHER SENIOR MANAGEMENT OF THE REGISTRANT

As of March 30, 2002, our executive officers and other senior management were as follows:

<u>Name</u>	<u>Age</u>	<u>Title</u>
S. Kumar Chandrasekaran, Ph.D. . . . .	59	Chairman of the Board, President, Chief Executive Officer and Chief Financial Officer
Lyle M. Bowman, Ph.D. . . . .	53	Vice President, Development and Operations
Charles G. Chavdarian, Ph.D. . . . .	53	Senior Director, Analytical Research and Development
Cheryl E. Chen . . . . .	42	Senior Director, Clinical Operations
T. Raymond Chen, Ph.D. . . . .	51	Senior Director, Regulatory, Quality Assurance and Quality Control
Sandra C. Heine . . . . .	40	Senior Director, Finance and Administration
Samir D. Roy, Ph.D. . . . .	43	Senior Director, Formulation Development and Operations
Erwin C. Si, Ph.D. . . . .	48	Senior Director, Preclinical Research

*S. Kumar Chandrasekaran* joined us in September 1987 as Vice President, Development. From 1988 to 1989, Dr. Chandrasekaran served as Vice President, Research and Development. From 1989 to 1993, he served as President and Chief Operating Officer. Since August 1993, Dr. Chandrasekaran has served as Chairman of the Board of Directors, President, Chief Executive Officer and, since January 1999, as Chief Financial Officer, a position he also held from December 1995 to December 1997. Dr. Chandrasekaran holds a Ph.D. in Chemical Engineering from the University of California, Berkeley.

*Lyle M. Bowman* joined us in October 1988 as Director of Drug Delivery Systems. From 1989 to 1991, Dr. Bowman served as Vice President, Science and Technology. From 1991 to 1995, he served as Vice President, Development, and since 1995 has served as Vice President Development and Operations. Dr. Bowman holds a Ph.D. in Physical Chemistry from the University of Utah.

*Charles G. Chavdarian* joined us in February 2001 as Senior Director of Analytical Research and Development. Before joining us, Dr. Chavdarian held pharmaceutical management positions in analytical chemistry at Cellegy Pharmaceuticals from April 1998 to February 2001, ALZA Corporation from December 1996 to April 1998, Penederm Incorporated from April 1993 to November 1996, and Syntex Corporation from May 1987 to March 1993; and earlier was a researcher in the chemical industry. Dr. Chavdarian holds a Ph.D. in Organic Chemistry from the University of California, Berkeley, and has post-doctoral training in pharmaceutical chemistry at the University of California, San Francisco.

*Cheryl E. Chen* joined us in January 1990 as the Manager of Clinical Research. From 1994 to 1998, Ms. Chen served as Director of Clinical Operations. In 1999, Ms. Chen became the Senior Director of Clinical Operations. Ms. Chen holds a B.S. in Biological Science from University of California at Irvine and an M.B.A. in Business from Pepperdine University.

*T. Raymond Chen* joined us in August 1990 as a Senior Staff Researcher. From 1994 to August 1997, he served as the Director of Analytical Research. Since September 1997, Dr. Chen has served as Senior Director of Regulatory, Quality Assurance and Quality Control. Dr. Chen holds a Ph.D. in Analytical Research from Indiana University.

*Sandra C. Heine* joined us in March 1997 as Contoller. Since October 1999, Ms. Heine has served as Senior Director of Finance and Administration. Before joining us, Ms. Heine served as General Accounting Manager of Software Logistics Corporation from 1995 to 1997; Systems Engineer for Platinum Software Corporation from 1994 to 1995; General Audit Manager for Genentech, Inc. from 1991 to 1994 and was an Audit Manager at Deloitte & Touche from 1989 to 1991. Ms. Heine holds a B.S. in Business Administration from Colorado State University.

*Samir D. Roy* joined us in May 1997 as Director of Formulation Development. Since 1998, Dr. Roy has served as Senior Director of Formulation Development and Operations involving clinical supply and scale-up activities. Dr. Roy holds a Ph.D. in Pharmaceutical Sciences from the University of Saskatchewan, Canada, and has post-doctorial training in drug transport at the University of Michigan.

*Erwin C. Si* joined us in April 1989 as Manager of Pharmacology and Toxicology. From 1992 to 1996, he served as Manager of Drug Discovery. From 1996 to 1999, he served as Principal Scientist. Since October 1999, he has served as Senior Director of Pre-clinical Research. Dr. Si holds a Ph.D. in Pharmacology and Toxicology from Purdue University.

Officers are appointed to serve, at the discretion of the Board of Directors, until their successors are appointed. There are no family relationships between any members of our Board of Directors and our executive officers.

**Item 2. PROPERTIES**

We currently lease approximately 29,402 square feet of research laboratory and office space located in Alameda, California. The facility includes laboratories for formulation, analytical, microbiology, pharmacology, quality control and development as well as a pilot manufacturing plant. The lease expires on December 31, 2006, and may be renewed by us for an additional 5-year term. We believe our existing facilities will be suitable and adequate to meet our needs for the immediate future.

**Item 3. LEGAL PROCEEDINGS.**

- (a) We are not a party to any legal proceedings.
- (b) No legal proceedings were terminated in the fourth quarter.

**Item 4. SUBMISSION OF MATTERS TO A VOTE OF SECURITY HOLDERS.**

No matters were submitted to a vote of our stockholders during the quarter ended December 31, 2001.

**PART II**

**Item 5. MARKET FOR REGISTRANT'S COMMON EQUITY AND RELATED STOCKHOLDER MATTERS**

Since June 10, 1998, our common stock has traded on The American Stock Exchange under the symbol "ISV." From our initial public offering on October 18, 1993 until June 9, 1998, our common stock traded on The Nasdaq National Market under the symbol "INSV." Prior to our initial public offering, there was no public market for our common stock. The following table sets forth the high and low sales prices for our common stock as reported by The American Stock Exchange for the periods indicated. These prices do not include retail mark-ups, mark-downs or commissions.

<u>2001</u>	<u>High</u>	<u>Low</u>
First Quarter .....	\$3.94	\$1.91
Second Quarter.....	\$2.40	\$0.90
Third Quarter .....	\$1.49	\$0.95
Fourth Quarter .....	\$2.00	\$0.90
 <u>2000</u>	 <u>High</u>	 <u>Low</u>
First Quarter .....	\$7.50	\$2.50
Second Quarter.....	\$5.94	\$3.06
Third Quarter .....	\$7.69	\$3.56
Fourth Quarter .....	\$8.50	\$2.18

(b) Holders

As of March 25, 2002, we had approximately 300 stockholders of record. On March 25, 2002, the last sale price reported on The American Stock Exchange for our common stock was \$2.21 per share.

(c) Dividends

We have never paid dividends and do not anticipate paying any dividends in the foreseeable future. It is the present policy of our Board of Directors to retain our earnings, if any, for the development of our business.

**Item 6. SELECTED FINANCIAL DATA**

The comparability of the following selected financial data is affected by a variety of factors, and this data is qualified by reference to and should be read in conjunction with the consolidated financial statements and notes thereto elsewhere in this Annual Report on Form 10-K and the Management's Discussion and Analysis of Financial Condition and Results of Operations. The following table sets forth selected consolidated financial data for us for the five years ended December 31, 2001 (in thousands except per share amounts):

	Year Ended December 31,				
	2001	2000	1999	1998	1997
<b>Consolidated Statements of Operations Data</b>					
Revenues, net	\$ 5	\$ 4,513	\$ 4,760	\$ 16	\$ 50
Operating expenses:					
Research and development, net	6,610	1,674	1,397	6,227	7,224
General and administrative	3,523	2,584	2,293	2,656	3,034
Total expenses	10,133	4,258	3,690	8,883	10,258
Interest and other income (expense), net	572	791	85	299	390
Net income (loss) before taxes	(9,556)	1,046	1,155	(8,568)	(9,818)
Income tax provision	—	—	5	—	—
Net income (loss) before cumulative effect of accounting change	(9,556)	1,046	1,150	(8,568)	(9,818)
Cumulative effect of accounting change (1)	—	(4,486)	—	—	—
Net income (loss)	(9,556)	(3,440)	1,150	(8,568)	(9,818)
Non cash preferred dividend	—	3	22	514	1,326
Net income (loss) applicable to common stockholders	<u>\$(9,556)</u>	<u>\$(3,443)</u>	<u>\$ 1,128</u>	<u>\$(9,082)</u>	<u>\$(11,144)</u>
Basic earnings (loss) per share:					
Net income (loss) per share applicable to common stockholders before cumulative effect of accounting change	\$ (0.38)	\$ 0.04	\$ 0.06	\$ (0.60)	\$ (0.85)
Cumulative effect of accounting change (1)	—	(0.19)	—	—	—
Net income (loss) per share applicable to common stockholders	<u>\$ (0.38)</u>	<u>\$ (0.15)</u>	<u>\$ 0.06</u>	<u>\$ (0.60)</u>	<u>\$ (0.85)</u>
Diluted earnings (loss) per share:					
Net income (loss) per share applicable to common stockholders before cumulative effect of accounting change	\$ (0.38)	\$ 0.04	\$ 0.06	\$ (0.60)	\$ (0.85)
Cumulative effect of accounting change (1)	—	(0.18)	—	—	—
Net income (loss) per share applicable to common stockholders	<u>\$ (0.38)</u>	<u>\$ (0.14)</u>	<u>\$ 0.06</u>	<u>\$ (0.60)</u>	<u>\$ (0.85)</u>
Pro-forma net income (loss) assuming the accounting change is applied retroactively	<u>\$(9,556)</u>	<u>\$ 1,043</u>	<u>\$(3,358)</u>	<u>\$(9,082)</u>	<u>\$(10,894)</u>
Pro-forma net income (loss) per share assuming the accounting change is applied retroactively, basic and diluted	<u>\$ (0.38)</u>	<u>\$ 0.04</u>	<u>\$ (0.17)</u>	<u>\$ (0.60)</u>	<u>\$ (0.83)</u>
Shares used to calculate basic net income (loss) per share	<u>24,897</u>	<u>23,574</u>	<u>19,285</u>	<u>15,079</u>	<u>13,053</u>
Shares used to calculate diluted net income (loss) per share	<u>24,897</u>	<u>24,483</u>	<u>19,856</u>	<u>15,079</u>	<u>13,053</u>
Shares used to calculate pro-forma basic net income (loss) per share	<u>24,897</u>	<u>23,574</u>	<u>19,285</u>	<u>15,079</u>	<u>13,053</u>
Shares used to calculate pro-forma diluted net income (loss) per share	<u>24,897</u>	<u>24,483</u>	<u>19,285</u>	<u>15,079</u>	<u>13,053</u>

(1) Reflects the impact of the adoption of SAB 101 on revenue recognition effective January 1, 2000.

	December 31,				
	2001	2000	1999	1998	1997
<b>Consolidated Balance Sheet Data</b>					
Cash and cash equivalents .....	\$ 10,095	\$ 18,904	\$ 6,746	\$ 1,037	\$ 8,660
Working capital .....	8,747	18,305	6,167	544	7,983
Total assets .....	11,051	20,000	7,463	2,086	10,546
Long term notes payable .....	45	26	—	—	—
Redeemable preferred stock .....	—	—	30	1,511	7,533
Accumulated deficit .....	(97,753)	(88,197)	(84,754)	(85,882)	(76,800)
Total stockholders' equity (deficit) .....	9,485	18,770	6,256	(108)	2,031

No cash dividends have been declared or paid by us since our inception.

## **Item 7. MANAGEMENT'S DISCUSSION AND ANALYSIS OF FINANCIAL CONDITION AND RESULTS OF OPERATIONS**

The following discussion should be read in conjunction with the financial statements and notes thereto included in Item 8 of this Form 10-K.

### **Overview**

In addition to the historical information contained herein, the discussion in this Annual Report on Form 10-K may contain certain forward-looking statements that involve risks and uncertainties, such as statements of our plans, objectives, expectations and intentions. The cautionary statements made in this document should be read as being applicable to all related forward-looking statements wherever they appear in this document. Our actual results could differ materially from those discussed herein. Factors that could cause or contribute to such differences include those discussed below and under "Risk Factors" in Item 1 of this Form 10-K, as well as those discussed elsewhere in this 10-K.

We are an ophthalmic product development company focused on developing genetically based tools, for the diagnosis, prognosis and management of glaucoma, as well as ophthalmic pharmaceutical products based on our proprietary DuraSite® eyedrop-based drug delivery technology. Our retinal programs include both a therapeutic agent and a retinal drug delivery technology.

We are focusing our commercial efforts and research and development on the following:

- launching our OcuGene™ glaucoma genetic test based on our ISV-900 technology;
- expanding our ISV-900 technology for the diagnosis, prognosis and management of glaucoma;
- ISV-205, a DuraSite formulation for the treatment of glaucoma;
- ISV-401, a DuraSite formulation of a novel antibiotic not currently used in ophthalmology;
- ISV-403, a DuraSite formulation of a fourth generation fluoroquinolone;
- ISV-014, a retinal drug delivery device; and
- treatments for diabetic retinopathy and macular degeneration.

Since our inception through the end of 2001, we had not received any revenues from the sale of our products, although we have received a small amount of royalties from the sale of products using our licensed technology. However, at the end of 2001, we commercially launched our OcuGene glaucoma genetic test and in the beginning of 2002 we began to receive a small amount of revenues from the sale of this test. With the exception of 1999, we have been unprofitable since our inception due to continuing research and development efforts, including preclinical studies, clinical trials and manufacturing of our product candidates. We have financed our research and development activities and operations primarily through private and public placement of our equity securities and, to a lesser extent, from collaborative agreements.

## **Critical Accounting Policies and Use of Estimates**

The preparation of financial statements in conformity with generally accepted accounting principles in the U.S. requires us to make estimates and assumptions that affect the amounts reported in the financial statements and accompanying notes. Actual results could differ from those estimates.

The following are items in our financial statements that require significant estimates and judgments:

*Inventory.* Our inventories are stated at the lower of cost or market. The cost of the inventory is based on the first-in first-out method. If the cost of the inventory exceeds the expected market value a provision is recorded for the difference between cost and market. At December 31, 2001, our inventories solely consisted of OcuGene kits.

*Property and Equipment.* Property and equipment is stated at cost, less accumulated depreciation. Depreciation of property and equipment is provided over the estimated useful lives of the respective assets, which range from three to five years, using the straight-line method. Leasehold improvements are amortized over the lives of the related leases or their estimated useful lives, whichever is shorter, using the straight-line method. It is our policy to write-off our fully depreciated assets.

Additionally, we record impairment losses on long-lived assets used in operations when events and circumstances indicate that the assets might be impaired and the undiscounted cash flows estimated to be generated by those assets are less than the carrying amounts of those assets.

*Revenue Recognition.* We recognize up-front fees over the expected term of the research and development services using the straight-line method. When changes in the expected term of ongoing services are identified, the amortization period for the remaining fees is appropriately modified.

Revenue related to performance milestones is recognized when the milestone is achieved based on the terms set forth in the related agreements.

We directly reduce expenses for amounts reimbursed due to cost sharing agreements. We recognize the received cost sharing payments when persuasive evidence of an arrangement exists, the services have been rendered, the fee is fixed or determinable and collectibility is reasonably assured.

We receive royalties from licensees based on third-party sales and the royalties are recorded as earned in accordance with contract terms, when third party results are reliably measured and collectibility is reasonably assured.

*Research and Development (R&D) Expenses.* R&D expenses include salaries, benefits, facility costs, services provided by outside consultants and contractors, administrative costs and materials for research and development activities. We also fund research at a variety of academic institutions based on agreements that are generally cancelable. We recognize such costs as they are incurred.

*General and Administrative (G&A) Expenses.* G&A expenses include salaries, benefits, facility costs, services provided by outside consultants and contractors, investor relations, financial reporting, materials and other expenses related to general corporate activities.

## **Results of Operations**

We had total net revenues of \$5,000, \$4,513,000, and \$4,760,000 for the years ended December 31, 2001, 2000 and 1999, respectively. Our net revenues in 2001 only represented royalties while the net revenues in 2000 included licensing revenue. Our net revenues in 1999 were attributable to the ISV-900 license fee received from Pharmacia. The net revenues in 2000 included the impact of the implementation of Staff Accounting Bulletin 101 (SAB 101). SAB 101 included new guidelines from the Securities and Exchange Commission regarding revenue recognition of non-refundable up-front license fees, such as the \$4,750,000 net licensing fee we received from Pharmacia in 1999. To implement SAB 101, the net licensing fee from Pharmacia, previously recognized as revenue in 1999, was deferred in our cumulative effect of accounting change and was amortized over the term of the ongoing research and development activities. As a result, we recorded a charge for the cumulative effect of the change in accounting principle of \$4,486,000 as of January 1, 2000. Upon the termination of the related licensing agreement in Decem-

ber 2000, the remaining unamortized deferred revenue was recognized. Amortization of revenue deferred in the cumulative effect was \$4,486,000 of the total net revenues for 2000.

We earned royalty income of \$5,000, \$27,000 and \$10,000 for the years ended December 31, 2001, 2000 and 1999, respectively, from sales of AquaSite by CIBA Vision and Global Damon who began selling AquaSite in Korea in 2000. We have not relied on royalty revenues to fund our activities, and through December 31, 2001 we have received revenues from the sale of products.

Our R&D expenses in 2001 increased 13% to \$7.3 million from \$6.5 million in 2000. R&D expenses in 2000 increased 14% to \$6.5 million from \$5.6 million in 1999. The increase in 2001 related primarily to the cost of preparing for, and filing, an IND and the subsequent initiation of clinical studies for the ISV-401 antibiotic program. Additionally, the cost of filing and maintaining our owned and licensed patents increased as our patent portfolio grew. The increase in 2000 primarily related to outside laboratory services supporting the ISV-401, 402 and 403 antibiotic programs and a 13% increase in R&D headcount.

In 2001, our R&D cost reimbursements decreased 85% to \$0.7 million from \$4.8 million in 2000. This reflected the termination of both the ISV-900 and the ISV-205 licenses by Pharmacia in 2000 and 2001, respectively. In 2000, cost reimbursement increased 13% to \$4.8 million from \$4.2 million in 1999. This increase reflects cost reimbursement by Pharmacia for the ISV-900 and ISV-402 programs in 2000, in addition to the ISV-205 program.

Our R&D activities can be separated into two major segments, research and clinical development. Research includes activities involved in evaluating a potential product and the related pre-clinical testing. Clinical development includes activities related to filings with the FDA and the related human clinical testing required to obtain marketing approval for a potential product. We estimate that the following represents the approximate cost of these activities for 2001, 2000 and 1999 (in thousands):

	<u>2001</u>	<u>2000</u>	<u>1999</u>
Research .....	\$5,050	\$4,670	\$4,005
Clinical development .....	<u>2,273</u>	<u>1,783</u>	<u>1,640</u>
Total research and development.....	<u>\$7,323</u>	<u>\$6,453</u>	<u>\$5,645</u>

Due to our limited personnel and number of projects that we are developing, our personnel are involved in a number of projects at the same time. Accordingly, the majority of our R&D expenses are not linked to a specific project but are allocated across projects, based on personnel time expended on each project. Accordingly, the allocated costs may not reflect the actual costs of each project.

The increase in our research activities from 1999 through 2001 reflects the addition of antibiotic programs to our portfolio and the expansion of our glaucoma genetics research projects. A portion of these activities is conducted through research agreements with academic centers in the U.S., Canada, Europe and Japan. Expenses for such activities are expensed when incurred as these research agreements may be terminated when the appropriate notice is provided as required in each agreement.

The increase in our clinical development expenses from 1999 through 2001 reflects the initiation of clinical studies on our ISV-401 antibiotic project, the conduct of clinical studies to support our glaucoma genetics projects and the increased number of projects we have filed with the FDA.

Most of our projects are in the early stages of the product development cycle and may not result in commercial products. Please see "Products and Product Candidates" in the business section for further information as to what stage in the development cycle each project is in as of December 31, 2001. Projects in development may not proceed into clinical trials due to a number of reasons even though the project looks promising early in the process. Once a project reaches clinical studies it may be found to be ineffective or there may be harmful side effects. Additionally, during the development cycle, other companies may develop new treatments that decrease the market potential for our project and we may decide not to proceed. Other factors including the cost of manufacturing at a commercial scale and the availability of quality manufacturing capabilities could negatively impact our ability to bring the project

to the market. Also, our business strategy is to license projects to third parties to complete the development cycle and to market and sell the product. These collaborative arrangements may either speed the development or they may extend the anticipated time to market. For a more detailed review of these uncertainties, please see the risks discussed under "Risk Factors" in Item 1 of this Report, as well as those discussed elsewhere in the Report. Because of these factors, as well as others, we cannot be certain if, or when, our projects in development will complete the development cycle and be commercialized.

General and administrative expenses increased 36% in 2001 to \$3.5 million from \$2.6 million in 2000, and increased 13% in 2000 to \$2.6 million from \$2.3 million in 1999. The increase in 2001 is primarily related to \$0.9 million we expended on preparing for, and executing, the commercial launch of the OcuGene glaucoma genetic test. The increase in 2000 from 1999 mainly reflected the increase in finance, investor relations and public relations consulting and activities.

Net interest and other income was \$572,000, \$791,000, and \$85,000 in 2001, 2000, and 1999, respectively. These fluctuations are due principally to changes in average cash balances and decreased interest rates. Interest earned in the future will be dependent on our funding cycles and prevailing interest rates.

We had a net loss for the years ended December 31, 2001 and 2000 of \$9.6 million and \$3.4 million, respectively, and net income of \$1.1 million in 1999. The increase in the net loss in 2001 mainly reflects the 85% decrease in cost reimbursement from Pharmacia, the higher cost of our development projects and the launch of the OcuGene glaucoma genetic test. The net income in 1999 is mainly the result of licensing revenue of \$4.8 million and cost reimbursement of \$4.2 million received from Pharmacia.

### **Liquidity and Capital Resources**

Through 1995, we financed our operations primarily through private placements of preferred stock totaling approximately \$32.0 million and an October 1993 initial public offering of Common Stock, which resulted in net proceeds of approximately \$30.0 million. After 1995, we financed our operations through a January 1996 private placement of Common Stock and warrants resulting in net proceeds of approximately \$4.7 million and an April 1996 public offering which raised net proceeds of approximately \$8.1 million. In accordance with a July 1996 agreement with B&L, we received a total of \$2.0 million from the sale of Common Stock in August 1996 and 1997. In September 1997, we completed a \$7.0 million private placement of 7,000 shares of redeemable convertible Series A Preferred Stock resulting in net proceeds of approximately \$6.5 million. In January 1999, we entered into a transaction with Pharmacia from which we received a total of \$3.5 million from the sale of Common Stock in January and September. In November 1999, we entered into another transaction with Pharmacia from which we received a \$5.0 million licensing fee and, in January 2000, received \$2.0 million from the sale of Common Stock. In April 2000, we received \$0.6 million from the exercise of warrants issued as part of the 1995 private placement. In May 2000, we completed a private placement of Common Stock and warrants from which we raised net proceeds of approximately \$13.0 million. During 2000 and 2001, we also received \$243,000 and \$71,000, respectively, from the issuance of Common Stock related to the exercise of stock options and sales of Common Stock through our Employee Stock Purchase Plan. At December 31, 2001, we had cash and cash equivalents totaling \$10.1 million. It is our policy to invest these funds in highly liquid securities, such as interest bearing money market funds, Treasury and federal agency notes and corporate debt.

For the years ended December 31, 2001 and 2000, cash used for operating activities and to acquire capital equipment, was \$8.9 million and \$3.6 million, respectively. For the year ended December 31, 1999, cash provided by operating activities, less cash used to acquire capital equipment, was \$1.8 million. Of those amounts, \$474,000, \$450,000, and \$88,000 were for additions to laboratory and other property and equipment in 2001, 2000, and 1999, respectively. In 1999, we sold the equipment and improvements we had installed at B&L's Tampa facility, to B&L for \$410,000, which resulted in a loss on the sale of \$107,000.

Our future capital expenditures and requirements will depend on numerous factors, including the progress of our research and development programs and preclinical and clinical testing, the time and costs involved in obtaining regulatory approvals, our ability to establish additional collaborative arrangements,

changes in our existing collaborative and licensing relationships, the cost of filing, prosecuting, defending and enforcing patent claims and other intellectual property rights, competing technological and market developments, acquisition of new businesses, products and technologies, the completion of commercialization activities and arrangements, the timing of additional product development and the purchase of additional property and equipment. Starting in 1997, we wrote-off our fully depreciated assets. This resulted in a decrease in both property and equipment and accumulated depreciation of \$57,000, \$44,000 and \$300,000 in 2001, 2000 and 1999, respectively, with no change in net property and equipment.

As of December 31, 2001, our accumulated deficit was approximately \$97.8 million. There can be no assurance that we will ever achieve or be able to maintain either significant revenues from product sales or profitable operations.

We do not anticipate any material capital expenditures to be incurred for environmental compliance in fiscal year 2002. Based on our good environmental compliance record to date, and our current compliance with applicable environmental laws and regulations, environmental compliance is not expected to have a material adverse effect on our operations.

Our commitments as of December 31, 2001 were as follows (in thousands):

	<u>Total</u>	<u>Due in 2002</u>	<u>Due in 2003</u>	<u>Due in 2004</u>	<u>Due in 2005</u>	<u>Due in 2006</u>
Capital lease obligations (1).....	\$ 86	\$ 38	\$ 38	\$ 10	\$ —	\$ —
Operating leases (2).....	3,582	658	694	718	743	769
Research and development agreements (3) .....	343	343	—	—	—	—
Licensing agreements (4) .....	160	15	15	30	50	50
Total commitments.....	<u>\$4,171</u>	<u>\$1,054</u>	<u>\$747</u>	<u>\$758</u>	<u>\$793</u>	<u>\$819</u>

- (1) We lease certain laboratory equipment under capital lease agreements, which expire through 2005.
- (2) We lease our facilities under a non-cancelable operating lease that expires in 2006.
- (3) We have research and development agreements with academic centers in the U.S., Canada, Europe and Japan. The terms of most of these agreements is one year with the option to extend the term with the consent of both the academic center and us.
- (4) We have certain licensing agreements that require minimum royalty payments for the life of the licensed patents. The life of the patents which may be issued and covered by the licensing agreements cannot be determined at this time, but the minimum royalties due under such agreements is approximately \$60,000 per year after 2006 until the expiration of the related patents.

We believe our cash and cash equivalents will be sufficient to meet our operating expenses and cash requirements through 2002. We will require substantial additional funds prior to reaching sustained profitability, and we may seek private or public equity investments, future collaborative agreements, and possibly research funding to meet such needs. Even if we do not have an immediate need for additional cash, we may seek access to the private or public equity markets if and when we believe conditions are favorable. However, there is no assurance that additional funds will be available to us to finance our operations, on acceptable terms, or at all.

#### **Recent Accounting Pronouncements**

In June 2001, the Financial Accounting Standards Board or FASB, issued Statements of Financial Accounting Standards No. 141, *Business Combinations*, and No. 142, *Goodwill and other Intangible Assets*, effective for fiscal years beginning after December 15, 2001. Under the new rules, goodwill and intangible assets deemed to have indefinite lives will no longer be amortized but will be subject to an annual impairment test in accordance with the Statements. Other intangible assets will continue to be amortized over their useful lives. We do not expect that the adoption of Statement 142 will have a material effect on our consolidated financial position or results of operations.

In October 2001, FASB issued Statements of Financial Accounting Standards No. 144, *Accounting for the Impairment or Disposal of Long-Lived Assets*, effective for fiscal years beginning after December 15, 2001, with transition provisions for certain matters. The FASB's new rules on asset impairment supersedes FASB Statement No. 121, *Accounting for Impairment of Long-Lived Assets and for Long-Lived Assets to be Disposed Of*, and provide a single accounting model for long-lived assets to be disposed of. We do not expect that the adoption of Statement 144 will have a material effect on our consolidated financial position or results of operations.

**Item 7A. QUALITATIVE AND QUANTITATIVE DISCLOSURES ABOUT MARKET RISK**

The following discusses our exposure to market risk related to changes in interest rates.

We invest our excess cash in investment grade, interest-bearing securities. At December 31, 2001, we had \$10.1 million invested in money market mutual funds. While a hypothetical decrease in market interest rates by 10 percent from the December 31, 2001 levels would cause a decrease in interest income, it would not result in a loss of the principal. Additionally, the decrease in interest income would not be material.

**Item 8. FINANCIAL STATEMENTS AND SUPPLEMENTARY DATA**

The following Consolidated Financial Statements and Report of Independent Auditors are included on the pages that follow:

	<u>Page</u>
Report of Independent Auditors .....	32
Consolidated Statements of Operations Years Ended December 31, 2001, 2000 and 1999 .....	33
Consolidated Balance Sheets — December 31, 2001 and 2000 .....	34
Consolidated Statements of Stockholders' Equity Years ended December 31, 2001, 2000 and 1999 .....	35
Consolidated Statements of Cash Flows Years Ended December 31, 2001, 2000 and 1999 .....	36
Notes to Consolidated Financial Statements .....	37-47

## REPORT OF ERNST & YOUNG LLP, INDEPENDENT AUDITORS

The Board of Directors and Stockholders  
InSite Vision Incorporated

We have audited the accompanying consolidated balance sheets of InSite Vision Incorporated as of December 31, 2001 and 2000, and the related consolidated statements of operations, stockholders' equity and cash flows for each of the three years in the period ended December 31, 2001. These consolidated financial statements are the responsibility of the Company's management. Our responsibility is to express an opinion on these consolidated financial statements based on our audits.

We conducted our audits in accordance with auditing standards generally accepted in the 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 includes examining, on a test basis, evidence supporting the amounts and disclosures in the financial statements. An audit also includes assessing the accounting principles used and significant estimates made by management, as well as evaluating the overall financial statement presentation. We believe that our audits provide a reasonable basis for our opinion.

In our opinion, the consolidated financial statements referred to above present fairly, in all material respects, the consolidated financial position of InSite Vision Incorporated at December 31, 2001 and 2000, and the consolidated results of its operations and its cash flows for each of the three years in the period ended December 31, 2001, in conformity with accounting principles generally accepted in the United States.

/s/ Ernst & Young LLP

Palo Alto, California  
February 1, 2002

**INSITE VISION INCORPORATED**  
**CONSOLIDATED STATEMENTS OF OPERATIONS**

<u>(in thousands, except per share amounts)</u>	<u>Year Ended December 31,</u>		
	<u>2001</u>	<u>2000</u>	<u>1999</u>
Revenues:			
License fee .....	\$ —	\$ 4,486	\$ 4,750
Royalties .....	5	27	10
Total .....	<u>5</u>	<u>4,513</u>	<u>4,760</u>
Operating expenses:			
Research and development .....	7,323	6,453	5,645
Cost reimbursement .....	713	4,779	4,248
Research and development, net .....	<u>6,610</u>	<u>1,674</u>	<u>1,397</u>
Selling, general and administrative .....	3,523	2,584	2,293
Total .....	<u>10,133</u>	<u>4,258</u>	<u>3,690</u>
Income (loss) from operations .....	<u>(10,128)</u>	<u>255</u>	<u>1,070</u>
Interest and other income (expense), net .....	572	791	85
Net income (loss) before taxes .....	<u>(9,556)</u>	<u>1,046</u>	<u>1,155</u>
Income tax provision .....	—	—	5
Net income (loss) before cumulative effect of accounting change .....	<u>(9,556)</u>	<u>1,046</u>	<u>1,150</u>
Cumulative effect of accounting change .....	—	(4,486)	—
Net income (loss) .....	<u>(9,556)</u>	<u>(3,440)</u>	<u>1,150</u>
Non-cash preferred dividend .....	—	3	22
Net income (loss) applicable to common stockholders .....	<u>\$ (9,556)</u>	<u>\$ (3,443)</u>	<u>\$ 1,128</u>
Basic income (loss) per share:			
Net income (loss) per share applicable to common stockholders before cumulative effect of accounting change .....	\$ (0.38)	\$ 0.04	\$ 0.06
Cumulative effect of accounting change .....	—	(0.19)	—
Net income (loss) per share applicable to common stockholders .....	<u>\$ (0.38)</u>	<u>\$ (0.15)</u>	<u>\$ 0.06</u>
Diluted income (loss) per share:			
Net income (loss) per share applicable to common stockholders before cumulative effect of accounting change .....	\$ (0.38)	\$ 0.04	\$ 0.06
Cumulative effect of accounting change .....	—	(0.18)	—
Net income (loss) per share applicable to common stockholders .....	<u>\$ (0.38)</u>	<u>\$ (0.14)</u>	<u>\$ 0.06</u>
Pro-forma amounts assuming the accounting change is applied retroactively:			
Net income (loss) applicable to common stockholders .....	<u>\$ (9,556)</u>	<u>\$ 1,043</u>	<u>\$ (3,358)</u>
Net income (loss) per share applicable to common stockholders, basic and diluted .....	<u>\$ (0.38)</u>	<u>\$ 0.04</u>	<u>\$ (0.17)</u>
Shares used to calculate basic net income (loss) per share .....	<u>24,897</u>	<u>23,574</u>	<u>19,285</u>
Shares used to calculate diluted net income (loss) per share .....	<u>24,897</u>	<u>24,483</u>	<u>19,856</u>
Shares used to calculate pro-forma basic net income (loss) per share .....	<u>24,897</u>	<u>23,574</u>	<u>19,285</u>
Shares used to calculate pro-forma diluted net income (loss) per share .....	<u>24,897</u>	<u>24,483</u>	<u>19,285</u>

See accompanying notes to consolidated financial statements.

**INSITE VISION INCORPORATED**  
**CONSOLIDATED BALANCE SHEETS**

<u>(in thousands, except share and per share amounts)</u>	<u>December 31,</u>	
	<u>2001</u>	<u>2000</u>
<b>ASSETS</b>		
Current assets:		
Cash and cash equivalents .....	\$ 10,095	\$ 18,904
Inventory .....	70	—
Prepaid expenses and other current assets .....	103	605
Total current assets .....	10,268	19,509
Property and equipment, at cost:		
Laboratory and other equipment .....	1,056	647
Leasehold improvements .....	68	9
Furniture and fixtures .....	3	3
	1,127	659
Accumulated depreciation .....	344	168
	783	491
Total assets .....	\$ 11,051	\$ 20,000
<b>LIABILITIES AND STOCKHOLDERS' EQUITY</b>		
Current liabilities:		
Accounts payable .....	\$ 344	\$ 181
Accrued liabilities .....	356	376
Accrued compensation and related expense .....	821	647
Total current liabilities .....	1,521	1,204
Long-term notes payable .....	45	26
Commitments (Note 3)		
Redeemable preferred stock, \$0.01 par value, 5,000,000 shares authorized; no shares issued and outstanding at December 31, 2001 and 2000 .....	—	—
Common stockholders' equity:		
Common stock, \$0.01 par value, 60,000,000 shares authorized; 24,930,350 issued and outstanding at December 31, 2001; 24,853,767 issued and outstanding at December 31, 2000 .....	249	248
Additional paid-in capital .....	107,246	106,976
Notes receivable from stockholder .....	(257)	(257)
Accumulated deficit .....	(97,753)	(88,197)
Common stockholders' equity .....	9,485	18,770
Total liabilities, redeemable preferred stock and stockholders' equity .....	\$ 11,051	\$ 20,000

See accompanying notes to consolidated financial statements.

**INSITE VISION INCORPORATED**  
**CONSOLIDATED STATEMENTS OF STOCKHOLDERS' EQUITY**

<u>(dollars in thousands)</u>	<u>Common Stock</u>	<u>Additional Paid In Capital</u>	<u>Note Receivable From Stockholder</u>	<u>Accumulated Deficit</u>	<u>Total Stockholders' Equity</u>
<b>Balances, January 1, 1999</b> .....	\$169	\$ 85,605	\$ —	\$(85,882)	\$ (108)
Issuance of 1,942,419 shares of common stock to Pharmacia & Upjohn in private placements .....	19	3,480	—	—	3,499
Issuance of 33,073 shares of common stock from exercise of options and employee stock purchase plan .....	—	40	—	—	40
Issuance of 1,471,416 shares of common stock from conversion of preferred shares .....	15	1,488	—	—	1,503
Non-employee stock option compensation .....	—	194	—	—	194
Net income and comprehensive income .....	—	—	—	1,150	1,150
Non-cash preferred dividend .....	—	—	—	(22)	(22)
Net income applicable to common stockholders .....	—	—	—	1,128	1,128
<b>Balances, December 31, 1999</b> .....	<b>\$203</b>	<b>\$ 90,807</b>	<b>\$ —</b>	<b>\$(84,754)</b>	<b>\$ 6,256</b>
Issuance of 723,195 shares of common stock to Pharmacia & Upjohn in private placements .....	7	1,993	—	—	2,000
Issuance of 192,308 shares of common stock from exercise of warrants .....	2	623	—	—	625
Issuance of 3,349,722 shares of common stock in a private placement .....	33	13,007	—	—	13,040
Issuance of 261,582 shares of common stock from exercise of options and employee stock purchase plan .....	3	316	(257)	—	62
Issuance of 28,037 shares of common stock from conversion of preferred stock .....	—	33	—	—	33
Non-employee stock option compensation .....	—	197	—	—	197
Net loss and comprehensive loss .....	—	—	—	(3,440)	(3,440)
Non-cash preferred dividend .....	—	—	—	(3)	(3)
Net loss applicable to common stockholders .....	—	—	—	(3,443)	(3,443)
<b>Balances, December 31, 2000</b> .....	<b>\$248</b>	<b>\$106,976</b>	<b>\$(257)</b>	<b>\$(88,197)</b>	<b>\$18,770</b>
Issuance of 76,583 shares of common stock from exercise of options and employee stock purchase plan .....	1	70	—	—	71
Non-employee stock option compensation .....	—	200	—	—	200
Net loss and comprehensive loss .....	—	—	—	(9,556)	(9,556)
<b>Balances, December 31, 2001</b> .....	<b><u>\$249</u></b>	<b><u>\$107,246</u></b>	<b><u>\$(257)</u></b>	<b><u>\$(97,753)</u></b>	<b><u>\$ 9,485</u></b>

See accompanying notes to consolidated financial statements.

**INSITE VISION INCORPORATED**  
**CONSOLIDATED STATEMENTS OF CASH FLOWS**

<i>(in thousands)</i>	Year Ended December 31,		
	2001	2000	1999
<b>Operating activities:</b>			
Net income (loss) .....	\$(9,556)	\$(3,440)	\$1,150
Adjustments to reconcile net income (loss) to net cash provided (used) by operating activities:			
Depreciation and amortization .....	233	117	311
Stock-based compensation .....	200	197	194
Loss on sale of property and equipment .....	—	—	107
Changes in:			
Prepaid expenses and other current assets .....	432	(7)	(408)
Accounts payable and accrued liabilities .....	292	20	494
Net cash provided by (used in) operating activities .	(8,399)	(3,113)	1,848
<b>Investing activities:</b>			
Sale of property and equipment .....	—	—	410
Purchases of property and equipment .....	(474)	(450)	(88)
Net cash provided by (used in) investing activities ..	(474)	(450)	322
<b>Financing activities:</b>			
Payment of capital lease obligation .....	(7)	(6)	—
Issuance of common stock, net .....	71	15,727	3,539
Net cash provided by financing activities .....	64	15,721	3,539
Net increase (decrease) in cash and cash equivalents .....	(8,809)	12,158	5,709
Cash and cash equivalents, beginning of period ....	18,904	6,746	1,037
Cash and cash equivalents, end of period .....	\$10,095	\$18,904	\$6,746
<b>Supplemental disclosures:</b>			
Non-cash preferred dividends .....	\$ —	\$ 3	\$ 22
Non-cash conversion of redeemable preferred stock to common stock .....	\$ —	\$ 33	\$1,503
Capital lease obligation incurred .....	\$ 51	\$ 39	\$ —

See accompanying notes to consolidated financial statements.

**INSITE VISION INCORPORATED**  
**NOTES TO CONSOLIDATED FINANCIAL STATEMENTS**  
**DECEMBER 31, 2001**

**1. Summary of Significant Accounting Policies**

**Basis of Presentation.** The accompanying consolidated financial statements include the accounts of InSite Vision and its wholly-owned United Kingdom subsidiary, InSite Vision Limited. InSite Vision Incorporated (the "Company" or "InSite Vision") operated in one segment and is focused on ophthalmic genetics and developing ophthalmic drugs and ophthalmic drug delivery systems. InSite Vision Limited was formed for the purpose of holding and licensing intellectual property rights. All intercompany accounts and transactions have been eliminated.

The Company's consolidated financial statements have been presented on a basis that contemplates the realization of assets and the satisfaction of liabilities in the normal course of business. Except for 1999, the Company has incurred losses since its inception and the Company expects to incur substantial additional development costs prior to reaching sustained profitability, including costs related to clinical trials and manufacturing expenses. The Company is actively pursuing various sources of additional funds, including new license and collaboration agreements and securing additional equity financing, and believes that sufficient funding will be available to meet its projected operating and capital requirements through December 31, 2002. There is no assurance that such additional funds will be available for the Company to finance its operations on acceptable terms, if at all. If such funds are not available, management will be required to delay, scale back or eliminate one or more of its research, discovery or development programs. Such actions may include significantly reducing its anticipated level of expenditures and/or the sale of rights to certain of its technologies, product candidates or products. The financial statements do not include any adjustments to reflect the possible future effects on the recoverability and classification of assets or the amounts and classification of liabilities that may result from the outcome of this uncertainty.

**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 amounts reported in the financial statements and accompanying notes. Actual results could differ from those estimates.

**Cash and Cash Equivalents.** The Company invests its excess cash in investment grade, interest-bearing securities. As of December 31, 2001 and 2000, cash equivalents consisted of money market funds. All cash and cash equivalents are available for sale and stated at fair market value. The Company considers highly liquid investments with original maturities of three months or less as cash equivalents.

**Inventory.** The Company states its inventories at the lower of cost or market. The cost of the inventory is based on the first-in first-out method. If the cost of the inventory exceeds the expected market value a provision is recorded for the difference between cost and market. The Company's inventories consisted of OcuGene glaucoma genetic test kits at December 31, 2001.

**Property and Equipment.** Property and equipment is stated at cost, less accumulated depreciation. Depreciation of property and equipment is provided over the estimated useful lives of the respective assets, which range from three to five years, using the straight-line method. Leasehold improvements are amortized over the lives of the related leases or their estimated useful lives, whichever is shorter, using the straight-line method. It is the Company's policy to write-off its fully depreciated assets. This resulted in a decrease in both property and equipment and accumulated depreciation in 2001 and 2000 of \$57,000 and \$44,000, respectively, with no change in net property and equipment. The amortization of the cost of capital lease assets is included in depreciation expense.

In accordance with FASB Statement No. 121, "Accounting for the Impairment of Long-Lived Assets and for Long-Lived Assets to Be Disposed Of," the Company records impairment losses on long-lived assets used in operations when events and circumstances indicate that the assets might be impaired and the undiscounted cash flows estimated to be generated by those assets are less than the carrying amounts of those assets. During 1998, the Company evaluated certain assets and determined that assets with a

## INSITE VISION INCORPORATED

### NOTES TO CONSOLIDATED FINANCIAL STATEMENTS (Continued)

carrying value of \$946,000 were impaired and reduced their carrying value by \$87,000. This loss was included in the 1998 research and development expense. In July 1999, the Company sold this equipment and recorded a loss of \$107,000 which is included in the 1999 research and development expense in the Consolidated Statements of Operations.

**Revenue Recognition.** Effective January 1, 2000, in accordance with Staff Accounting Bulletin No. 101, "Revenue Recognition in Financial Statements" ("SAB 101"), the Company changed its method of accounting for up-front technology license fees when ongoing research and development services will be performed. Previously, on the only such arrangement it had executed, the Company had recognized the up-front fee as revenue upon the effective date of the arrangement. Under the new accounting method adopted retroactive to January 1, 2000, (a) the Company recognized the up-front fee over the expected term of the research and development services, which was 36 months, using the straight-line method. As a result of the termination of this arrangement in December 2000, the Company recognized the then remaining deferred revenue in the fourth quarter of 2000. The cumulative effect of the change on prior years resulted in a charge to operations of \$4,486,000, which is included in net loss for the year ended December 31, 2000. The effect of the change on the year ended December 31, 2000 was to increase income before the cumulative effect of the accounting change by \$4,486,000 (\$.19 per share). The pro forma amounts presented in the statement of operations were calculated assuming the accounting change was made retroactively to prior periods.

**Accounting for Royalties.** Royalties from licensees are based on third-party sales and are recorded as earned in accordance with contract terms, when third party results are reliably measured and collectibility is reasonably assured.

**Accounting for Cost Sharing Agreements.** The Company directly reduces expenses for amounts reimbursed pursuant to cost sharing agreements. During 2001, 2000 and 1999, research and development expenses were reduced by \$713,000, \$4,779,000 and \$4,248,000, respectively, for costs reimbursed primarily by Pharmacia Corporation (Pharmacia) and another research collaboration partner under the terms of the collaborations described in Note 2.

In accordance with SAB 101, the Company recognizes the received cost sharing payments when persuasive evidence of an arrangement exists, the services have been rendered, the fee is fixed or determinable and collectibility is reasonably assured.

**Accounting for Employee Stock Options.** The Company accounts for stock options granted to employees and directors in accordance with Accounting Principles Board ("APB") Opinion No. 25, "Accounting for Stock Issued to Employees" and, accordingly, does not recognize compensation expense for options granted to employees and directors at an exercise price equal to the fair value of the underlying common stock.

In April 2000, the Financial Accounting Standards Board issued Interpretation No. 44 (FIN 44), "Accounting for Certain Transactions Involving Stock Compensation: An Interpretation of APB No. 25." The Company has adopted the provisions of FIN no. 44. The adoption of these provisions did not materially impact the Company's results of operations. Note 6 provides the pro-forma effects on reported net income and earnings per share for 2001, 2000 and 1999 based on the fair value of options and shares granted as prescribed by Statement 123.

**Accounting for Stock Options Exchanged for Services.** The Company issues stock options to consultants of the Company in exchange for services. The Company has valued these options using the Black-Scholes option valuation model at each reporting period and has recorded charges to operations over the vesting periods of the individual stock options. Such charges amounted to approximately \$200,000, \$197,000 and \$194,000 in 2001, 2000 and 1999, respectively.

**Earnings (Loss) per Share.** Basic and diluted net income (loss) per share information for all periods is presented under the requirement of SFAS No. 128, "Earnings per Share." Basic earnings per share has

**INSITE VISION INCORPORATED**

**NOTES TO CONSOLIDATED FINANCIAL STATEMENTS (Continued)**

been computed using the weighted-average number of common shares outstanding during the period, and excludes any dilutive effects of stock options and convertible securities. Potentially dilutive securities have been excluded from the computation of diluted net loss per share in 2001 and 2000, as their inclusion would be antidilutive.

The following table sets forth the computation of basic and diluted earnings (loss) per share:

<b>(in thousands, except per share amounts)</b>	<u>2001</u>	<u>2000</u>	<u>1999</u>
<b>Numerator:</b>			
Net income (loss) before cumulative effect of accounting change	\$(9,556)	\$ 1,046	\$ 1,150
Cumulative effect of accounting change	—	(4,486)	—
Net income (loss)	(9,556)	(3,440)	1,150
Non-cash preferred dividend	—	(3)	(22)
Net earnings (loss) applicable to common stockholders	<u>\$(9,556)</u>	<u>\$(3,443)</u>	<u>\$ 1,128</u>
<b>Denominator:</b>			
Denominator for basic earnings (loss) per share — weighted-average shares outstanding	24,897	23,574	19,285
<b>Effect of diluted securities:</b>			
Employee & director stock options, warrants and preferred stock warrant (determined using the treasury stock method)	—	909	260
Convertible preferred stock (using the if-converted method)	—	—	311
Denominator for diluted earnings per share — weighted-average shares outstanding	<u>24,897</u>	<u>24,483</u>	<u>19,856</u>
Basic earnings (loss) per share	<u>\$ (0.38)</u>	<u>\$ (0.15)</u>	<u>\$ 0.06</u>
Diluted earnings (loss) per share	<u>\$(0.38)</u>	<u>\$(0.14)</u>	<u>\$0.06</u>

Due to the loss from operations, earnings (loss) per share for 2001 is based on the weighted average number of common shares only, as the effect of including equivalent shares from stock options would be anti-dilutive. If the Company had recorded net income, the calculation of earnings per share would have included approximately 343,000 common equivalent shares related to the outstanding stock options and warrants (determined using the treasury stock method).

**Accounting for Materials Purchased for Research and Development.** The Company expenses materials for research and development activities when the obligation for the items is incurred.

**Key Suppliers.** The Company is dependent on single or limited source suppliers for certain materials used in its research and development activities. The Company has generally been able to obtain adequate supplies of these components. However, an extended interruption in the supply of these components currently obtained from single or limited source suppliers could adversely affect the Company's research and development efforts.

**Recent Accounting Pronouncements.** In June 2001, the Financial Accounting Standards Board or FASB, issued Statements of Financial Accounting Standards No. 141, *Business Combinations*, and No. 142, *Goodwill and other Intangible Assets*, effective for fiscal years beginning after December 15, 2001. Under the new rules, goodwill and intangible assets deemed to have indefinite lives will no longer be amortized but will be subject to an annual impairment test in accordance with the Statements. Other intangible assets will continue to be amortized over their useful lives. The Company does not expect that the adoption of Statements 141 and 142 will have a material effect on its consolidated financial position or results of operations.

## INSITE VISION INCORPORATED

### NOTES TO CONSOLIDATED FINANCIAL STATEMENTS (Continued)

In October 2001, FASB issued Statements of Financial Accounting Standards No. 144, *Accounting for the Impairment or Disposal of Long-Lived Assets*, effective for fiscal years beginning after December 15, 2001, with transition provisions for certain matters. The FASB's new rules on asset impairment supersedes FASB Statement No. 121, *Accounting for Impairment of Long-Lived Assets and for Long-Lived Assets to be Disposed Of*, and provide a single accounting model for long-lived assets to be disposed of. The Company does not expect that the adoption of Statement 144 will have a material effect on its consolidated financial position or results of operations.

#### 2. Licenses

In November 2001, the Company entered into a one-year agreement with Quest Diagnostics Incorporated to provide laboratory services in the U.S. for the Company's recently introduced OcuGene genetic test for the early prognosis and diagnosis of glaucoma. The Company will pay Quest a fee for each test performed and royalties on product sales.

In April 2001, the Company signed a licensing agreement with SSP Co., Ltd. of Tokyo, Japan ("SSP"), for two fourth generation fluoroquinolones, which have indicated increased sensitivity against gram positive and negative bacteria. The Company has exclusive rights to any products developed using these compounds, with the exception of Japan, where SSP will retain the rights and the rest of Asia, where the Company will share joint rights with SSP. One of the compounds, SS734, is currently under development under the designation ISV-403.

In December 1999, the Company entered into an exclusive worldwide license agreement with INSERM for the diagnostic, prognostic and therapeutic uses of a gene for chronic open angle glaucoma. The Company has paid a licensing fee and will make royalty payments on future product sales, if any.

On November 11, 1999, the Company entered into a license agreement, stock purchase agreement and credit agreement pursuant to which InSite granted Pharmacia an exclusive worldwide royalty-bearing license to its ISV-900 technology for diagnostic, prognostic and therapeutic applications in the area of glaucoma. The transaction included the following payments from Pharmacia (i) a \$5.0 million licensing fee, (ii) up to \$5.0 million in research and development payments over a three year period, (iii) royalties on product sales, and (iv) up to \$3 million if certain milestones were achieved. In December 2000, the Company and Pharmacia terminated the ISV-900 license agreement and the related credit agreement. All rights that had been granted to Pharmacia were returned to the Company and any future payment obligations by Pharmacia were cancelled.

The Company recognized \$4.8 million as license revenue from Pharmacia during the fourth quarter of 1999 (\$264,000 on a pro-forma basis), due to the persuasive evidence of the existence of an arrangement, delivery had occurred, the fee was fixed and determinable and collectibility was reasonably assured. The technology represented a separate element of the arrangement that was recognized when the technology was delivered to Pharmacia for commercialization.

The stock purchase agreement provided for a \$2.0 million equity investment by Pharmacia in the Company. A total of 723,195 shares were purchased in January 2000, 45 days after the execution of the agreement. The stock purchase agreement also provided for a standstill period of thirty (30) months during which Pharmacia and its subsidiaries will not purchase additional shares of the Company, other than those provided for under any existing agreements between the companies, without the prior written consent of the Company.

The credit agreement with Pharmacia, which expired unused, provided for a \$4 million revolving line of credit that would have been available to the Company on November 11, 2001 for a period of three (3) years.

In August 1999, the Company entered into a license agreement with SSP Co., Inc., a Japanese company, to be the exclusive manufacturer and distributor of AquaSite in Japan. AquaSite is an over-the-counter product that uses the Company's DuraSite technology and demulcents for the symptomatic treatment of dry eye.

**INSITE VISION INCORPORATED**

**NOTES TO CONSOLIDATED FINANCIAL STATEMENTS (Continued)**

In March 1999, the Company entered into a royalty-bearing license agreement with Global Damon, a Korean company, to be the exclusive distributor of AquaSite in the Republic of Korea. Concurrently, the Company entered into a manufacturing agreement with Kukje, a Korean company, to produce the AquaSite to be sold by Global Damon.

On January 28, 1999, the Company entered into a license agreement and stock purchase agreement pursuant to which InSite granted Pharmacia an exclusive worldwide license to ISV-205 for the treatment of glaucoma. The transaction also called for equity investments from Pharmacia of \$3,500,000 for which they received 1,942,419 shares of common stock in February 1999 and September 1999. In May 2001, Pharmacia Corporation terminated the ISV-205 licensing agreement. All global development and commercialization rights that had been granted to Pharmacia were returned to the Company at the end of a ninety-day termination period and any future payment obligations by Pharmacia were cancelled.

The Company has a license agreement with CIBA Vision, an ophthalmic company which is an affiliate of CIBA-GEIGY Limited. Under the terms of the agreement, CIBA Vision has co-exclusive rights to manufacture and market AquaSite and ToPreSite in the U.S. and AquaSite in Canada. The Company also has a license agreement with Global Damon, and a manufacturing agreement with Kukje, to produce and sell AquaSite in Korea. Both of the license agreements require royalty payments on net sales of the licensed products. The Company recognized \$5,000, \$27,000 and \$10,000 of royalty revenue for sales of AquaSite in 2001, 2000 and 1999, respectively

**3. Lease Commitments**

The Company leases its facilities under non-cancelable operating lease agreements that expire in 2006. Rent expense was \$445,000, \$430,000, and \$431,000 for 2001, 2000 and 1999, respectively. The 2001, 2000 and 1999 rent expense reflects \$74,000, \$64,000 and \$63,000, respectively, received by the Company related to the January 1999 sublease of a portion of the Company's facility. The sublease continues through February 2002 and provides for annual payments of \$12,400 in 2002.

Capital lease obligations represent the present value of future rental payments under capital lease agreement for laboratory equipment. The original cost and accumulated amortization on the equipment under capital leases is \$103,600 and \$20,000, respectively, at December 31, 2001 and \$39,900 and \$10,000, respectively, at December 31, 2000.

Future minimum payments under capital and operating leases are as follows:

<u>Year ending December 31,</u>	<u>Capital Leases</u>	<u>Operating Leases</u>
2002.....	\$37,665	\$ 657,988
2003.....	38,162	693,826
2004.....	10,052	718,113
2005.....	—	743,253
2006.....	—	769,245
Total minimum lease payments .....	85,879	<u>\$3,582,425</u>
Amount representing interest.....	<u>8,619</u>	
Present value of net minimum lease payments .....	77,260	
Current portion.....	32,197	
Long-term portion .....	<u>45,063</u>	

## INSITE VISION INCORPORATED

### NOTES TO CONSOLIDATED FINANCIAL STATEMENTS (Continued)

#### 4. Income Taxes

Significant components of the Company's deferred tax assets for federal and state income taxes as of December 31, 2001 and 2000 are as follows (in thousands):

	2001	2000
Deferred tax assets:		
Net operating loss carryforwards .....	\$ 27,106	\$ 25,093
Tax credit carryforwards .....	4,742	3,939
Capitalized research and development .....	9,014	7,723
Depreciation .....	468	502
Other .....	275	175
Total deferred tax assets .....	41,605	37,432
Valuation allowance .....	(41,605)	(37,432)
Net deferred tax assets .....	\$ —	\$ —

The valuation allowance increased by \$4.2 million and \$1.3 million during the years ended December 31, 2001 and 2000, respectively.

At December 31, 2001, the Company has net operating loss carryforwards for federal income tax purposes of approximately \$74.0 million, which expire in the years 2002 through 2021 and federal tax credits of approximately \$2.8 million which expire in the years 2002 through 2021. The Company also has net operating loss carryforwards for state income tax purposes of approximately \$28.0 million which expire in the years 2002 through 2011, and state research and development tax credits of approximately \$1.7 million which carryforward indefinitely.

Utilization of the Company's federal and state net operating loss carryforwards and research and development tax credits are subject to an annual limitation against taxable income in future periods due to the ownership change limitations provided by the Internal Revenue Code of 1986. As a result of this annual limitation, a significant portion of these carryforwards will expire before ultimately becoming available for offset against taxable income. Additional losses and credits will be subject to limitation if the Company incurs another change in ownership in the future.

#### 5. Redeemable Preferred Stock

In September 1997, the Company received net proceeds of approximately \$6.5 million from a private placement of 7,000 shares of Series A Convertible Preferred Stock with a \$0.01 par value ("Series A Preferred"). The number of shares of Common Stock issuable upon conversion of the Series A Preferred was equal to the face value of each share of Series A Preferred divided by the lower of the fixed conversion price of \$2.127 or a variable conversion price. The variable conversion price was determined by applying a discount, which ranged from 10% for shares converted prior to June 10, 1998, to 17.5% for shares converted after December 7, 1998, to an average of closing bid prices of the Company's common stock at the time of conversion. Such conversion prices were subject to adjustment in accordance with the terms of the Certificate of Designations, Preferences and Rights of the Series A Preferred. The value of the Series A Preferred shares to be converted also included a 6% per annum premium, which accrued from the date of issuance until the date of conversion. Three years after issuance, any remaining unconverted preferred shares would have automatically been converted into common stock. All of the outstanding shares of Series A Preferred have been converted into 5,089,250 shares of common stock. In September 1997, the Company also issued a warrant to purchase 70 shares of Series A Preferred that was subject to the same conversion terms and premium as described above. The warrant was exercised in September 2000, and immediately converted by the holder, using their net exercise right, into 28,037

**INSITE VISION INCORPORATED**

**NOTES TO CONSOLIDATED FINANCIAL STATEMENTS (Continued)**

shares of common stock. Holders of the Series A Preferred had no voting rights, except as required by applicable Delaware law. The Company has authorized 5,000,000 shares of Preferred Stock, 7,070 of which have been designated Series A Preferred. Pursuant to this private placement, 6,000,000 shares of common stock had been reserved for issuance to the holders of the Series A Preferred of which 910,750 shares remain reserved at December 31, 2001.

For the years ended December 31, 2000 and 1999, in accordance with SEC Rules and Regulations, the Company reported non-cash preferred dividends of \$3,000, and \$22,000, respectively. The dividends are related to the discount at which Series A Preferred could be converted to common stock and the 6% per annum premium, payable in additional common stock, earned on the outstanding Series A Preferred Stock. The dividends are used to determine the net loss per share applicable to common stockholders.

The following table summarizes information concerning the issuance and conversion of the Series A Preferred Stock (in thousands):

	<u>Amount</u>
Issuance of 7,000 shares of Series A Preferred Stock and a warrant for 70 shares of Series A Preferred Stock .....	\$ 6,516
Conversion of 300 shares of Series A Preferred Stock into common stock ...	(309)
Non-cash preferred dividend .....	<u>1,326</u>
Balance at December 31, 1997 .....	7,533
Reduction in accrued stock issuance costs .....	39
Conversion of 5,530 shares of Series A Preferred Stock into common stock ..	(6,575)
Non-cash preferred dividend .....	<u>514</u>
Balance at December 31, 1998 .....	1,511
Conversion of 1,170 shares of Series A Preferred Stock into common stock ..	(1,503)
Non-cash preferred dividend .....	<u>22</u>
Balance at December 31, 1999 .....	30
Non-cash preferred dividend .....	3
Exercise of 70 warrants for Series A Preferred Stock and conversion into common stock .....	<u>(33)</u>
Balance at December 31, 2000 .....	<u><u>\$ —</u></u>

**6. Common Stockholders' Equity**

In February 2001, the Company filed a shelf registration for the issuance of up to \$40.0 million of Common Stock or securities convertible into or exercisable into the Company's Common Stock. The Common Stock, if issued, will be sold through a placement agent. As of December 31, 2001 no shares had been issued under this shelf registration.

In May 2000, the Company received net proceeds of \$13,040,000 from a private placement of 3,349,722 shares of Common Stock and warrants. Each warrant entitles its holder to purchase shares of the Company's Common Stock for \$5.64 per share until April 2004. As of December 31, 2001, warrants to purchase 1,172,381 shares of Common Stock were outstanding. In connection with this private placement the Company also issued the placement agent warrants to purchase 334,972 shares of the Company's Common Stock for \$5.01 per share until April 2004, all of which were outstanding as of December 31, 2001. Also, the Company issued warrants to a placement agent to purchase 150,000 shares of the Company's Common Stock for \$5.25 per share until March 2004, all of which were outstanding as of December 31, 2001. These warrants were valued using a Black-Scholes option pricing model with the following assumptions: risk-free interest rate of 4.85%, volatility of 1.0162 and an expected life of 4 years, resulting in a valuation of \$794,000 which has been recorded as an issuance cost.

**INSITE VISION INCORPORATED**

**NOTES TO CONSOLIDATED FINANCIAL STATEMENTS (Continued)**

In April 2000, the Company received \$625,000 from the exercise of warrants issued as part of a January 1996 private placement. Each warrant entitles its holder to purchase shares of the Company's Common Stock for \$3.25 per share until January 2001. As of December 31, 2001, the remaining warrants issued as part of the January 1996 private placement to purchase 125,000 shares of Common Stock, which had not been exercised, had been cancelled.

In January 2000, the Company received \$2,000,000 from Pharmacia for the purchase of 723,195 shares of Common Stock in connection with the November 1999 license for the Company's ISV-900 glaucoma genetics program.

In September 1999, the Company received \$1,500,000 from Pharmacia for the purchase of 846,913 shares of Common Stock for a milestone reached in connection with the January 1999 license of the Company's ISV-205 glaucoma product.

In February 1999, the Company received \$2,000,000 from Pharmacia for the purchase of 1,095,506 shares of Common Stock in connection with the January 1999 license for the Company's ISV-205 glaucoma product. The agreement also provides for additional equity purchases by Pharmacia at average prevailing market prices if the Company achieves certain milestones, the first of which was reached in September of 1999.

*Stock Option Plan.*

At December 31, 2001, a total of 3,162,705 shares of Common Stock were reserved under the 1994 Stock Plan for issuance upon the exercise of options or by direct sale to employees, including officers, directors and consultants. Options granted under the plan expire 10 years from the date of grant and become exercisable at such times and under such conditions as determined by the Company's Board of Directors (generally ratably over four years, with the first 25% vesting after one year). Activity under the 1994 Stock Plan is as follows:

	Shares			
	Options Available for Grant	Options Outstanding	Option Price	Weighted Average Exercise Price of Shares Under Plan
Balances at January 1, 1999 .....	584,683	1,633,132	0.60 - 9.25	3.03
Additional shares reserved .....	336,981	—	—	—
Granted .....	(715,932)	715,932	1.06 - 2.44	1.28
Exercised .....	—	(13,496)	2.00 - 2.63	1.25
Forfeited .....	158,749	(158,749)	0.60 - 6.38	4.69
Balances at December 31, 1999 .....	364,481	2,176,819	0.60 - 9.25	2.34
Additional shares reserved .....	405,916	—	—	—
Granted .....	(98,750)	98,750	4.56 - 5.88	5.05
Exercised .....	—	(241,117)	0.60 - 4.38	1.21
Forfeited .....	116,349	(116,349)	1.13 - 6.38	3.94
Balances at December 31, 2000 .....	787,996	1,918,103	\$0.60 - 9.25	\$2.53
Additional shares reserved .....	497,014	—	—	—
Granted .....	(444,500)	444,500	\$1.02 - 2.20	\$1.52
Exercised .....	—	(40,406)	\$0.60 - 1.13	\$0.66
Forfeited .....	35,443	(35,443)	\$1.45 - 5.88	\$3.71
Balances at December 31, 2001 .....	<u>875,953</u>	<u>2,286,754</u>	\$0.60 - 9.25	\$2.35

**INSITE VISION INCORPORATED**

**NOTES TO CONSOLIDATED FINANCIAL STATEMENTS (Continued)**

The following table summarizes information concerning currently outstanding and exercisable options:

Range of Exercise Prices	Options Outstanding			Options Exercisable	
	Number Outstanding	Weighted Average		Number Exercisable	Weighted Average Exercise Prices
		Contractual Life	Exercise Price		
\$0.60 — \$1.13 .....	707,809	5.67	\$0.97	640,391	\$0.97
\$1.20 — \$2.75 .....	926,697	6.67	2.06	551,285	2.42
\$2.81 — \$5.25 .....	572,034	5.97	3.97	550,568	3.95
\$5.63 — \$9.25 .....	80,214	5.52	6.25	73,398	6.28
	<u>2,286,754</u>	<u>6.14</u>	<u>\$2.35</u>	<u>1,815,642</u>	<u>\$2.53</u>

The weighted average grant date fair values of options granted during 2001, 2000 and 1999 was 1.52, \$5.05 and \$1.28, respectively

Pursuant to the terms of the 1994 Stock Plan, generally each non-employee director who is newly elected or appointed after October 25, 1993, is granted an option to purchase 10,000 shares of common stock at a price per share equal to the fair market value of the common stock on the grant date. Each continuing non-employee director also receives an annual grant of an option to purchase 10,000 shares. Such options vest one year after the grant date.

The Company has elected to follow Accounting Principles Board Opinion No. 25, "Accounting for Stock Issued to Employees" (APB 25), and related Interpretations in accounting for its employee stock options because, as discussed below, the alternative fair value accounting provided for under FASB Statement No. 123, "Accounting for Stock-Based Compensation," requires use of option valuation models that were not developed for use in valuing employee stock options. Under APB 25, because the exercise price of the Company's employee stock options equals the market price of the underlying stock on the date of grant, no compensation expense is recognized.

The Black-Scholes option valuation model was developed for use in estimating the fair value of traded options that have no vesting requirements and are fully transferable. In addition, option valuation models require the input of highly subjective assumptions including the expected stock price volatility. Because the Company's employee stock options have characteristics significantly different from those of traded options, and because changes in the subjective input assumptions can materially affect the fair value estimate, in management's opinion, the existing models do not necessarily provide a reliable single measure of the fair value of its employee stock options.

Pro forma information regarding net loss and loss per share is required by Statement 123, and has been determined as if the Company had accounted for its employee stock options under the fair value method of that Statement. The fair value for these options was estimated at the date of grant using a Black-Scholes option pricing model with the following weighted-average assumptions for 2001, 2000 and 1999, respectively: risk-free interest rates ranging from 4.64% to 6.87%; volatility factors for the expected market price of the Company's common stock of 1.09, 1.14 and 1.15; and a weighted-average expected life for the options of 4 years.

For purposes of pro forma disclosure, the estimated fair value of the options is amortized to expense over the vesting period of the related options. The Company's pro forma information follows (in thousands except for loss per share information):

**INSITE VISION INCORPORATED**

**NOTES TO CONSOLIDATED FINANCIAL STATEMENTS (Continued)**

	<u>2001</u>	<u>2000</u>	<u>1999</u>
Net income (loss) applicable to common stockholders — as presented	\$ (9,556)	\$(3,443)	\$1,128
Net loss applicable to common stockholders — pro forma .....	(10,200)	(4,619)	(35)
Basic net income (loss) per share applicable to common stockholders			
— as presented .....	(0.38)	(0.15)	0.06
Basic net income (loss) per share applicable to common stockholders			
— pro forma .....	(0.41)	(0.20)	(0.00)
Diluted net income (loss) per share applicable to common			
stockholders — as presented .....	(0.38)	(0.14)	0.06
Diluted net income (loss) per share applicable to common			
stockholders — pro forma .....	(0.41)	(0.19)	(0.00)

The pro forma impact of options on the net income (loss) for 2001, 2000 and 1999 is not representative of the effects on net income (loss) for future years, as future years will include the effects of additional stock option grants.

*Employee Stock Purchase Plan.*

On April 1, 1994, employees of the Company began participating in an Employee Stock Purchase Plan which provides the opportunity to purchase Common Stock at prices not more than 85% of market value at the time of purchase. In June 2000, the Company's shareholders approved an additional 85,000 shares of Common Stock be reserved for issuance under the 1994 Employee Stock Purchase Plan. During the years ended December 31, 2001, 2000 and 1999, respectively, 45,759, 20,465 and 19,577 shares of Common Stock were issued pursuant to this plan. At December 31, 2001, an additional 37,129 shares are reserved for issuance under this plan. The effects of this plan on the pro forma disclosures above are not material.

**7. Notes Receivable from Stockholder**

In May 2000, the Company issued loans to Dr. Chandrasekaran, the Company's President, Chief Executive Officer (CEO), Chief Financial Officer (CFO) and Chairman of the Board, related to his exercise of 126,667 options to acquire common stock. In May 2001, the terms on the loans were extended from 4 years to 5 years. The loans are full recourse and bear interest at 7% per annum. Interest payments are due semi-annually and principal payments are due annually. While the 126,667 shares of common stock issued secure the loans, the Company is not limited to these shares to satisfy the loan.

**8. Legal Proceedings**

From time to time, the Company may be subject to legal proceedings and claims in the ordinary course of business, including claims of alleged infringement of trademarks and other intellectual property rights. The Company currently is not aware of any such legal proceedings or claims that it believes will have, individually or in the aggregate, a material adverse effect on its business, prospects, financial condition and operating results.

**9. Quarterly Results (Unaudited)**

The following table is a summary of the quarterly results of operations for the years ended December 31, 2001 and 2000. The Company believes that the following information reflects all normal recurring adjustments necessary for a fair presentation of the information for the periods presented. The operating results for any quarter are not necessarily indicative of results for any future period.

**INSITE VISION INCORPORATED**

**NOTES TO CONSOLIDATED FINANCIAL STATEMENTS (Continued)**

	(in thousands, except per share amounts)				
	2001				
	First Quarter	Second Quarter	Third Quarter	Fourth Quarter	Total Year
Revenues.....	\$ 2	\$ 1	\$ 1	\$ 1	\$ 5
Loss from operations .....	(2,292)	(2,433)	(2,562)	(2,841)	(10,128)
Net loss .....	(2,059)	(2,266)	(2,457)	(2,774)	(9,556)
Basic and diluted net loss per share:	\$ (0.08)	\$ (0.09)	\$ (0.10)	\$ (0.11)	\$ (0.38)
Shares used to calculate basic and diluted net loss per share .....	24,873	24,891	24,907	24,915	24,897

	(in thousands, except per share amounts)				
	2000				
	First Quarter*	Second Quarter*	Third Quarter*	Fourth Quarter	Total Year
Revenues.....	\$ 402	\$ 398	\$ 410	\$ 3,303	\$ 4,513
Income (loss) from operations .....	(418)	(422)	(1,121)	2,216	255
Net income (loss) applicable to common stockholders before cumulative effect of change in accounting principle .....	(337)	(253)	(850)	2,483	1,043
Cumulative effect of accounting change .....	(4,486)	—	—	—	(4,486)
Net income (loss) applicable to common stockholders .....	(4,823)	(253)	(850)	2,483	(3,443)
Basic earnings (loss) per share:					
Net income (loss) per share applicable to common stockholders before cumulative effect of accounting change .....	\$ (0.02)	\$ (0.01)	\$ (0.03)	\$ 0.10	\$ 0.04
Cumulative effect of accounting change .....	(0.21)	—	—	—	(0.19)
Net income (loss) per share applicable to common stockholders .....	(0.23)	(0.01)	(0.03)	0.10	(0.15)
Diluted earnings (loss) per share:					
Net income (loss) per share applicable to common stockholders before cumulative effect of accounting change .....	(0.02)	(0.01)	(0.03)	0.10	0.04
Cumulative effect of accounting change .....	(0.21)	—	—	—	(0.18)
Net income (loss) per share applicable to common stockholders .....	(0.23)	(0.01)	(0.03)	0.10	(0.14)
Shares used to calculate basic net income (loss) per share .....	21,058	23,601	24,795	24,843	23,574
Shares used to calculate diluted net income (loss) per share .....	21,058	23,601	24,795	25,965	24,483

\* The first, second and third quarter differ from Form 10Q originally filed with the SEC for the respective periods because of a cumulative accounting change related to the implementation of SAB 101. In Note 1, see Revenue Recognition, for additional information about the cumulative accounting change.

**Item 9. CHANGES IN AND DISAGREEMENTS WITH ACCOUNTANTS ON ACCOUNTING AND FINANCIAL DISCLOSURE**

None.

**PART III**

**Item 10. DIRECTORS AND EXECUTIVE OFFICERS OF THE REGISTRANT**

The information required by this item with respect to the identification of Directors is hereby incorporated by reference from the information under the caption "Proposal One-Election of Directors" in the Company's Proxy Statement for its Annual Meeting of Stockholders which will be held on June 3, 2002 (the "Proxy Statement").

The information required by this item with respect to the identification of Executive Officers is contained in Item 1 of Part I of this report under the caption "Executive Officers."

The information required by Item 405 of Regulation S-K regarding compliance with Section 16(a) of the Securities Exchange Act of 1934 is hereby incorporated by reference from the information under the caption "Compliance with Section 16(a) of the Securities Exchange Act of 1934" in the Proxy Statement.

**Item 11. EXECUTIVE COMPENSATION**

The information required by this item is hereby incorporated by reference from the information under the caption "Executive Compensation and Related Information" in the Proxy Statement.

**Item 12. SECURITY OWNERSHIP OF CERTAIN BENEFICIAL OWNERS AND MANAGEMENT**

The information required by this item is hereby incorporated by reference from the information under the caption "Principal Stockholders" in the Proxy Statement.

**Item 13. CERTAIN RELATIONSHIPS AND RELATED TRANSACTIONS**

The information required by this item is hereby incorporated by reference from the information under the captions "Executive Compensation and Related Information" and "Certain Relationships and Related Transactions" in the Proxy Statement.

**PART IV**

**Item 14. EXHIBITS, FINANCIAL STATEMENT SCHEDULES AND REPORTS ON FORM 8-K**

(a)(1) Financial Statements

The Financial Statements and Report of Independent Auditors are included in a separate section of this Annual Report on Form 10-K.

(2) Financial Statement Schedules

All financial statement schedules have been omitted because they are not applicable or are not required or the required information to be set forth therein is included in the Financial Statements or notes thereto included in a separate section of this Annual Report on Form 10-K.

(3) Exhibits

See Exhibit Index on page 51 of this Annual Report on Form 10-K.

(b) Reports on Form 8-K

None.

(c) Exhibits

See Exhibit Index on page 51 of this Annual Report on Form 10-K.

(d) Financial Statement Schedules

See (a)(2) above.

## SIGNATURES

Pursuant to the requirements of Section 13 or 15(d) of 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.

Dated: March 29, 2002

INSITE VISION INCORPORATED

By: /s/ S. Kumar Chandrasekaran

S. Kumar Chandrasekaran, Ph.D.  
*Chairman of the Board, President,  
Chief Executive Officer and  
Chief Financial Officer*

## POWER OF ATTORNEY

KNOW ALL PERSONS BY THESE PRESENTS:

That the undersigned officers and directors of InSite Vision Incorporated, a Delaware corporation, do hereby constitute and appoint S. Kumar Chandrasekaran as his true and lawful attorney-in-fact and agent, with the power and authority to do any and all acts and things and to execute any and all instruments which said attorney and agent determines may be necessary or advisable or required to enable said corporation to comply with the Securities Exchange Act of 1934, as amended, and any rules or regulations or requirements of the Securities and Exchange Commission in connection with this Annual Report on Form 10-K. Without limiting the generality of the foregoing power and authority, the powers granted include the power and authority to sign the names of the undersigned officers and directors in the capacities indicated below to this Annual Report on Form 10-K, to any and all amendments, and to any and all instruments or documents filed as part of or in conjunction with this Annual Report on Form 10-K or amendments or supplements thereof, and each of the undersigned hereby ratifies and confirms all that said attorney and agent shall do or cause to be done by virtue hereof. This Power of Attorney may be signed in several counterparts.

IN WITNESS WHEREOF, each of the undersigned has executed this Power of Attorney as of the date indicated.

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.

<u>Name</u>	<u>Capacity</u>	<u>Date</u>
<u>/s/ S. Kumar Chandrasekaran</u> S. Kumar Chandrasekaran, Ph.D.	Chairman of the Board, President, Chief Executive Officer and Chief Financial Officer	March 29, 2002
<u>/s/ Mitchell H. Friedlaender</u> Mitchell H. Friedlaender, M. D.	Director	March 29, 2002
<u>/s/ John L. Mattana</u> John L. Mattana	Director	March 29, 2002
<u>/s/ Jon S. Saxe</u> Jon S. Saxe	Director	March 29, 2002
<u>/s/ Anders P. Wiklund</u> Anders P. Wiklund	Director	March 29, 2002

## EXHIBIT INDEX

<u>Number</u>	<u>Exhibit Table</u>
3.1 <sup>1</sup>	Restated Certificate of Incorporation.
3.2 <sup>7</sup>	Amended and Restated Bylaws.
4.1 <sup>4</sup>	Registration Rights Agreement, dated January 24, 1996 (the "Registration Rights Agreement"), between the Registrant and the investors listed on Schedule 1 thereto.
4.2 <sup>4</sup>	Form of Warrant to Purchase Shares of Common Stock between the Registrant and each of the investors listed on Schedule 1 to the Registration Rights Agreement.
4.3 <sup>10</sup>	Certificate of Designations, Preferences and Rights of Series A Convertible Preferred Stock as filed with the Delaware Secretary of State on September 11, 1997.
4.4 <sup>10</sup>	Certificate of Correction of the Certificate of Designations, Preferences and Rights of Series A Convertible Preferred Stock as filed with the Delaware Secretary of State on September 26, 1997.
10.1 <sup>13</sup>	InSite Vision Incorporated 1994 Employee Stock Purchase Plan (As amended and restated through April 17, 2000).
10.2 <sup>2</sup>	Form of Indemnity Agreement Between the Registrant and its directors and officers.
10.3 <sup>2</sup>	Form of Employee's Proprietary Information and Inventions Agreement.
10.4 <sup>3H</sup>	License Agreement dated as of October 9, 1991 by and between the Company and CIBA Vision Corporation, as amended October 9, 1991.
10.5 <sup>3</sup>	Letter Agreement dated February 27, 1992 by and among the Company, Columbia Laboratories, Inc. and Joseph R. Robinson, as amended October 23, 1992.
10.6 <sup>2H</sup>	Collaboration Agreement dated as of November 24, 1992 by and between the Company and British Bio-technology Limited.
10.7 <sup>2H</sup>	Collaboration Agreement dated as of April 30, 1993 by and between the Company and British Bio-technology Limited.
10.8 <sup>8</sup>	Facilities Lease, dated September 1, 1996, between the Registrant and Alameda Real Estate Investments.
10.9 <sup>1H</sup>	Agreement dated as of February 15, 1994 by and between the Company and Timm A. Carpenter.
10.10 <sup>9HH</sup>	InSite Vision Incorporated 1994 Stock Option Plan (Amended and Restated as of June 8, 1998).
10.11 <sup>1HH</sup>	Form of InSite Vision Incorporated Notice of Grant of Stock Option and Stock Option Agreement, with Addenda.
10.12 <sup>9H</sup>	Form of InSite Vision Incorporated Notice of Automatic Option Grant and Non-Employee Director Option Agreement.
10.13 <sup>1</sup>	InSite Vision Incorporated 1994 Employee Stock Purchase Plan.
10.14 <sup>1</sup>	Form of InSite Vision Incorporated Stock Purchase Agreement.
10.15 <sup>1</sup>	Form of InSite Vision Incorporated Employee Stock Purchase Plan Enrollment/Change Form.
10.16 <sup>4</sup>	Letter Agreement dated February 3, 1995 between the Company and David G. Harper.

<u>Number</u>	<u>Exhibit Table</u>
10.17 <sup>4</sup>	Settlement Agreement and General Release dated March 3, 1995 between the Company and Clifford Orent.
10.18 <sup>5</sup>	Commo Stock Purchase Agreement dated January 19, 1996 between the Registrant and the Investors listed on Schedule 1 thereto.
10.19 <sup>6H</sup>	ISV-205 License Agreement dated May 28, 1996 by and between the Company and CIBA Vision Ophthalmics.
10.20 <sup>6H</sup>	ToPreSite License Agreement dated May 28, 1996 by and between the Company and CIBA Vision Ophthalmics.
10.21 <sup>6H</sup>	BetaSite Contract Manufacturing Agreement dated July 18, 1996 by and between the Company and Bausch & Lomb Pharmaceuticals, Inc.
10.22 <sup>6H</sup>	PilaSite License Agreement dated July 18, 1996 by and between the Company and Bausch & Lomb Pharmaceuticals, Inc.
10.23 <sup>6H</sup>	Timolol Development Agreement dated July 18, 1996 by and between the Company and Bausch & Lomb Pharmaceuticals, Inc.
10.24 <sup>6H</sup>	Stock Purchase Agreement dated July 18, 1996 by and between the Company and Bausch & Lomb Pharmaceuticals, Inc.
10.25 <sup>10</sup>	Engagement Agreement, dated April 1, 1997, by and between the Company and William Blair & Company LLC.
10.26 <sup>10H</sup>	License Agreement, dated July 1, 1997, by and between the University of Connecticut Health Center and the Company.
10.27 <sup>10H</sup>	License Agreement, dated August 19, 1997, by and between the University of Rochester and the Company.
10.28 <sup>10</sup>	Form of Securities Purchase Agreement, dated September 12, 1997, by and among the Company and the Selling Stockholders thereunder.
10.29 <sup>10</sup>	Form of Registration Rights Agreement, dated September 12, 1997, by and among the Company and the Selling Stockholders thereunder.
10.30 <sup>10</sup>	Form of Warrant, dated September 12, 1997, to William Blair & Company LLC.
10.31 <sup>11H</sup>	License Agreement, dated January 28, 1999, by and between the Company and Pharmacia & Upjohn AB.
10.32 <sup>11H</sup>	Stock Purchase Agreement, dated January 28, 1999, by and between the Company and Pharmacia & Upjohn AB and Pharmacia & Upjohn, SA.
10.33 <sup>12</sup>	Project Agreement, dated November 11, 1999, by and between the Company and Pharmacia & Upjohn AB.
10.34 <sup>12</sup>	Stock Purchase Agreement, dated November 11, 1999, by and between the Company and Pharmacia & Upjohn AB.
10.35 <sup>12</sup>	Credit Agreement, dated November 11, 1999, by and between the Company and Pharmacia & Upjohn Company.
10.36 <sup>14</sup>	Form of Stock and Warrant Purchase Agreement, dated May 1, 2000 by and among the Company and the purchasers thereto.
10.37 <sup>15</sup>	ISV-900 Project Agreement Termination and Release, dated December 10, 2000, by and between the Company and Pharmacia & Upjohn AB.

<u>Number</u>	<u>Exhibit Table</u>
10.38 <sup>15</sup>	Credit Agreement Termination and Release, dated December 10, 2000, by and between the Company and Pharmacia & Upjohn Company.
10.39 <sup>16</sup>	Placement Agent Agreement with Ladenburg Thalmann & Co., Inc. dated January 9, 2001.
10.40 <sup>17</sup>	Amendment No. 1 to Marina Village Office Tech Lease, dated July 20, 2001 and effective January 1, 2002.
10.41 <sup>18</sup>	License Agreement, dated December 21, 2001 by and between the Company and The University of Connecticut Health Center.
23.1	Consent of Ernst & Young LLP, Independent Auditors.
24.1	Power of Attorney (included in Part IV of this Annual Report on Form 10-K under the caption "Signatures").

- 
- <sup>1</sup> Incorporated by reference to an exhibit in the Company's Annual Report on Form 10-K for the year ended December 31, 1993.
- <sup>2</sup> Incorporated by reference to an exhibit in the Company's Registration Statement on Form S-1 (Registration No. 33-68024) as filed with the Securities and Exchange Commission on August 27, 1993.
- <sup>3</sup> Incorporated by reference to an exhibit in Amendment No. 1 the Company's Registration Statement on Form S-1 (Registration No. 33-68024) as filed with the Securities and Exchange Commission on September 16, 1993.
- <sup>4</sup> Incorporated by reference to an exhibit in the Company's Quarterly Report on Form 10-Q for the quarter ended June 30, 1995.
- <sup>5</sup> Incorporated by reference to an exhibit in the Company's Annual Report on Form 10-K for the year ended December 31, 1995.
- <sup>6</sup> Incorporated by reference to an exhibit in the Company's Quarterly Report on Form 10-Q for the quarter ended June 30, 1996.
- <sup>7</sup> Incorporated by reference to an exhibit in the Company's Quarterly Report on Form 10-Q for the quarter ended March 31, 1997.
- <sup>8</sup> Incorporated by reference to an exhibit in the Company's Annual Report on Form 10-K for the year ended December 31, 1996.
- <sup>9</sup> Incorporated by reference to exhibits in the Company's Registration Statement on Form S-8 (Registration No. 333-60057) as filed with the Securities and Exchange Commission on July 28, 1998.
- <sup>10</sup> Incorporated by reference to exhibits in the Company's Registration Statement on Form S-3 (Registration No. 333-36673) as filed with the Securities and Exchange Commission on September 29, 1997.
- <sup>11</sup> Incorporated by reference to an exhibit in the Company's Annual Report on Form 10-K for the year ended December 31, 1998.
- <sup>12</sup> Incorporated by reference to an exhibit in the Company's Annual Report on Form 10-K for the year ended December 31, 1999.
- <sup>13</sup> Incorporated by reference to an exhibit to the Company's Registration Statement on Form S-8 (Registration No. 333-43504) as filed with the Securities and Exchange Commission on August 11, 2000.
- <sup>14</sup> Incorporated by reference to an exhibit to the Company's Registration Statement on Form S-3 (Registration No. 333-38266) as filed with the Securities and Exchange Commission on June 1, 2000.
- <sup>15</sup> Incorporated by reference to an exhibit in the Company's Annual Report on Form 10-K for the year ended December 31, 2000.
- <sup>16</sup> Incorporated by reference to an exhibit to the Company's Registration Statement on Form S-3 (Registration No. 333-54912) as filed with the Securities and Exchange Commission on February 2, 2001.
- <sup>17</sup> Incorporated by reference to an exhibit to the Company's Quarterly Report on Form 10-Q for the quarter ended September 30, 2001.
- <sup>18</sup> Confidential treatment has been requested as to certain portions of this agreement. Such omitted confidential information has been designated by an asterisk and has been filed separately with the Securities and Exchange Commission pursuant to Rule 24b-2 under the Securities Exchange Act of 1934, as amended, pursuant to an application for confidential treatment.
- <sup>H</sup> Confidential treatment has been granted with respect to certain portions of this agreement.
- <sup>HH</sup> Management contract or compensatory plan.

**CONSENT OF ERNST & YOUNG LLP, INDEPENDENT AUDITORS**

We consent to the incorporation by reference in the Registration Statements on Forms S-8 No. 33-75268 pertaining to the 1994 Stock Option Plan and 1994 Stock Purchase Plan, No. 33-80662 pertaining to the 1994 Stock Option Plan, No. 33-93394 pertaining to the 1994 Employee Stock Purchase Plan, No. 333-29801 pertaining to the 1994 Stock Option Plan, No. 333-60057 pertaining to the 1994 Stock Option Plan, No. 333-79789 pertaining to the 1994 Stock Option Plan, No. 333-43504 pertaining to the 1994 Stock Option Plan and 1994 Stock Purchase Plan and No. 333-72098 pertaining to the 1994 Stock Option Plan and Registration Statements on Forms S-3 No. 333-38266 and No. 333-54912 of InSite Vision Incorporated of our report dated February 1, 2002, with respect to the consolidated financial statements of InSite Vision Incorporated included in the Annual Report (Form 10-K) for the year ended December 31, 2001.

/s/ Ernst & Young LLP

Palo Alto, California  
March 28, 2002

# Corporate and Stockholder Information

## Board of Directors

S. Kumar Chandrasekaran, Ph.D.  
*Chairman of the Board, Chief Executive Officer, President and Chief Financial Officer*  
InSite Vision Incorporated

Mitchell H. Friedlaender, M.D. (1)  
*Head, Division of Ophthalmology and Director Laser Vision Center, Scripps Clinic*

John L. Mattana (1) (2) (3)  
*Vice President*  
Ceptor Corporation

Jon S. Saxe, Esq. (3)  
*Retired President*  
Protein Design Labs, Inc.

Anders P. Wiklund (2) (3)  
*Principle*  
Wiklund International

- (1) Nominating Committee
- (2) Stock Plan and Compensation Committee
- (3) Audit Committee

## Officers & Senior Management

S. Kumar Chandrasekaran, Ph. D.  
*Chairman of the Board, Chief Executive Officer, President and Chief Financial Officer*

Lyle M. Bowman, Ph.D.  
*Vice President, Development and Operations*

Charles G. Chavdarian, Ph.D.  
*Senior Director, Analytical Research and Development*

Cheryl E. Chen  
*Senior Director, Clinical Operations*

T. Raymond Chen, Ph.D.  
*Senior Director, Regulatory, Quality Assurance and Quality Control*

Sandra Heine  
*Senior Director, Finance and Administration*

Samir Roy, Ph.D.  
*Senior Director, Formulation Development and Operations*

Erwin Si, Ph.D.  
*Senior Director, Preclinical Research*

## Corporate Headquarters

965 Atlantic Avenue  
Alameda, CA 94501  
Phone (510) 865-8800  
Fax (510) 865-5700  
Website <http://www.insitevision.com>

## General Counsel

Brobeck, Phleger & Harrison, LLP  
Palo Alto, California

## Independent Auditors

Ernst & Young, LLP  
Palo Alto, California

## Transfer Agent and Registrar

For change of address, lost stock certificates and related matters, please direct inquiries to:

Mellon Investor Services  
Overpeck Centre  
85 Challenger Road  
Ridgefield, NJ 07660  
Phone (800) 522-6645  
From outside U.S. (201) 329-8660  
Website <http://www.melloninvestor.com>  
TTD for Hearing Impaired (800) 231-5469  
TTD Foreign Shareholders (201) 329-8354

## Annual Meeting

The Annual Meeting of Stockholders is scheduled to be held at 10:00 a.m. (Pacific Time) on June 3, 2002 at the Oakland Yacht Club, 1101 Pacific Marina, Alameda, California 94501.

## Annual Report on Form 10-K

A copy of the Company's Annual Report on Form 10-K as filed with the Securities and Exchange Commission has been delivered along with this Annual Report. Additional copies are available upon request to:

Lippert/Heilshorn & Associates  
1900 Avenue of the Stars, Suite 2840  
Los Angeles, CA 90067  
Phone (310) 691-7100

## Common Stock Listing

InSite Vision's Common Stock is listed on the American Stock Exchange under the symbol ISV.

## Holders of Common Stock

As of December 31, 2001, there were approximately 6,500 beneficial holders of the Company's Common Stock.

## Price Range of Common Stock

	High	Low
2001		
First Quarter	\$3.94	\$1.91
Second Quarter	2.40	0.90
Third Quarter	1.49	0.95
Fourth Quarter	2.00	0.90
2000		
First Quarter	\$7.50	\$2.50
Second Quarter	5.94	3.06
Third Quarter	7.69	3.56
Fourth Quarter	8.50	2.18

InSite Vision has not paid any cash dividends on its Common Stock and does not anticipate paying any dividends in the foreseeable future.

In addition to the historical information contained in the document, the discussion in the Annual Report to Stockholders contains forward-looking statements, within the meaning of Section 27A of the Securities Act of 1933, as amended, and Section 21E of the Securities Exchange Act of 1934, as amended, that involve risks and uncertainties, such as statements of our plans, objectives, expectations and intentions. The cautionary statements made in this Annual Report to Stockholders should be read as being applicable to all related forward-looking statements whenever they appear in this Annual Report to Stockholders. Our actual results could differ materially from those discussed herein. Factors that could cause or contribute to such differences include, but are not limited to, those discussed herein, as well as market acceptance of our products; our ability to maintain and develop additional collaborations and commercial agreements with corporate partners, including with respect to OcuGene, ISV-205 and ISV-401; our need for significant additional funding for our capital requirements; our reliance on third parties for the development, marketing and sale of our products; and the results of preclinical and clinical studies and determinations by the U.S. Food & Drug Administration, including those with respect to OcuGene, ISV-205 and ISV-401. For further discussion of our business, and risk factors affecting our results of operations, please refer to our 2001 Annual Report on Form 10-K which is included along with this Annual Report to Stockholders, incorporated herein and considered an integral component of this Annual Report to Stockholders.



## INSITE*VISION*

InSite Vision Incorporated

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Alameda, CA 94501

Phone (510) 865-8800

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Websites

<http://www.insitevision.com>

<http://www.ocugene.com>

AMEX: ISV