AEROGEN INC
Form 10-K
March 31, 2003

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UNITED STATES
SECURITIES AND EXCHANGE COMMISSION

Washington, DC 20549

FORM 10-K

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

FOR THE FISCAL YEAR ENDED DECEMBER 31, 2002
Commission File Number 0-31913

Aerogen, Inc.

(Exact Name of Registrant as Specified in Its Charter)

Delaware	**33-0488580**
(State or Other Jurisdiction of Incorporation or Organization)	(IRS Employer Identification No.)
2071 Stierlin Court, Mountain View, CA	**94043**
(Address of Principal Executive Offices)	(Zip Code)

Registrant's telephone number, including area code: **(650) 864-7300**

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

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

Common Stock, par value $0.001

(Title of Class)

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

Indicate by check mark whether the registrant is an accelerated filer (as defined in Rule 12b-2 of the Act): Yes o No ý

The aggregate market value of the common stock held by non-affiliates of the registrant based upon the closing price on the Nasdaq National Market reported on June 28, 2002 was $17,839,000.

The number of shares of common stock outstanding as of March 26, 2003 was 20,403,747.

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 statement incorporated by reference in Part III of this form 10-K or any amendment to this form 10-K. o

Aerogen, Inc.
FORM 10-K ANNUAL REPORT
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PART I

Item 1. BUSINESS

Notice Concerning Forward-Looking Statements

This Annual Report on Form 10-K ("Form 10-K") of Aerogen, Inc. contains forward-looking statements. These forward-looking statements are not historical facts, but rather are based on current expectations, estimates and projections about our industry, our beliefs and our assumptions. Words such as "anticipate," "expect," "intend," "plan," "believe," "seek" and "estimate," variations of these words, and similar expressions, are intended to identify forward-looking statements. These statements are not guarantees of our future performance and are subject to risks, uncertainties and other factors, some of which are beyond our control, are difficult to predict and could cause actual results to differ materially from those expressed, implied or forecast in the forward-looking statements. In addition, the forward-looking events discussed in this Form 10-K might not occur. These risks and uncertainties include, among others, those described in "Risk Factors" and elsewhere in this Form 10-K. Readers are cautioned not to place undue reliance on these forward-looking statements, which reflect our management's view only as of the date of this Form 10-K. Except as required by law, we undertake no obligation to update any forward-looking statement, whether as a result of new information, future events or otherwise.

Introduction

Aerogen, Inc. ("Aerogen" or the "Company") is a specialty pharmaceutical company focusing on respiratory therapy in the acute care setting. Based on our proprietary technology for aerosolizing liquids, we have developed, and commercially introduced, nebulizers that optimize aerosol production for use in both the home and hospital. We are developing, and intend to commercialize, drug products that specifically target treatment of respiratory disorders in the acute care setting. In addition, we are developing pulmonary drug delivery products in collaboration with partner companies for respiratory therapy and systemic drug input.

Our current products address many of the limitations presented by use of traditional nebulizers for pulmonary drug delivery. We believe our drug products in development for pulmonary drug delivery using our proprietary technology should have a major impact on treatment of respiratory diseases in the acute care setting.

Our goal is to become the leading provider of aerosol-based pulmonary drug delivery products in the acute care setting, particularly for patients on ventilators. We have identified a multi-billion dollar market opportunity where our technology, coupled with drugs already commercialized but not previously delivered by the pulmonary route and/or drugs novel to inhalation, addresses an unfulfilled market need.

We launched our first product, the Aeroneb® Portable Nebulizer System, in June 2001, and our second product, the Aeroneb® Professional Nebulizer System (the "Aeroneb Pro" nebulizer), in June 2002. We have next generation versions of both products in development.

Our lead therapeutic product in development is an aerosolized antibiotic product in which a formulation of amikacin is delivered via a next generation Aeroneb Pro nebulizer for the treatment of patients on ventilators with respiratory infections. Our business plan also includes the development, in collaboration with pharmaceutical and biotechnology company partners, of respiratory products that will combine our technology with the partners' proprietary compounds. The partner companies generally will commercialize the products developed in the collaborations. These products may utilize one of our Aeroneb Pro nebulizers or one of our nebulizers or inhalers for the home market.

In addition to our respiratory therapy activities, we intend to develop novel pulmonary drug delivery products for systemic drug input in collaboration with pharmaceutical and biotechnology companies and other partners. Systemic drug delivery of biotechnology products via the lungs provides significant market opportunities. We have developed an Aerodose® inhaler for the pulmonary delivery of insulin to Type 1 and 2 diabetic patients, and have successfully taken the product through Phase 2a testing. We have completed design verification testing of the commercial version of the inhaler. Product development activities have been placed on hold, pending an agreement with an appropriate partner willing to commit the financial resources required to complete the clinical studies and commercialize the product.

Aerogen was incorporated in the state of California in November 1991 under the name Fluid Propulsion Technologies, Inc. Our name was changed to AeroGen, Inc. in April 1997 and then to Aerogen, Inc. in May 2002. In March 1998, we changed our domicile to the state of Delaware. Our principal executive offices are located at 2071 Stierlin Court, Mountain View, California 94043; telephone number (650) 864-7300. Our business comprises one industry segment the development, manufacture and commercialization of pulmonary drug delivery products.

In May 2000, we acquired Cerus Limited, which is now Aerogen (Ireland) Limited and our wholly-owned subsidiary. Cerus was a development stage company engaged in the development of pulmonary inhalation products utilizing our core aerosol generator technology. Aerogen (Ireland) developed our Aeroneb Pro nebulizer, and is responsible for its assembly, utilizing aerosol generators produced in our Mountain View facilities.

As of December 31, 2002, we had $8.9 million in cash, cash equivalents and available-for-sale securities. During 2003, our expenditures have been approximately $1.6 million per month. We will need to raise additional funds through public or private financings, collaborative relationships or other arrangements within the next 30 to 60 days in order to continue as a going concern. We cannot be certain that such additional funding will be available on terms attractive to us, or at all. Furthermore, additional equity or debt financing may involve substantial dilution to our existing stockholders, restrictive covenants or high interest rates. Collaborative arrangements, if necessary to raise additional funds, may require us to relinquish rights to either certain of our products or technologies or desirable marketing territories, or all of these.

"Aerogen," "Aerodose," "Aeroneb" and the Aerogen logo are our trademarks. This Form 10-K also includes references to registered service marks and trademarks of other companies, which are indicated when used in this Form 10-K.

Pulmonary Drug Delivery

Pulmonary drug delivery is widely used to treat respiratory diseases and is also believed to be a viable means to deliver drugs to the bloodstream via the lungs. The size of the inhaled droplets generally influences where the drug will be deposited in the lungs. Large droplets, greater than three microns in diameter, typically are deposited in the upper airways of the lung, where they may be useful in treating diseases such as asthma, chronic obstructive pulmonary disease and cystic fibrosis. Small droplets, less than three microns in diameter, are more likely to pass through the upper airways into the deep lung, where they may be absorbed into the bloodstream to treat diseases such as diabetes. Our technology permits drug delivery to the lungs in a liquid aerosol of a defined average droplet size.

Acute Care Market Respiratory Disorders

Respiratory disorders are associated with impaired quality of life, reduced life expectancy and significant treatment costs. Approximately 1.2 million patients are treated in the intensive care units (ICUs) of U.S. hospitals each year for respiratory disorders, including pneumonia, chronic obstructive pulmonary disease, asthma and respiratory distress syndrome. The cost of drugs for treatment of these

patients totals approximately $3.5 billion per year, averaging approximately $500 per day. There are also less prevalent diseases, such as neonatal pulmonary hypertension and infant respiratory distress syndrome (IRDS) that have few but costly treatments available. Other than for treatment of airways diseases, virtually all drug therapy for treatment of respiratory disorders in the ICU is given systemically by injection or infusion. This reflects, in part, the lack of sufficiently reproducible and efficient pulmonary drug delivery technology.

We are currently focusing on development of our own products for treating two respiratory disorders in the acute care setting: respiratory infections in ventilated patients and pulmonary hypertension. We are also focusing on improving pulmonary drug delivery generally for patients using nebulizers and those receiving therapy via ventilators.

Approximately 1.5 million patients are placed on ventilators in U.S. hospitals each year. We estimate that as many as one third of the patients develop tracheobronchitis, which is an infection of the upper airways. If not treated, tracheobronchitis can develop into ventilator associated pneumonia (VAP). Despite aggressive intravenous therapy, a very high mortality rate (20-50%) is associated with VAP. Current therapy relies almost exclusively upon intravenous antibiotics. Treatment with the required high doses of intravenous antibiotics can be associated with severe side effects. Historically, aerosol therapy has not been utilized due to the low efficiency of available devices in delivering drugs to the lungs. Approximately 150,000 patients in the U.S. are diagnosed with VAP annually.

Pulmonary hypertension affects approximately 50,000-60,000 neonates annually in the United States. The approved treatment for infants of greater than 34 weeks gestation age is inhaled nitric oxide. Ttreatment is expensive and side effects are significant. There is no currently approved treatment for pulmonary hypertension in infants of less than 34 weeks gestational age.

Systemic Drug Delivery

In addition to our focus on pulmonary drug delivery in the acute care setting, we pursue systemic drug input via the pulmonary route on an opportunistic basis. The physiology of the lungs makes pulmonary delivery an attractive method for delivery of drugs to the bloodstream. The absorptive surface area of the deep lung in the adult approximates 70 square meters, and is only one to two cells in thickness. This large surface area is available for the free exchange of oxygen, carbon dioxide and other molecules between the air and the bloodstream. This permits drugs deposited in the deep lung to be transported rapidly into the bloodstream.

Pulmonary drug delivery is being evaluated for non-invasive delivery of drugs to the bloodstream to treat non-respiratory diseases. There is increasing interest in pulmonary drug delivery as a result of the inability of currently available non-injectable dosage forms to deliver molecules such as proteins and peptides to the bloodstream effectively. For these large molecules, oral delivery is thwarted due to rapid breakdown of the molecules following ingestion. Dosage forms such as intravenous or intramuscular injections and implants, while effective for delivering proteins, have many drawbacks, including pain, inconvenience, expense, risk of infection and poor compliance. Alternatives like transdermal and nasal dosage forms do not allow reproducible delivery of large molecules. We believe that systemic drug delivery of biotechnology products via the lungs may provide significant market opportunities. For example, pulmonary delivery is being considered for drugs such as insulin, which require rapid input to the bloodstream for optimal therapy.

Traditional and New Methods of Pulmonary Drug Delivery and Their Limitations

Three basic classifications of devices are currently being used for pulmonary drug delivery: metered dose inhalers, dry powder inhalers and nebulizers. These devices were developed originally for local treatment of respiratory diseases, including asthma and chronic obstructive pulmonary disease, and have inherent limitations in delivering drugs to the lungs. Metered dose inhalers consist of a portable

canister containing the drug as a suspension or solution mixed with a volatile propellant, traditionally a chlorofluorocarbon. In order to administer the drug, the patient must activate the inhaler by pressing down on the canister while simultaneously inhaling slowly and evenly. Even with repeat training, many patients using metered dose inhalers have difficulty coordinating activation of the device with their breathing. Once the inhaler is activated, particles are released at an initial velocity of at least 30 miles per hour. Metered dose inhalers typically deliver only 10% to 20% of the drug to the lungs. Newer HFA versions deliver a higher percentage of the dose, but are only available for a few drug formulations. Most of the remainder of the drug is deposited in the mouth and swallowed. To overcome these limitations, patients are sometimes prescribed holding chambers, or spacers, to use with their metered dose inhalers. These spacers increase the complexity of use and reduce the portability of metered dose inhalers. In the acute care setting, for patients on ventilators, MDIs are used by opening the ventilator circuit and spraying into the tubing via a spacer. This interruption of assisted breathing poses significant inherent risks, including the introduction of infectious agents to a patient with already compromised pulmonary function. In addition, it takes several actuations for a metered-dose inhaler, spaced over several minutes, to deliver the dose levels typically prescribed in an intensive care unit. This requires the significant time and the associated expense of an attendant respiratory therapist.

Traditional dry powder inhalers were introduced to overcome some of the problems inherent with the use of metered dose inhalers. Dry powder inhalers deliver dry powdered aerosols without using a compressed propellant. Dry powder inhalers are breath activated and thus eliminate the need for the press and breath coordination associated with metered dose inhalers; however, traditional dry powder inhalers have meaningful limitations that may prevent their broad use in pulmonary drug delivery. Dry powder inhalers usually require a strong, deep inhalation to create the air velocity that generates the aerosol and delivers the drug. Children, the elderly and patients with breathing difficulties often cannot achieve the strong inhalation necessary to generate the required dose. In addition, these devices do not allow the patient to inhale the desired drug in multiple breaths and moisture entering into the dry powder inhaler from the environment or a patient's own breath can result in dose-to-dose variation. Because there is no mechanism in ventilator circuits for actuating dry powder inhalers, they are not generally used to administer drugs to the lungs of patients on ventilators in clinical practice.

Traditional nebulizers create a continuous liquid aerosol that can be inhaled by patients through a mask or mouthpiece. Nebulizers allow patients to breathe normally, thereby requiring less patient coordination and cooperation than metered dose inhalers or dry powder inhalers. Traditional jet nebulizers typically require an external source of compressed air or oxygen and are therefore bulky and generally noisy. Nebulizer treatments are time-consuming and inefficient, with less than 20% of the drug typically reaching the lungs in ambulatory patients. The remainder of the drug is either aerosolized during the patient's exhalation, released into the surrounding air or left behind in the nebulizer. Because of these limitations, traditional nebulizers are only appropriate for relatively inexpensive, small-molecule drugs that can be formulated and stored as liquids. In the acute care setting, compressor nebulizers are used to introduce aerosol into the ventilator circuit for inhalation by the patient.

Use of compressor nebulizers can introduce additional air into the ventilator circuit, disturbing the precise balance of air pressures used to ventilate patients and to monitor their pulmonary function. Perhaps most significantly, these delivery devices are inefficient, resulting in only a very small amount of the drug dose (1-3%) ever reaching the patient's lungs. Ultrasonic nebulizers (which rely on droplets breaking free from standing waves at the surface of the drug solution) are more efficient than compressor nebulizers, but are expensive, heat the administered drug and are unable to nebulize suspensions.

Several companies are developing technologies to improve the efficiency and accuracy of pulmonary drug delivery in the home setting. Because systemic drug delivery requires the ability to create and deliver small particles to the deep lung, research has centered on developing devices capable

of consistently delivering fine particle aerosols. One technique involves the processing and stabilizing of drugs in dry powder form. Another uses mechanical pressure to aerosolize custom formulations of drugs in solution. Both of these technologies will require an extensive investment in new formulations, new packaging, new materials and customized manufacturing, as well as an extensive validation effort for Good Manufacturing Practices. The dry powder technology will also face the challenge of consistently creating a cloud of uniform fine particles in varying environmental conditions that can include both high humidity and electrostatic charge.

To date there has been little emphasis on improving the efficiency of pulmonary drug delivery in the hospital setting. Of the $3.5 billion in annual drug sales for treatment of patients with respiratory infections in the ICU, virtually all are given intravenously, due to the inefficiency of currently available devices in delivering drugs to the lungs.

Our Core Technology and Marketed Products

Aerosol Generator

Our proprietary aerosol generator contains a domed aperture plate that contains hundreds of apertures, or holes, of a discrete shape and size. The aperture plate is produced through an electroforming process using a metal alloy which is strong, corrosion resistant and durable. The plate is placed within a vibrational element that, when energy is applied to this element, causes the aperture plate to vibrate. This creates a micro-pumping action that draws drug solutions or suspensions in contact with the concave surface of the plate through the apertures to form a fine droplet aerosol. The aerosol droplet size formed is determined by the size of the holes in the aperture plate. A controllable manufacturing process is used to produce aperture plates with selected hole sizes that result in aerosol droplets of the same sizes. The micro-pumping action creates a low velocity aerosol, the flow rate of which is controlled by the voltage and frequency applied to the vibrational element. When the aerosol generator is incorporated into one of our nebulizers or inhalers, it is capable of producing aerosols of consistent droplet size in a low velocity aerosol, which can be optimized for a specific indication.

We have demonstrated the ability to aerosolize solutions and suspensions of drugs of both small and large molecular weight. Results to date indicate that the aerosol generator does not affect the integrity of proteins or peptides.

Benefits of Our Technology

Optimization and Customization of Aerosol Droplet Size. Our aerosol generator delivers a low-velocity liquid aerosol of precisely defined average droplet size. The aerosol generator enables us to provide either an aerosol with droplets averaging three to five microns in diameter for respiratory therapy, or an aerosol with droplets averaging one to three microns in diameter for deposition in the deep lung for systemic drug delivery.

Ease of Formulation. Drugs can be aerosolized in solution or suspension. The aerosol generator uses no propellants or pressure, and generates negligible heat, so it is not likely to degrade drug molecules. In many cases, we can use existing drug formulations, eliminating the need to demonstrate the stability of new formulations.

Flexibility of Dosing. Our technology can be used to administer drugs as a single dose, or as a unit dose from a multi-dose canister. For example, our Aerodose® insulin inhaler contains a titration mechanism, developed with Disetronic Medical Systems, which allows the diabetic patient to deliver a specific dose of insulin from a glass cartridge designed to hold 1-2 weeks of inhaleable insulin.

Breath-Activation. We have developed a breath-activation feature which triggers aerosol formation and is designed to enable a broad range of patients to obtain consistent dosing over

one or more breaths. This feature is designed so that drug will be aerosolized only when the patient's inhalation flow rate has reached a predetermined threshold, which can be pre-programmed for a particular target patient population. If a patient exhales or coughs, the aerosolization will stop and will only resume when the patient begins inhaling again. Our electronic controls are designed to allow us to customize products for both relaxed and controlled breathing.

Dosage Guidance. We can incorporate electronic features to provide information to the patient or respiratory attendant. Lights can indicate when a dose is ready for inhalation and when the total dose has been inhaled. Audible/vibratory signals can be used to indicate other system modes. Additional features may include indicators of patient compliance with the prescribed regimen and lock-out features to prevent abuse or overdose.

Convenience. Our products are designed to be lightweight and easy to use for patients and care-providers. Aerodose inhalers fit in the palm of the hand and can be carried in a shirt pocket or small purse. We believe our products will require minimal patient training, will be easy to use for the very young and the elderly and will have the potential to increase compliance with prescribed treatment regimens. The Aeroneb® Portable Nebulizer System is quieter and more compact than currently commercialized nebulizers. The Aeroneb Pro nebulizer is lightweight, allowing it to be placed close to the ventilated

patient's windpipe, providing efficient generation of aerosol close to the lung. The next generation of products will also be lightweight and compact.

Our core aerosol generator technology is being incorporated into our nebulizers and inhalers. In 2002, much of our effort was directed to streamlining and improving the manufacturing processes for our aerosol generator as we moved into our new laboratories and manufacturing facilities, including a Class 10,000 clean room, in our Mountain View, California headquarters. We also undertook development of a lower cost aerosol generator using components similar to those used in our commercially available nebulizers, but with a changed configuration. We completed the design verification testing of the commercial form of our Aerodose insulin inhaler, and produced clinical quantities of our Aerodose respiratory inhaler.

Our Nebulizer Products

We have two nebulizer products currently on the market, the Aeroneb® Portable Nebulizer System and the Aeroneb® Professional Nebulizer System.

Aeroneb® Portable Nebulizer Systems. Our first commercial product, the Aeroneb® Portable Nebulizer System, was launched in June 2001, and is marketed in the United States to home medical equipment dealers, pharmacies and directly to patients over the Internet. We distribute the product through Cardinal Health, CareFore Medical, Inc. and other regional distributors. Recently, the product has been featured on the top shelf of "The Asthma and Allergy Place," a display featured at more than 200 pharmacies which contains devices and supportive products necessary for asthma patients to treat their condition. Total sales of this product in 2002 and 2001 were approximately $0.3 million and $0.2 million, respectively.

We are developing a smaller, less expensive version of the Aeroneb® Portable Nebulizer System, which is targeted for launch in the third quarter of 2003, upon CE marking in Europe and 510(k) clearance in the U.S. The product will use a lower-cost aerosol generator and will be offered with both an AC wall controller and a battery pack to allow for portability.

Aeroneb® Professional Nebulizer Systems. Our second commercial product, the Aeroneb® Professional Nebulizer System (Aeroneb Pro nebulizer) was introduced worldwide in June 2002. The product is CE marked in Europe and received 510(k) clearance in the United States as a general-

purpose nebulizer intended to aerosolize physician-prescribed solutions for inhalation. This nebulizer, which produces a continuous flow of aerosol, is targeted to improve pulmonary delivery of drugs to patients on or off ventilators. The nebulizer is small and lightweight, allowing it to be positioned close to the patient's airway. It is designed to allow the addition of medication to the nebulizer without opening the ventilator tubing, thereby potentially reducing a major source of infection. The drug is aerosolized without the use of a compressor and avoids the introduction of additional air into the ventilator tubing. This nebulizer provides the first significant innovation in aerosolized drug therapy in 20 years specifically designed for patients on ventilators in the ICU.

The Aeroneb Pro nebulizer is flexible because it can be used not only on the ventilator, but also on the hospital floor or in the ambulance. It can interfit with both adults' and children's masks. The device is autoclaveable and therefore available for multi-patient use. Its low residual volume allows efficient drug delivery to the lungs. Using the Aeroneb Pro nebulizer on the ventilator, efficiency of drug deposition in the lungs of patients, when compared *in vitro* with use of small volume jet nebulizers, is improved more than four fold, to the 10-15% range.

We have a worldwide agreement with Puritan Bennett ("PB") under which PB sells the Aeroneb Pro nebulizer with its newer ventilators in the United States, and with both its 840 series and the installed base of ventilators outside the United States. We also have an agreement with Cardinal Health under which Cardinal's Respiratory Care Products Group sales force is targeting the Aeroneb Pro nebulizer to the installed base of ventilators in the United States (approximately 100,000 ventilators from several manufacturers). These distributors are supported by our small group of contract clinical specialists. In Europe, we have agreements with additional distributors on a country-by-country basis who are targeting the installed base of ventilators in those countries.

Aerogen's sales of the Aeroneb Pro nebulizer were approximately $1.6 million in 2002 (the product was introduced in June 2002), and the product is now available in more than 20 countries.

We are developing a phasic version of the Aeroneb® Pro general-purpose nebulizer, which we plan to launch in Europe in late 2003, after CE marking. Phasic nebulizers, which are commonly used in Europe with ventilators, release the drug only during the inhalation phase of the ventilator cycle, rather than continuously. We have also developed an optimized phasic version of the Aeroneb Pro nebulizer, which is capable

of sensing the performance of the ventilator and aerosolizing the drug during a predetermined fraction of the inhalation phase of the ventilator cycle. *In vitro* deposition of drug in the lung is typically greater than 60% of the starting dose with this optimized nebulizer. This product has been CE marked in Europe, where it is currently in use in our Phase 2 clinical trial delivering amikacin. We do not intend to market the optimized phasic nebulizer as a stand-alone device, but rather for use exclusively with drug products.

Finally, we have developed a version of the Aeroneb® Pro specifically for use in animal testing laboratories, called the Aeroneb® Lab**.** In 2002, we sold approximately 100 units of the product to a company that packages and sells it with the company's testing equipment systems for use in animal testing. We also plan to sell the product in 2003 on a stand-alone basis directly to contract research organizations for use in animal testing.

Sales of our Aeroneb® products accounted for 75% of our total revenues in 2002.

Our Drug Product Pipeline

We intend to incorporate our versatile and flexible technology into a portfolio of devices and drug products, some to be developed for commercialization by us and some to be developed with partners for who will market the product themselves. We also intend to continue to out-license our technology for applications outside of the field of pulmonary drug delivery.

Aerogen Products Under Development for Treatment of Respiratory Diseases

We intend to create and market a respiratory disease product portfolio consisting of products delivering drug-containing aerosols in the acute care setting.

Our activities for therapeutic products to be marketed by Aerogen will be focused on development, clinical testing, U.S. regulatory approval and market introduction. The rights to the products outside the United States will most likely be licensed to partners who will undertake the studies and other activities necessary to obtain regulatory approvals in their territories.

Amikacin. Our lead drug product is the aminoglycoside amikacin, under development to address the large unmet need for more effective treatment of respiratory infections in patients requiring mechanical ventilation. We are targeting the product to treat early infection (tracheobronchitis) and VAP. Aminoglycosides, as a class of antibiotics, are effective in treating pulmonary infections associated with gram negative organisms such as pseudomonas aeruginosa when administered systemically. However, they penetrate poorly from the blood to the lung, relative to other classes of antibiotics, which often leads to unwanted systemic toxicities (including damage to kidneys and hearing). The potential to administer nebulized amikacin allows for the possibility of treating tracheobronchitis either via aerosol alone or in concert with antibiotics less toxic than systemically administered aminoglycosides. There is also the potential that the treatment of tracheobronchitis using this product will be clinically demonstrated to prevent the progression of the pulmonary infection into VAP.

Our first Phase 2 study in 12 patients is underway in France. In this study, we are comparing drug deposition in the lungs of ventilated patients when the drug is administered by the Aeroneb Pro nebulizer, the optimized phasic version of the Aeroneb Pro nebulizer and the commercially available Airlife Misty Neb nebulizer. We are using a preservative-free solution of amikacin approved for intravenous administration that is commercially available in France. This particular formulation has been associated with off-label use administered by aerosol for treatment of infections in children with cystic fibrosis. We anticipate that we will conduct a second Phase 2 study and then seek a development and commercialization partner to sponsor pivotal clinical studies and worldwide registration for this product. In any such partnering arrangement, we intend to negotiate to receive royalties on product sales.

Pulmonary Vasodilators. Neonatal pulmonary hypertension affects approximately 50,000-60,000 neonates in the United States each year. The most common treatment is inhaled nitric oxide, which is expensive and can result in serious side effects. Pulmonary vasodilators are currently approved for the intravenous treatment of pulmonary hypertension in adults. To date, use of aerosolized pulmonary vasodilators has been very limited due to the inefficiency of the available aerosol delivery devices. Our product is in pre-clinical development. We plan to develop the drug product for aerosolized delivery using the optimized phasic version of the Aeroneb Pro nebulizer, so that the aerosol particle size and the aerosolization time during the inspiratory phase of the ventilator will be preset to optimize deposition of drug in the lung.

Aerosolized Humanized Surfactant. We signed an agreement in July 2002 with Discovery Laboratories, Inc. (Discovery Labs) to explore pulmonary delivery of aerosolized human surfactant in the hospital setting. Discovery Labs has a synthetic surfactant consisting of phospholipids and a protein that mimics endogenous surfactant B protein. Discovery Labs currently has two Phase 3 trials in infants and one

Phase 2 trial in ventilated adults underway for treatment of respiratory conditions. In these studies, the liquid surfactant is administered in a bolus either through an endotracheal tube (a tube inserted into the mouth and down the trachea) or by a lavage technique through a bronchoscope. Aerosolized surfactant has the potential for treatment of many respiratory conditions. The preclinical data developed as a result of our agreement with Discovery Labs has indicated that our technology can effectively aerosolize the surfactant while maintaining the integrity of the formulation.

Other Product Development Opportunities

Additional drug development opportunities in the acute care setting include treatment of asthma (with bronchodilators and anti-inflammatory agents), COPD (with anti-inflammatory agents, phosphodiesterase inhibitors, mucoactive agents), pulmonary hypertension (vasodilators) and ARDS (protease inhibitors, anti-coagulative agents, inhibitors of fibrosis). We have several drugs in the preclinical stage of evaluation.

We plan to explore additional drugs in 2003 and beyond, including available drugs and drugs in-licensed or available for in-license from third parties, starting with feasibility, preclinical and initial clinical activities. We also plan to explore the potential for commercializing appropriate drug combinations for delivery via our nebulizers and inhalers.

Our Product Development Process

Feasibility is the first stage of development for our drug products. In the feasibility stage, we determine the solubility of the drug, the type of solution or suspension we would likely need in order to use the drug in our inhalers or nebulizers, our ability to aerosolize the drug and the likely stability of the drug when used with our nebulizers or inhalers. In this stage, we conduct laboratory studies primarily focused on the drug itself, and its compatibility with the aerosol generator.

During the preclinical development stage, we focus on the customization of our nebulizer or inhaler for use with a particular drug. We determine the appropriate container to hold the drug in the nebulizer or inhaler, the method of delivery of the drug to be aerosolized, the type of breath activation mechanism or ventilator sensing algorithm that is likely to be needed and the configuration of the aperture plate for the product. Preclinical development is conducted primarily in the laboratory and is targeted toward development and the initial production of the nebulizer or inhaler to be used in the clinical studies.

After feasibility testing and preclinical development, the products are tested in human subjects. Our products differ from dry powder inhalers and metered dose inhalers, in that our products are combinations of discrete devices and drugs, and therefore the regulatory pathway, and the clinical programs that will be required for product approvals are complex due to the presence of both drug and device elements in our products. As the regulatory requirements are discussed in detail with the United States Food and Drug Administration (FDA) and clarified, it is possible that certain products will be less attractive commercial targets for Aerogen marketing than others. For example, in 2001 and 2002, we were developing products to deliver albuterol and ipratropium via our hand-held Aerodose respiratory inhaler for home use. Based on the regulatory climate in 2002, we have put these products on hold due to the likely need for costly clinical programs and the extended time to regulatory approval for generic drug products delivered from a new device. The Aerodose respiratory inhaler developed for these programs has proven of interest for partnered activities where partners have proprietary drugs for treatment of either a respiratory problem or for systemic drug input that will require a full New Drug Application (NDA). Feasibility activities are underway for products using this inhaler to deliver partner drugs.

Partnered Activities

We are collaborating, and intend to continue to collaborate, with pharmaceutical and biotechnology companies to develop novel pulmonary drug delivery products for respiratory therapy and for systemic drug input via the pulmonary route. Such collaborations can take one of two approaches: either a company contacts us with a proprietary drug to be delivered to the lungs, or we proactively identify product opportunities and approach potential partners after obtaining preclinical data, if possible.

Respiratory Therapy

The flexibility of our technology to facilitate improved respiratory therapy has attracted potential development partners. We currently have feasibility activities with potential partners with undisclosed compounds for respiratory therapy and systemic drug input underway. A feasibility study can be paid for by us or by the other company. Generally, development agreements and the associated activities can be canceled at any time by the company funding the work. In the drug delivery area, it is common for pharmaceutical and biotechnology companies to conduct feasibility studies with multiple partners. Once feasibility of a particular drug has been established, the pharmaceutical and biotechnology companies typically fund additional development work. Following collaborative development of a product, the partner will commercialize the product and pay us a royalty on sales.

In March 2002, we signed a Cooperative Research and Development Agreement (CRADA) with the United States Army for pulmonary delivery of novel vaccines. The initial work was done by the United States Army Medical Research Institute for Infectious Diseases (USAMRIID), and a grant proposal has been submitted to fund the next stage of the activities at Aerogen. The CRADA was expanded in June 2002 to also cover antiviral applications.

Our Aerodose respiratory inhaler is available for use with partner drugs in programs funded by the partners, and that inhaler can be, and has been, customized for different programs.

Systemic Drug Delivery

In addition to our respiratory therapy activities, our strategy includes collaborating with pharmaceutical and biotechnology companies to develop novel pulmonary drug delivery products for systemic therapy.

We have developed an Aerodose inhaler for delivery of insulin to diabetic patients. The Aerodose insulin inhaler is designed to utilize a patient-adjustable cartridge for pulmonary delivery of insulin, allowing patients to precisely adjust their insulin dose based on anticipated caloric intake and other factors. The titration mechanism was developed with Disetronic Medical Systems.

Phase 1 clinical studies using prototype Aerodose inhalers delivering insulin have been completed in the United Kingdom and Germany. The studies compared insulin inhalation to subcutaneous injection, focusing on both the absorption of insulin into the bloodstream and its glucose-lowering effects. Subjects used Aerodose inhalers configured for slow, deep inhalations and production of a small-droplet aerosol appropriate for systemic drug delivery. Results from the first study indicated that the absorption and glucose-lowering effects of inhaled insulin, relative to injected insulin, were consistent with the published literature. In the second study, optimal aerosolization parameters were evaluated.

Phase 2 trials were initiated in Europe and the United States at the end of 2000. These studies were designed to provide additional evidence of Aerodose inhaler performance, inter- and intra-subject variability and dose proportionality of circulating levels of insulin following inhalation in Type 2 (non-insulin dependent) diabetic patients. The results indicated that delivery of insulin into the bloodstream by inhalation was no more variable within a patient than when insulin was delivered subcutaneously. In the four studies we have completed, there were no serious adverse events or clinically significant differences in lung function between the inhaled and subcutaneous treatments.

We have an agreement with Diosynth B.V., a business unit of Akzo Nobel, for the supply of clinical and commercial quantities of recombinant human insulin for use in the product. We successfully completed our design verification testing for the Aerodose insulin inhaler during the fourth quarter of 2002.

We had planned to enter into an agreement with a marketing partner for the Aerodose insulin inhaler for the further development, clinical testing and commercialization of the product before the end of 2002. We believe that the nature of the diabetes market requires a major pharmaceutical company partner with a diabetes franchise to market the product. We were unable to enter into such an agreement in 2002 under favorable financial conditions; therefore further activities for the product were placed on hold until and unless we enter into an agreement with a commercialization partner.

In addition to insulin, we are continuing to evaluate the market opportunities for other drugs that we believe can be delivered to the bloodstream using with our Aerodose inhaler. We intend to collaborate with pharmaceutical and biotechnology companies for development, clinical testing and commercialization of other Aerodose inhaler products. We currently have an undisclosed feasibility agreement with a pharmaceutical company targeting a protein for systemic therapy.

Technology Out-licensing

Our aerosol generator technology has proven to be of value to industries focusing outside the field of pulmonary drug delivery. In October 1999, we entered into an exclusive license agreement with a consumer company permitting it to use the aerosol generator in the fields of air fresheners and insect repellants worldwide. Under the license agreement, we receive minimum annual payments and will receive royalties based on net sales of units and refills above a certain threshold. The license also gives us access to any improvements in the technology made by the consumer company during the conduct of its development and manufacturing activities. We have the right to terminate the agreement with respect to either the air freshener products or insect repellant products if products are not introduced within specific time limits. The first product covered by the agreement was launched outside the U.S. in January 2003, which triggered an increase in the minimum royalty payments to Aerogen. We have been advised that launches in additional countries are planned for 2004. We will continue to explore out-licensing opportunities for our technologies outside the field of pulmonary drug delivery.

Research and Development Spending

During 2002, 2001 and 2000 we spent approximately $17.4 million, $19.7 million and $10.4 million, respectively, on our own research and development activities, and approximately $0.4 million, $2.0 million and $5.8 million in 2002, 2001 and 2000, respectively, for customer sponsored research and development activities.

Manufacturing

We plan to manufacture our aerosol generators and outsource the manufacture of the other components used in our products. We manufacture the aperture plates and assemble the aerosol generators at our Mountain View, California facility. We design the remaining components of the products, such as molded parts and electronic circuitry, and outsource the manufacture and/or assembly of these parts to qualified vendors. The manufacture of cartridges and sterile drug filling will also be outsourced, minimizing the need for capital investment in specialized drug filling facilities. We assemble the Aeroneb® Portable Nebulizer System in our California facilities, and the Aeroneb Pro nebulizer is assembled for us in Ireland.

We outsource production of many components of our products to manufacturers in the United States and elsewhere. Generally, there is more than one potential supplier for these components, but some are manufactured to our specifications and an interruption in supply could adversely affect our ability to manufacture and supply our products. The brazing process used in assembly of our aerosol generators is conducted at a third party's facilities. Loss of the use of those facilities would result in several months' delay in our supply of components while we establish an alternative brazing site. Palladium, which we use in our aerosol generator, is expensive and is subject to price volatility. The

palladium plating bath chemicals we use to manufacture our aerosol generator are formulated by a single supplier. It would be difficult to replace this supplier, if it were necessary to do so.

Sales and Marketing

The Aeroneb® Portable Nebulizer System has been marketed in the United States to home medical equipment dealers and pharmacies, and directly to patients over the Internet. We distribute the product through a division of Cardinal Health and other regional distributors throughout the United States. The product has recently been featured on the top shelf of "The Asthma And Allergy Place," a pharmacy program exclusively offered by Cardinal Consumer Health that features devices and supportive products necessary for asthma patients to treat their condition. The Aeroneb Pro nebulizer is sold to U.S. hospitals by Aerogen's contract clinical specialists, Cardinal Health, and Puritan Bennett. Outside the United States, we have agreements with independent distributors on a country-by-country basis, and also with Puritan Bennett. We generally intend to maintain the marketing rights for our acute care respiratory drug products in the United States and to commercialize the products in other countries through marketing partners or distributors. Products developed in collaboration with partner companies will generally be commercialized by the partners.

At December 31, 2002, we had a backlog of orders for the Aeroneb Pro nebulizers of approximately $1.0 million; the orders were filled during the first quarter of 2003.

Competition

There is intense competition in our target markets. We currently compete with device and medical equipment companies for sales of our nebulizer products; as we introduce our drug products, we will compete with pharmaceutical and biotechnology companies, hospitals, research organizations, individual scientists and nonprofit organizations engaged in developing non-invasive drug delivery dosage forms. In the area of systemic drug delivery, competing non-invasive alternatives to injectable drug delivery include oral, buccal, intranasal, transdermal and colonic

absorption dosage forms. We also compete with entities producing and developing injectable dosage forms. Several of these entities are working on sustained-release injectable systems. While these systems still require injections, the lower number of injections could allow these products to compete effectively with non-invasive therapies.

The pulmonary drug delivery market in particular is intensely competitive. Several companies, including Alkermes, Inc., Aradigm Corporation, Battelle Pharma and Nektar Therapeutics (formerly Inhale Therapeutic Systems, Inc.), are developing competing pulmonary drug delivery dosage forms. These competing dosage forms typically are designed to treat respiratory disorders or to deliver drugs systemically. We also face competition from existing pulmonary drug delivery dosage forms such as metered dose inhalers, dry powder inhalers and nebulizers, which have been used effectively to treat respiratory diseases in certain patient populations for years. There can be no assurance that competitors will not develop and introduce products or technologies that are competitive with, or superior to, ours.

Some of our products are expected to be more expensive than metered dose inhalers and currently available dry powder inhalers, as the products are expected to provide significant advantages over currently marketed devices. It is difficult to predict whether, and to what extent, our products will be reimbursed by insurance companies, health maintenance organizations or government healthcare providers. In addition, although we believe that physicians are likely to recommend our products to their patients, it is impossible to predict to what extent or how quickly this may occur.

Most competitors have greater research and development capabilities, experience, manufacturing, marketing, financial and managerial resources than we do. Accordingly, they may succeed in developing competing products and technologies, obtaining regulatory approval for products or gaining market

acceptance more rapidly than we can. We believe that our products will compete on the basis of patient convenience, efficiency, dose reproducibility, safety and cost.

Intellectual Property and Proprietary Rights

Our ability to compete effectively depends in part on developing and maintaining the proprietary aspects of our aerosolization technology. As of December 31, 2002, we held ten issued U.S. patents and eleven issued international patents. In addition, we had 37 pending U.S. patent applications and 39 pending international patent applications as of that date. None of the issued patents expire earlier than 2011. Our patents are directed at, among other things, the following: (i) apparatus and methods for generating aerosols, including vibrating dome technology in which liquid is drawn through tiny tapered holes in the dome to be emitted as a mist of controlled droplet size and speed; (ii) particular aspects of aperture plate dome construction and use; and (iii) particular embodiments of the aerosolization devices. The pending patent applications include coverage for numerous improvements on the fundamental aspects of the aerosolization technology.

We cannot assure that the patents which we have obtained, or any patents that we may obtain as a result of our U.S. or international patent applications, will provide any competitive advantages for our products or that they will not be successfully challenged, invalidated or circumvented in the future. In addition, we cannot assure that competitors, many of whom have substantial resources and have made substantial investments in competing technologies, have not applied for and will not obtain patents that will prevent, limit or interfere with our ability to make, use and sell our products either in the United States or in international markets.

A number of other companies, universities and research institutions have filed patent applications or have issued patents relating to vibratory aerosolization technology. In addition, we have become aware of, and may become aware of in the future, patent applications and issued patents that relate to our products. We do not believe that our current products infringe any valid and enforceable claims of the issued patents that we have reviewed. However, if third party patents (or patent applications that may issue as patents) contain valid and enforceable claims held by a court to be infringed by our products, we cannot assure that we would be able to obtain licenses to those patents at a reasonable cost, if at all, or be able to develop or obtain alternative technology. The inability to do either would have a material, adverse effect on our business, financial condition, results of operations and future growth prospects. We cannot assure that we will not have to defend ourselves in court against allegations of infringement of third-party patents.

In addition to patents, we rely on trade secrets and proprietary know-how, which we make every effort we can to protect, in part, through confidentiality and proprietary information agreements. We require our employees and key consultants to execute confidentiality agreements upon the commencement of employment or a consulting relationship with us. These agreements generally provide that all confidential information developed or made known to the individual by us during the course of the individual's relationship with us is to be kept confidential and not disclosed to third parties. These agreements are also assignments to Aerogen, exclusively, of inventions conceived by the individual in the course of rendering services to Aerogen, and any patent rights arising therefrom, all such material being Aerogen's exclusive property.

However, we cannot assure that employees and consultants will not breach the agreements, that we would have adequate remedies for any breach or that our trade secrets will not otherwise become known to or be independently developed by competitors.

The pharmaceutical and medical device industries have been characterized by extensive litigation regarding patents and other intellectual property rights, and companies in these industries have employed intellectual property litigation to gain a competitive advantage. We cannot assure that we will not become subject to patent infringement claims or litigation or interference proceedings declared by

the United States Patent and Trademark Office to determine the priority of inventions. In 1999, we settled a patent interference involving U.S. Patent No. 5,261,601, assigned to Bespak plc concerning methods and apparatus for dispensing atomized sprays by vibrating a membrane to atomize the liquid in contact with the membrane through flared holes in the membrane. The settlement provided for a cross-license between Aerogen and Bespak, as a result of which Bespak has a license to certain of our technology. The scope of the granted license was limited to products employing technology which was disclosed by Bespak in U.S. Patent No. 5,261,601. The license would not extend to any of our technology which was not disclosed in this patent.

Our patent position involves complex legal and factual questions and is generally uncertain. The field of aerosolized drug delivery is crowded, and a substantial number of patents have been issued to others. We are aware of several issued U.S. and international patents that cover certain aspects of vibratory aerosolization technology. Legal standards relating to the validity and scope of patent claims in the biotechnology and pharmaceutical field are evolving. Therefore, the degree of protection which our patents will afford is uncertain. Patents, if issued, may be challenged, invalidated or designed around. Thus, any patents that we own or license may not provide any, or significant, protection against competitors. Our pending patent applications or those which we may file in the future may not result in patents being issued. Also, patent rights may not provide us with proprietary protection or competitive advantages against competitors with similar technology. Furthermore, others may independently develop similar technologies or duplicate any technology that we have developed.

The defense and prosecution of intellectual property litigation, United States Patent and Trademark Office interference proceedings and related legal and administrative proceedings are both costly and time-consuming. If others violate our proprietary rights, litigation may be necessary to enforce our patents, to protect trade secrets or know-how owned by us or to determine the enforceability, scope and validity of the proprietary rights of others. Any litigation or interference proceedings will be costly and cause significant diversion of effort by our technical and management personnel. An adverse determination, or litigation or interference proceedings to which we may become a party could subject us to significant liabilities to third parties, require disputed rights to be licensed from third parties or require us to cease using such technology. Although patent and intellectual property disputes in the medical device area have often been settled through licensing or similar arrangements, costs associated with such arrangements may be substantial and could include ongoing royalties. Furthermore, we cannot be sure that we could obtain necessary licenses on satisfactory terms, if at all. Adverse determinations in a judicial or administrative proceeding or failure to obtain necessary licenses could prevent us from manufacturing and selling our products, which would have a material adverse effect on our business, financial condition, results of operations and future growth prospects.

At the time of commencement of employment, our employees generally sign offer letters specifying basic terms and conditions of employment. In general, our United States employees are not subject to written employment agreements. Each of our employees has entered into a standard form confidential information and invention assignment agreement that provides that the employee will not disclose any of our confidential information received during the course of their employment and that, with some limited exceptions, the employee will assign to us any and all inventions conceived or developed during the course of employment.

Government Regulation

Our products are subject to extensive regulation by numerous governmental authorities, principally the United States Food & Drug Administration (FDA) in the United States, as well as numerous state and foreign regulatory agencies. We need to obtain clearance of our products by the FDA before we can begin marketing our products in the United States. Similar requirements or approvals generally are required in other countries before our products can be marketed in those countries.

Product development and approval within this regulatory framework is uncertain, can be unpredictable with respect to review times and requires substantial resources. The nature and extent of the governmental premarket review process or requirements for our products will vary depending on the regulatory categorization of particular products. Because our products may be characterized as devices, drugs or biologics, the

regulatory approval path will not be the same for all of our products.

Those of our products which are regulated as medical devices will be classified into one of three classes on the basis of the controls deemed by the FDA to be necessary to reasonably ensure their safety and effectiveness. The class for any particular product, as follows, will determine the regulatory route:

Class I: General controls, e.g., labeling, premarket notification, if not exempted, and adherence to Good Manufacturing Practices (GMP) and the quality system regulation (QSR);

Class II: General controls and special controls, e.g., performance standards and postmarket surveillance; and

Class III: Premarket approval.

Device Regulatory Premarket Requirements in the United States. Before a new device can be marketed, its manufacturer must obtain marketing clearance through either a premarket notification under Section 510(k) of the United States Federal Food, Drug and Cosmetic Act or approval of a premarket approval application.

510(k) clearance. A 510(k) clearance typically will be granted if a company establishes that its device is "substantially equivalent" to a legally marketed Class I or II medical device or to a Class III device that was on the market prior to 1976 for which the FDA has not required the submission of a premarket approval application. A 510(k) clearance must contain information to support the claim of substantial equivalence, which may include laboratory test results or the results of other studies. Commercial distribution of a device subject to the 510(k) requirement may begin only after the FDA issues an order finding the device to be substantially equivalent to a predicate device. It generally takes from four to twelve months from the date of submission to obtain clearance of a 510(k) submission, but it may take longer. The FDA may determine that a proposed device is not substantially equivalent to a legally marketed device, that additional information is needed before a substantial equivalence determination may be made, or that the product must be approved through the premarket approval process. An FDA determination of "not substantially equivalent," a request for additional information, or the requirement that a premarket approval application be filed could delay market introduction of products that fall into this category. Furthermore, for any devices cleared through the 510(k) process, modifications or enhancements that could significantly affect safety or effectiveness, or constitute a major change in the intended use of the device, require new 510(k) submissions. We received 510(k) clearance for the Aeroneb® Portable Nebulizer System and the Aeroneb® Professional Nebulizer System, and we expect that future similar nebulizer products will also proceed through the 510(k) clearance route.

Premarket approval. If a device does not qualify for the 510(k) premarket notification procedure, a company must file a premarket approval application. The premarket approval application requires more extensive pre-filing testing than required for a 510(k) premarket notification, and usually involves a significantly longer review process. A premarket approval application must be supported by valid scientific evidence that typically includes extensive data, including preclinical and clinical trial data, to demonstrate the safety and efficacy of the device. If clinical trials are required, and the device presents a "significant risk," an investigational device exemption (IDE) application must be filed with the FDA and becomes effective prior to initiating clinical trials. An IDE application generally must be approved before a clinical trial begins. The IDE must be supported by appropriate data, such as animal and laboratory testing results. Clinical trials may begin if the FDA and the appropriate institutional review

boards both approve the IDE. Trials must be conducted in conformance with FDA regulations and the institutional review boards' requirements. The sponsor or the FDA may suspend the trials at any time if it is believed that they pose unacceptable health risks, or if the FDA finds deficiencies in the way that they are being conducted. Data from clinical trials are often subject to varying interpretations that could delay, limit or prevent FDA approval. If the device presents a "nonsignificant risk" to trial subjects, clinical trials may begin on the basis of appropriate institutional review board approval.

A premarket approval application may be denied if applicable regulatory criteria are not satisfied, or the FDA may impose certain conditions upon the applicant, such as postmarket testing and surveillance. The premarket approval application process can be expensive, uncertain and lengthy, and approvals may not be granted. A number of third parties' devices for which premarket approval has been sought have never been approved for marketing. After approval, a new application or a supplement is required if certain modifications are made to the device, its labeling or its manufacture.

New Drug Application and Biologics License Application. New chemical entities or biologics will be regulated as such and premarket approval will be required. If a specific inhaler or nebulizer is designed to be used in combination with the new chemical entity or biologic, it will need to be included in the application. The combination of an already-approved drug or biologic with an already-approved device may be treated in the same regulatory manner. If clinical studies of such drugs or drug-device combinations used in humans are required by the FDA, then an Investigational New Drug Application (IND) will be required before those studies can be initiated in the United States. Approval of a New Drug Application (NDA), or a Biologics License Application (BLA), will be required before the product can be marketed. In addition to reports of the preclinical and clinical trials conducted under an effective IND application, the NDA or BLA would include information pertaining to the preparation of the drug substance, the manufacture of the inhaler or nebulizer, analytical methods, details on the manufacture of finished products and proposed packaging and labeling. Submission of an NDA or BLA does not assure FDA approval for marketing. The application process generally takes several years to complete. The process may take substantially longer if, among other things, the FDA has questions or concerns about the safety or efficacy of a product. In general, the FDA requires at least two properly conducted, adequate prospective, randomized double-blinded and well-controlled clinical studies demonstrating efficacy with sufficient levels of statistical assurance. The process for approval of products regulated as drugs and biologics outside the United States is similar to the NDA/BLA process within the United States. For partner products that incorporate drugs or biologics, we anticipate that an NDA or BLA will be required in addition to, or separate from, any 510(k) clearance we may be required to obtain.

There can be no assurance that approval for any of our products will be granted on a timely basis, or at all. Notwithstanding the submission of safety and efficacy data, the FDA ultimately may decide that the application does not satisfy all of its regulatory criteria for approval. The FDA also may require additional clinical tests (i.e., Phase 4 clinical trials) following the NDA or BLA approval to confirm safety and efficacy. These studies can often extend for years after a product's launch. Upon approval, a product may only be marketed for the approved indications.

In addition, the FDA may in some circumstances impose restrictions on the use of a product that may be difficult and expensive. Product approvals may be withdrawn if compliance with regulatory requirements is not maintained or if problems occur after the product reaches the market. The FDA also requires reporting of certain safety and other information that becomes known to a manufacturer of an approved product.

European Union Clearance of Devices. Commercialization of medical devices in the European Union is regulated under a system which presently requires that all medical devices sold in the European Union bear the CE mark, an international symbol of adherence to quality assurance standards, demonstrated fulfillment of the essential requirement and clinical effectiveness. Medical

devices are classified in accordance with Annex IX of the Medical Device Directive (MDD). The classification determines which conformity assessment procedure the manufacturer must follow in order to affix the CE mark on its products. In October 2001, we obtained the CE mark for the Aeroneb Pro nebulizer, and in December 2002 we received the CE mark for our optimized phasic Aeroneb Pro, which we are using in a clinical study in France. We cannot be certain that we will obtain a CE mark, or that we will not have delays in obtaining a CE mark, for any other product.

Post-Approval Requirements. Regulatory approval, if granted, may entail limitations on the indicated uses for which a product may be marketed, and product approvals, once granted, may be withdrawn if problems occur after initial marketing. Manufacturers of FDA-regulated products are subject to pervasive and continuing governmental regulation, including extensive recordkeeping requirements and reporting of adverse experiences associated with product use. Compliance with these requirements is costly, and failure to comply properly can result in withdrawal of a product approval.

Good Manufacturing Practices. We will be required to adhere to applicable FDA current Good Manufacturing Practices as set forth in the Quality System Regulation, which include testing, controls and documentation requirements. Other countries have similar requirements. Failure to comply with these and other applicable regulatory requirements may result in, among other things, warning letters, fines, injunctions, civil penalties, recall or seizure of products, total or partial suspension of production, failure of the government to review pending marketing clearances or approval applications, withdrawal of marketing clearances or approvals and criminal prosecution.

Hazardous materials. Our operations involve use of hazardous and toxic materials and generate hazardous, toxic and other wastes. We are subject to federal, state and local laws and regulations governing the use, storage, handling and disposal of such materials and certain waste products. Although we believe that our safety procedures for using, handling, storing and disposing of such materials comply with these standards required by state and federal laws and regulations, we cannot completely eliminate the risk of accidental contamination or injury from these materials.

Employees

We had approximately 80 employees on March 1, 2003. Approximately 20 of those employees are located at our Irish facility. Our employees are not represented by a collective bargaining agreement. All employees participate in an employee stock option plan and generally receive options vesting over a four-year period at the time they join the Company, and subsequent options that generally vest over three to four years. We had approximately 155 employees at the beginning of 2002. We reduced our workforce twice during 2002 by a total of 48 employees, and once more on January 3, 2003 by 22 employees in connection with a restructuring, which reduced our number of employees to the current number. We believe our relations with our employees are good.

Certain Financial Information

As of December 31, 2002, 2001 and 2000, 73%, 70% and 48%, respectively, of our long-lived assets were maintained in the United States. For the years ended December 31, 2002, 2001 and 2000, 29%, 97% and 99%, respectively, of our consolidated revenues were generated in the United States.

Risk Factors

Our business and the value of our stock are subject to a number of risks, many of which are set out below. If any of these risks actually materialize, our business, financial condition or operating results could be materially adversely affected, which would likely have a corresponding impact on the value of our common stock. These risk factors should be reviewed carefully.

We have a history of losses, anticipate future losses and may never achieve or maintain profitability.

We have never been profitable. Through December 31, 2002, we have incurred a cumulative deficit of approximately $92.1 million. We expect to continue to incur substantial losses over at least the next several years as we:

expand our research and development efforts;

expand our preclinical and clinical testing activities;

expand our manufacturing efforts, including our commercial production capability; and

build our sales and marketing capabilities and launch our products currently being developed.

To achieve and sustain profitability, we must, alone or with others, develop, obtain regulatory approval for, manufacture, market and sell products. We cannot assure that we will generate sufficient product revenues, royalties or research and development revenues to become profitable or to sustain profitability.

We need additional capital. If we cannot secure additional funding on acceptable terms within the next 30 to 60 days, we may not be able to continue as a going concern.

As of December 31, 2002, we had cash, cash equivalents and available-for-sale securities of approximately $8.9 million. During 2003, our expenditures have been approximately $1.6 million per month. We will need to raise additional funds through public or private financings, collaborative relationships or other arrangements within the next 30 to 60 days in order to continue as a going concern. We cannot be certain that such additional funding will be available on terms attractive to us, or at all. Furthermore, additional equity or debt financing may involve substantial dilution to our existing stockholders, restrictive covenants or high interest rates. Collaborative arrangements, if necessary to raise additional funds, may require us to relinquish rights to either certain of our products or technologies or desirable marketing territories, or all of these. Even if we are successful at raising funds to continue our operations, our cash requirements may increase in the future because of our research and development efforts, including clinical trials, capital expenditures and the manufacture and marketing of our products.

Our operating results may fluctuate significantly and may fail to meet the expectations of investors.

We expect that our operating results may fluctuate in the future, and may vary from investors' expectations, depending on a number of factors described in this "Risk Factors" section including:

- the availability of additional funding and the terms of any such funding;
- the success of any restructuring actions we have taken or may take in the future;
- changes in domestic and international economic, business, industry and political conditions;
- demand for our existing products and any we may introduce in the future;
- timing of the introduction of new products and enhancements of existing products; and
- allocation of our resources, particularly when they are limited.

Our 2002 reductions in force and our January 2003 restructuring may not be sufficient to accomplish our goals.

In January and June 2002, we engaged in reductions in force in order to reduce our operating expenses. In December 2002, we began a restructuring that included the suspension of development of our Aerodose insulin inhaler product, and a workforce reduction in January 2003. While these changes

were designed to reduce spending, align resources with long-term growth opportunities and preserve cash, there can be no assurances that we will realize any of these expected benefits to the extent needed. Further, we cannot predict whether we will need to engage in additional restructuring actions, which may impact our operating results.

Our stock price may continue to be volatile.

The market prices for securities of many companies in the life sciences industry have historically been highly volatile, and the market from time to time has experienced significant price and volume fluctuations unrelated to the operating performance of particular companies. Prices for our common stock may be influenced by many factors, including:

- market conditions relating to the life sciences industry;
- investor perception of us as a company;
- securities analysts' recommendations;
- delays in the development, regulatory approval or commercialization of our products;
- announcements of technological innovations or new commercial products by us, our partners or competitors;
- failure to establish new collaborative relationships or termination of existing collaborative relationships;

developments or disputes concerning patent or intellectual property rights;

regulatory and pricing developments in both the United States and foreign countries;

public concern as to the safety of drugs and drug delivery technologies, including those of our competitors;

period-to-period fluctuations in financial results; or

economic and other external factors.

Our common stock is currently trading at a market price significantly below the initial public offering price; there can be no assurance that the price will increase in the future or will recover to the initial public offering price.

Our common stock may be delisted from The Nasdaq SmallCap Market, which may adversely affect the market liquidity and market price of our common stock.

Our common stock is currently listed on the Nasdaq SmallCap Market and has since July 1, 2002, had, a closing bid price of less than $1.00 per share on all but three days. Nasdaq rules do not permit listed companies to maintain closing bid prices below $1.00 per share for more than 30 consecutive trading days. Nasdaq has granted us a grace period until August 4, 2003 to regain compliance with this requirement.

If we fail to meet the minimum bid price requirement by that date, or fail to meet any of the other requirements of the Nasdaq SmallCap Market, our stock may be delisted and the trading of our common stock is likely to be conducted on the OTC Bulletin Board or in the over-the-counter market in what is commonly referred to as the "pink sheets," which may have an adverse affect on the market price of our common stock and on the ability of stockholders and investors to buy and sell the common stock. If delisting occurs, stockholders may lose some or all of their liquidity and/or value.

Many of our products are in research and development stages, which makes it difficult to evaluate our business and prospects.

Other than the Aeroneb® Portable Nebulizer System, which was introduced in 2001, and the Aeroneb® Professional Nebulizer System, which was introduced in 2002, our products are in the research or development stages. Before we can begin to sell our other products commercially, we will need to invest in substantial additional development activities, generally including the conduct of clinical trials. To further develop our products, we will need to obtain additional funds and address engineering and design issues, including ensuring that our products deliver a consistent and predictable amount of drug to the lung and that they can be manufactured successfully. We cannot assure that:

our research and development efforts will be successful;

any of our inhaler, nebulizer or drug products will prove safe and effective;

we will obtain regulatory clearance or approval to sell any additional products; or

any of our existing or future products can be manufactured in commercial quantities or at an acceptable cost or marketed successfully.

Our technologies are relatively unproven, so they may not work effectively or safely enough to commercialize inhalers, nebulizers or drug-containing products.

Since our pulmonary drug delivery technologies are new and relatively unproven, many of our products are currently in the research, development or clinical stages. Extensive additional testing will need to be performed to demonstrate that:

- drugs may be safely and effectively delivered using our technologies;
- our inhalers and nebulizers are safe across a range of drugs and formulations;
- our products consistently deliver accurate and predictable amounts of drug over time; and
- drug formulations are stable in our products.

If our products do not prove to be safe and effective, we may be required to abandon some or all of them. If we cannot develop new products, our business will suffer.

If clinical trials of our drug products are not successful, drug products using our Aerodose inhalers or Aeroneb nebulizers may not be commercialized.

Before either we or our partners can file for regulatory approval for the commercial sale of products using our Aerodose inhalers or our Aeroneb nebulizers, the FDA, and other governmental agencies in other countries will require extensive clinical trials to demonstrate product safety and efficacy. We are developing drug/inhaler and drug/nebulizer combinations, each of which will require clinical testing. To date, we have completed limited clinical trials using prototype Aerodose inhalers and Aeroneb nebulizers. If we do not successfully complete appropriate clinical trials, we will not be able to commercialize our products. The results of initial clinical trials do not necessarily predict the results of more extensive clinical trials. Furthermore, we cannot be certain that clinical trials of our products will demonstrate that they are safe and effective to the extent necessary to obtain regulatory approvals. Many companies in the pharmaceutical and biotechnology industries have suffered significant setbacks in advanced clinical trials, even after achieving promising results in earlier trials.

We have limited manufacturing experience and may not be able to manufacture our products in commercially sustainable quantities. We will depend on key suppliers and contract manufacturers, and their failure to supply us may delay or prevent commercialization of our products.

We have built our own manufacturing capabilities to produce key components of our products. We have manufactured only limited quantities of our first two products, and limited clinical supplies of other products. We currently plan to produce all of our aerosol generators for our products, partnered or not. We plan to use contract manufacturers to produce certain other key components and subassemblies of our products. We may assemble some or all of our products ourselves, or we may use contract manufacturers for the final assembly of some or all of our products. We do not have long-term supply contracts with most of our key suppliers or contract manufacturers. In addition, most of them are currently our sole source of supply. We may not be able to enter into, or maintain, satisfactory contracts or arrangements. In addition, manufacturing of our products could be delayed by supply problems at our suppliers or contract manufacturers. If we need to qualify a new supplier, there could be significant delay, and a regulatory filing could be required before we could use the new supplier to provide material for our products. There can be no assurance that we, or our contract manufacturers, can successfully manufacture in high volumes in a timely manner, at an acceptable cost, or at all. We cannot assure that:

- the design of our products will permit their manufacture on a commercially sustainable scale;
- manufacturing and quality control problems will not arise as we attempt to scale-up production; or
- any scale-up of production can be achieved in a timely manner or at a commercially reasonable cost.

Failure to address these issues adequately could delay or prevent clinical testing and commercialization of our products.

During 2002, our inhaled insulin product was our most mature product in development for systemic drug delivery; however, we have suspended development of that product.

We have only completed four small clinical trials (two Phase 1 and two Phase 2) of our Aerodose insulin inhaler product. Early studies generally focus on the safety of a product rather than its effectiveness in treating the disease. We cannot be sure that the results of these and/or other additional clinical trials will prove the safety and effectiveness of our product. During 2002, we did not sign an agreement with a marketing partner to fund the additional development and clinical trials necessary to obtain regulatory approval and to commercialize the product; therefore we have stopped our work on that product, and do not expect to re-start the program until we have an acceptable partner or sufficient funding to pay for additional clinical trials. We cannot assure that we will ever be able to enter into a satisfactory agreement with a marketing partner, and we currently do not have sufficient funds to conduct the necessary development and clinical programs ourselves.

We may not be able to develop certain products if we do not enter into additional collaborative relationships or gain access to compounds from third parties.

Our strategy depends partially on our ability to enter into collaborative relationships with partners to conduct and fund the clinical trials, manufacturing, marketing and sales activities necessary to commercialize products. To develop products to be marketed by us, we will need to purchase or license, and possibly reformulate and package, drugs for use with our Aerodose inhalers and Aeroneb nebulizers. We cannot assure that we will be able to establish these kinds of arrangements on favorable terms, or at all, or that our existing or future collaborative arrangements will be successful.

If our products do not gain commercial acceptance, we will not generate significant revenue.

Our success in commercializing our products depends on many factors, including acceptance by healthcare professionals and patients. Their acceptance of our products will depend largely on our ability to demonstrate that our products can compete with alternative delivery systems with respect to:

safety;

efficacy;

the benefits associated with pulmonary delivery;

ease of use; and

price.

We cannot be sure that our products will compete effectively, or that we, or our partners, will be able to successfully market any products in a timely manner.

If we are unable to develop a successful sales and marketing program, we will not be able to sustainably commercialize our products.

We currently have a very limited sales and marketing staff, and many of our competitors have substantial sales and marketing infrastructure. We rely on third party distributors to sell our products. Our success in commercializing our respiratory products in the United States will depend on our ability to develop and execute a successful sales and marketing program. There can be no assurance that our first two products, the Aeroneb® Portable Nebulizer System and the Aeroneb® Professional Nebulizer System, will be successful, and, in any event, these products are not expected to generate revenues sufficient enough to solely support the Company's operations in the foreseeable future. We will initially have financial losses resulting from the marketing expenditures necessary to launch and grow the products. Successful worldwide commercialization will depend upon finding effective marketing partners for our products outside the United States.

Our corporate partners may not commercialize our products or may develop products that compete against our products.

Our business model includes collaborations with pharmaceutical and biotechnology companies. There can be no assurance that we will be able to enter into arrangements that result in successful commercial products. Even if we do enter into such arrangements, we will depend on corporate partners to commercialize the products developed in collaboration with us. If any of our existing or future corporate partners do not complete the development and commercialization of products to which they have obtained rights from us, our business could be impaired. In the drug delivery industry, it is common for corporate partners to conduct feasibility studies with multiple partners. There can be no assurance that our existing or future corporate partners will continue to choose our technology over their own technology or that of our competitors. Collaboration agreements generally provide that the partner can terminate the agreement at any time.

If we are unable to attract and retain the highly skilled personnel necessary for our business, we may not be able to develop our products successfully.

Because of the specialized nature of our business, we depend upon qualified scientific, engineering, technical and managerial personnel. In particular, our business and prospects depend in large part upon the continued employment of Dr. Jane E. Shaw, our Chairman and Chief Executive Officer. We do not have an employment agreement with Dr. Shaw. Even with the recent downturn in the global economy, there is intense competition for qualified personnel in our business. In addition, our location in northern California makes recruiting qualified personnel from outside the San Francisco Bay area more

difficult due to the very high cost of housing. Therefore, we may not be able to attract and retain the qualified personnel necessary to grow our business. The loss of the services of existing personnel, as well as the failure to recruit additional key scientific, technical, engineering and managerial personnel in a timely manner, would harm our research and development programs and our business.

Our ability to market and sell our products depends upon receiving regulatory approvals, which we may not obtain.

Our products are subject to extensive regulation by the FDA, state and local government agencies, and by international regulatory authorities. These agencies regulate the development, testing, manufacture, labeling, storage, approval, advertising, promotion, sale and distribution of medical devices, drugs and biologics. If we, or our partners, fail to obtain regulatory clearances to develop or to market our products, our business will be harmed and we, or our collaborative partners, will not be able to market and sell our products. Even if granted, regulatory approvals may include significant limitations on the uses for which products may be tested or marketed. Once obtained, required approvals may be withdrawn, or we may not remain in compliance with regulatory requirements. The process for obtaining necessary regulatory approvals for drugs and biologics is generally lengthy, expensive and uncertain. Obtaining and maintaining foreign regulatory approvals in multiple countries is expensive, and we cannot be certain that we will receive approvals in any foreign country in which we or our partners plan to market our products. If we or our partners fail to obtain regulatory approval in the United States or in any foreign country in which we plan to market our products, our revenues will be lower. A longer than expected regulatory process, or more expensive clinical studies than we anticipate, may cause us to stop development of particular products, which we did with our albuterol and ipratropium inhaler products.

If our manufacturing facilities do not meet federal, state and international manufacturing standards, we may not be able to sell our products in the United States or internationally.

Our manufacturing facilities are subject to periodic inspection by regulatory authorities and our operations will continue to be regulated by the FDA for compliance with QSR (Quality System Regulation). We moved into a new facility in Mountain View, California during the second quarter of 2002. Prior to transferring product manufacturing to this facility, we underwent a successful inspection by the FDA, which was completed in May 2002. We received our registration in August 2002.

We also are required to comply with ISO 9001/EN46001 in order to produce products for sale in the European Union. ISO, the International Organization for Standardization, is a worldwide federation of national standards bodies. ISO has developed the ISO 9000 family of standards to assist companies in implementing and operating quality management systems. ISO 9001/EN46001 provides the requirements for a quality management system that a company must meet in order for our products to satisfy applicable regulatory requirements. We received ISO 9001/EN46001 certification for our Sunnyvale facility in July 2000. In August 2002, we passed the surveillance audit, updating our ISO 9001/EN46001 certification for our Mountain View facility.

If we fail to maintain our compliance with QSR requirements, ISO 9001/EN46001 or other international regulatory requirements, we may be required to cease all or part of our operations until we comply with the regulations. We cannot be certain that our facilities will be found to comply on an ongoing basis with QSR, ISO 9001/EN46001 or other international regulatory requirements.