MANNKIND CORP
Form 10-K
March 16, 2011

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UNITED STATES SECURITIES AND EXCHANGE COMMISSION
Washington, D.C. 20549
Form 10-K

þ **ANNUAL REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934**
For the fiscal year ended December 31, 2010

or

o **TRANSITION REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934**
For the transition period from to
Commission file number: 000-50865.

MannKind Corporation
(Exact name of registrant as specified in its charter)

Delaware	**13-3607736**
(State or other jurisdiction of incorporation or organization)	*(I.R.S. Employer Identification No.)*
28903 North Avenue Paine Valencia, California	**91355**
(Address of principal executive offices)	*(Zip Code)*

Registrant s telephone number, including area code
(661) 775-5300
Securities registered pursuant to Section 12(b) of the Act:

Title of Class	**Name of Each Exchange on Which Registered**
Common Stock, par value $0.01 per share	The Nasdaq Global Market

Securities registered pursuant to Section 12(g) of the Act:
None
(Title of Class)

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

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

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

Indicate by check mark whether the registrant has submitted electronically and posted on its corporate Web site, if any, every Interactive Data File required to be submitted and posted pursuant to Rule 405 of Regulation S-T during the preceding 12 months (or for such shorter period that the registrant was required to submit and post such files).
Yes o No o

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

Indicate by check mark whether the registrant is a large accelerated filer, an accelerated filer, a non-accelerated filer, or a smaller reporting company. See the definitions of large accelerated filer, accelerated filer and smaller reporting company in Rule 12b-2 of the Exchange Act. (Check one):

Large accelerated filer o	Accelerated filer þ	Non-accelerated filer o (Do not check if a smaller reporting company)	Smaller reporting company o

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

As of June 30, 2010, the aggregate market value of the voting stock held by non-affiliates of the registrant, computed by reference to the last sale price of such stock as of such date on the Nasdaq Global Market, was approximately $414,517,434.

As of February 18, 2011, there were 130,654,250 shares of the registrant s Common Stock outstanding.

DOCUMENTS INCORPORATED BY REFERENCE

Portions of the registrant s definitive Proxy Statement, or the Proxy Statement, for the 2011 Annual Meeting of Stockholders to be filed with the Securities and Exchange Commission pursuant to Regulation 14A not later than 120 days after the end of the fiscal year covered by this Form 10-K, are incorporated by reference in Part III of this Annual Report on Form 10-K.

MANNKIND CORPORATION
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Forward-Looking Statements

Statements in this report that are not strictly historical in nature are forward-looking statements. These statements include, but are not limited to, statements about: the progress or success of our research, development and clinical programs, including the application for and receipt of regulatory clearances and approvals, and the timing or success of the commercialization of AFREZZA, our ultra rapid-acting insulin product, or any other products or therapies that we may develop; our ability to market, commercialize and achieve market acceptance for AFREZZA, or any other products or therapies that we may develop; our ability to protect our intellectual property and operate our business without infringing upon the intellectual property rights of others; our estimates for future performance; our estimates regarding anticipated operating losses, future revenues, capital requirements and our needs for additional financing; and scientific studies and the conclusions we draw from them. In some cases, you can identify forward-looking statements by terms such as anticipates, believes, could, estimates, expects, goal, intends, may, plans, predicts, projects, should, will, would, and similar expressions intended to identify forward-looking statements. statements are only predictions or conclusions based on current information and expectations and involve a number of risks and uncertainties. The underlying information and expectations are likely to change over time. Actual events or results may differ materially from those projected in the forward-looking statements due to various factors, including, but not limited to, those set forth under the caption Risks and Uncertainties That May Affect Results and elsewhere in this report. Except as required by law, we undertake no obligation to publicly update or revise any forward-looking statements, whether as a result of new information, future events or otherwise.

AFREZZA®, MedTone®, Dreamboat® and Technosphere® are registered trademarks in the United States. We have also applied for or have registered company trademarks in other jurisdictions, including Europe and Japan. This document also contains trademarks and service marks of other companies that are the property of their respective owners.

PART I

Item 1. ***Business***

Unless the context requires otherwise, the words MannKind, we, company, us and our refer to MannKind Corporation. Unless explicitly stated otherwise, AFREZZA refers to the combination of AFREZZA inhalation powder and the AFREZZA inhaler.

OVERVIEW

MannKind Corporation is a biopharmaceutical company focused on the discovery, development and commercialization of therapeutic products for diseases such as diabetes and cancer. Our lead product candidate, AFREZZA (insulin human [rDNA origin]) Inhalation Powder, is an ultra rapid-acting insulin that is in late-stage clinical investigation for the treatment of adults with type 1 or type 2 diabetes for the control of hyperglycemia.

AFREZZA utilizes our proprietary Technosphere formulation technology, which is based on a class of organic molecules that are designed to self-assemble into small particles onto which drug molecules can be loaded. With AFREZZA, we load recombinant human insulin onto the Technosphere particles; however, this technology is not limited to insulin delivery. We believe it represents a versatile drug delivery platform that may allow pulmonary administration of certain drugs that currently require administration by injection. Beyond convenience, we believe the key advantage of drugs inhaled as Technosphere formulations is that they have been shown to be absorbed very rapidly into the arterial circulation, essentially mimicking intra-arterial administration.

In addition to our Technosphere platform, we are evaluating an investigational cancer immunotherapy product, MKC1106-MT, in a Phase 2 clinical trial. We are also conducting preclinical studies of a drug candidate, MKC204, that may have the potential to treat certain malignancies and inflammatory diseases.

In February 2011, we implemented a restructuring to streamline our operations, reduce our operating expenses, extend our cash runway and focus our resources on securing the approval of the new drug application, or NDA, for AFREZZA by the United States Food and Drug Administration, or FDA. In connection with this restructuring, we reduced our total workforce by approximately 41 percent and halted activity in certain development programs,

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although we retained the key assets and intellectual property required to restart development activities if and when we are able to do so.

The following chart indicates the current stage of development and status of each of our product candidates.

	Preclinical	Clinical Studies		
		Phase	Phase	Phase
	Development	1	2	3
Technosphere Platform				
AFREZZA (insulin)				active
MKC253 (GLP-1)		halted		
MKC180 (obesity compound)	halted			
Cancer Immunotherapy				
MKC1106-MT			active	
MKC1106-PP		halted		
MKC1106-NS	halted			
Cancer Drugs				
MKC204 (IRE-1 inhibitor)	active			

We were incorporated in the State of Delaware in 1991. Our principal executive offices are located at 28903 North Avenue Paine, Valencia, California 91355, and our telephone number at that address is (661) 775-5300. Our website address is http://www.mannkindcorp.com. Our filings with the Securities and Exchange Commission, or SEC, including our annual report on Form 10-K, quarterly reports on Form 10-Q, current reports on Form 8-K and any amendments to those reports are available free of charge through our website as soon as reasonably practicable after being electronically filed with or furnished to the SEC. We regularly post copies of our press releases as well as additional information on our website. Interested persons can subscribe on the website to e-mail alerts that are sent automatically when we issue press releases, file reports with the SEC or post certain other information to the website.

AFREZZA

Our lead product candidate, AFREZZA (insulin human [rDNA origin]) Inhalation Powder, has a time-action profile unlike other insulin products. In our clinical trials to date, we have consistently observed that AFREZZA Inhalation Powder is rapidly absorbed into the bloodstream following inhalation, reaching peak levels within 12 to 14 minutes. In this manner, AFREZZA produces a profile of insulin levels in the bloodstream that closely approximates the early insulin secretion normally seen in healthy individuals immediately following the beginning of a meal, but which is absent in patients with diabetes.

The AFREZZA Inhalation Powder is centered on a class of pH-sensitive organic molecules that self-assemble into small particles under acidic conditions. We refer to these particles as Technosphere particles. Certain drugs, such as insulin, can be loaded onto these particles by combining an acidic solution of the drug with a suspension of Technosphere material, which is then dried to a powder. This powder is then filled into plastic cartridges and packaged. To administer AFREZZA Inhalation Powder, a patient loads a cartridge containing the powder into our inhaler. By inhaling through this device, air is pulled through the cartridge, which aerosolizes the powder and pulls the particles into the air current and out through the mouthpiece. The individual particles within this aerosol are small and have aerodynamic properties that enable them to fly efficiently deep into the lungs. When the particles contact the moist lung surface with its neutral pH, the Technosphere particles dissolve immediately, releasing the insulin molecules to diffuse across a thin layer of cells into the bloodstream. We believe that the insulin absorption step is a passive process that occurs without any active assistance or enhancement and without disruption of either cell membranes or the tight junctions between cells.

To facilitate the delivery of Technosphere-formulated drugs to the deep lung, we developed an inhaler that utilizes single-use, disposable, plastic cartridges containing drug-loaded powder. Our first-generation inhaler, also known as the MedTone inhaler, is light and easy to use, and fits in the palm of the patient s hand. All of our pivotal safety and

efficacy clinical studies were conducted using the MedTone (model C) inhaler.

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To date, the AFREZZA clinical program has involved 56 different studies of AFREZZA and over 5,300 adult patients. In our clinical studies, we observed that AFREZZA produces the following clinical benefits:

Consistent decreases in A1C levels, comparable to current insulin therapies. In a number of clinical studies involving patients with type 1 and type 2 diabetes, we have evaluated levels of glycosylated hemoglobin, or A1C, which is a measure of average blood glucose. A consistent finding was that AFREZZA produced decreases in A1C levels that were essentially comparable to the decreases observed in the control arm of these studies, including studies that compared AFREZZA to rapid-acting insulin analogs, to pre-mixed insulin analogs and to metformin in combination with a sulfonylurea.

Superior post-meal glucose control. AFREZZA Inhalation Powder has a shorter duration of action than other insulin therapies, so its glucose-lowering effect better meets a patient s needs following a meal. Specifically, AFREZZA treatment produces lower blood glucose levels than comparators in the first hour following meal ingestion with comparable levels after two hours. Importantly, AFREZZA does not remain active for an extended period of time, thereby reducing the risk of hypoglycemia between meals.

Improved fasting glucose control. In clinical trials of both type 1 and type 2 diabetes, AFREZZA has consistently provided lower fasting blood glucose control than comparator insulin therapies. As we reported with external authors in a report of one of our earlier Phase 3 studies that was published in *The Lancet* in 2010, this observation might be the result of greater suppression of endogenous glucose production with AFREZZA combined with basal insulin than with a conventional insulin regimen**.**

Less hypoglycemia due to better synchronization with glucose absorption from meals. In clinical trials involving patients with type 2 diabetes, we observed that the incidence and frequency of hypoglycemia was significantly reduced. Similar results were observed in patients with type 1 diabetes. The overall hypoglycemic event rate was lower for AFREZZA at all times of the day, but in particular, there were fewer nocturnal hypoglycemic events, a condition much feared by patients with diabetes.

Little or no weight gain. In our clinical trials, patients treated with AFREZZA experienced weight reduction or significantly less weight gain compared to other insulin therapies.

There are no assurances, however, that these or any other advantages of AFREZZA will be agreed to by the FDA or otherwise included in final product labeling or advertising, if it is approved.

To date, our clinical trials have indicated that AFREZZA has a favorable safety profile. The most common adverse event associated with AFREZZA therapy was a transient, mild and non-productive cough, which occurred early in about 25-30% of subjects and diminished within the first few weeks after initiation of AFREZZA therapy. The occurrence of mild cough is well recognized with inhaled medications. In our studies, the incidence of cough leading to the discontinuation of AFREZZA was low.

After a two-year Phase 3 clinical trial of AFREZZA, we determined that the use of AFREZZA in patients with diabetes was non-inferior to usual diabetes care with respect to a decline in FEV1, a measure of lung function that assesses the volume of air that can be forcibly expired within one second. Similar results were obtained for other measures of lung function.

Our clinical trials for AFREZZA have not demonstrated an increased risk of pulmonary cancer. In addition, we conducted comprehensive nonclinical studies of AFREZZA and unloaded Technosphere particles, including a two-year rat carcinogenicity study and a six-month transgenic mouse study. These studies indicated that there was no increased risk of cancer, or any other pathological effects.

Regulatory Approval Status

In March 2009, we submitted an NDA for AFREZZA to the FDA. In this submission, we sought approval of the AFREZZA Inhalation Powder and the MedTone (model D) inhaler. The MedTone (model D) inhaler is a more rugged and less costly commercial version of the MedTone (model C) inhaler used in clinical trials. As part of our original NDA submission, we included the results of a study, known as study 138, that evaluated the bioequivalence

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of AFREZZA Inhalation Powder administered using the MedTone (model C) and the MedTone (model D) inhalers in 75 patients with type 1 diabetes.

At the time of our original NDA submission, we were also advancing the development of a next-generation inhaler, known internally as the Dreamboat inhaler, which is even smaller (thumb-sized), easier to use and lower in manufacturing cost than the MedTone inhaler and which allows for more efficient emptying of the cartridge. In August 2009, we submitted a request for a meeting with the FDA to review the path to transition from MedTone to the next-generation inhaler for AFREZZA. In November 2009, the FDA provided a letter with advice regarding this path which would include an assessment of the bioequivalence of insulin administered using the next-generation inhaler and the MedTone (model C) inhaler. We incorporated this advice into our development plan for the next-generation inhaler.

On March 12, 2010, we received a Complete Response letter from the FDA regarding the NDA for AFREZZA. A Complete Response letter is issued by the FDA s Center for Drug Evaluation and Research when the review of a submitted file is completed and questions remain that preclude the approval of the NDA in its current form. The March 2010 Complete Response letter requested several items, including:

- information and currently available clinical data that support the clinical utility of AFREZZA, a request that reflects a desire to understand the positioning of AFREZZA within the range of available therapies for patients with diabetes and a desire to know how, in whom and when in the course of therapy it should be used;
- information about the comparability of the commercial version of the inhaler, i.e., MedTone (model D), to the MedTone (model C) version of the device that was used in clinical trials;
- changes to the proposed labeling of the MedTone cartridges, foil pouches and cartons; and
- updated safety data related to AFREZZA.

We believe that the request about the comparability of the MedTone inhalers stemmed from a question raised by the FDA about the method utilized by our contract laboratory to analyze blood samples for insulin and glucose in study 138. Because blood samples degrade over time, it was not possible to re-analyze the material from study 138 using the analytical method preferred by the FDA. However, we were able to utilize this analytical method in our analysis of blood samples from a study, known as study 142, that assessed the bioequivalence of insulin administered using the next-generation inhaler and the MedTone (model C) inhaler in 66 healthy volunteers. The results of study 142 demonstrated that the MedTone (model C) and next-generation inhalers are bioequivalent that is, notwithstanding the fact that a cartridge used with the next-generation inhaler contains one-third less insulin powder than the corresponding MedTone (model C) cartridge, the same amount of the same insulin formulation passes quickly through the pulmonary membrane and reaches the bloodstream when either inhaler is used.

In June 2010, we held an End-of-Review meeting with the FDA to discuss our approach for addressing their questions. To address the agency s request related to the clinical utility of AFREZZA, we presented data from a newly completed study, known as study 117, that provided additional evidence of efficacy and further clarified the clinical utility of AFREZZA in 130 patients with type 1 diabetes. To address the agency s requests related to the comparability of the clinical and commercial devices, we discussed the bioequivalency results for the next-generation inhaler. Following the conclusion of this meeting, we determined that submitting our comparability data for the next-generation inhaler was the best approach for addressing the FDA s inhaler-related questions. Accordingly, in late June 2010, we submitted the results of studies 117 and 142 as part of our response to the March 2010 Complete Response letter.

On January 18, 2011, we received a second Complete Response letter from the FDA. The principal issue raised by the FDA in the January 2011 Compete Response letter was the usage of *in vitro* performance data and bioequivalence data to bridge our next-generation inhaler to the Phase 3 trials conducted using the MedTone (model C) inhaler. The FDA requested that we conduct two clinical studies with the next-generation inhaler (one in patients with type 1 diabetes and one in patients with type 2 diabetes), with at least one study including a treatment group using the MedTone (model C) inhaler in order to obtain a head-to-head comparison of the pulmonary safety data for

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the two devices. The FDA also stated that after an adequate titration of study medication there should be at least 12 weeks of relatively stable insulin dosing during the treatment period. In addition to this request, the FDA requested additional information concerning the performance characteristics, usage, handling, shipment and storage of the next-generation inhaler, an update of safety information related to AFREZZA as well as information on proposed user training and changes to the proposed labeling of the device, blister pack, foil wrap and cartons.

We are scheduled to hold an End-of-Review meeting with the agency in mid-April to discuss the protocols for the two studies, known as study 171 in type 1 patients and study 172 in type 2 patients, that we expect will generate data to form the basis of our response to the January 2011 Complete Response letter. The protocol for an earlier version of study 172, then known as study 162, was submitted to the FDA in September 2010. Study 162 was initiated in October 2010 and, by the time we halted enrollment in February 2011, approximately 39 patients had been enrolled into the study. In February 2011, the FDA sent us a letter suggesting changes to the study 162 protocol in light of its January 2011 Complete Response letter. In advance of our End-of-Review meeting, we have incorporated the agency s advice into the protocols for new studies 171 and 172, which are designed to evaluate A1C levels after an adequate titration of AFREZZA followed by a relatively stable insulin dose for at least 12 weeks. We plan to continue working closely with the FDA in our effort to ensure that studies 171 and 172 address the agency s requests. However, there can be no assurance that we will be able to satisfy all of the FDA s requirements or that the FDA will find our proposed approach to these and other future clinical studies acceptable. The FDA could also request that we conduct additional clinical trials to provide sufficient data for approval of the NDA.

As part of our original NDA submission, we proposed a Risk Evaluation and Mitigation Strategy, or REMS, for ensuring that the benefits of AFREZZA outweighed its risks. Our proposed REMS included communication tools, such as the prescribing information, medication guide, educational materials and training materials, as well as evaluation tools, such as prescriber and patient surveys, and a pharmacovigilance program including special monitoring of targeted medical events. We have been informed by the FDA that a REMS will be necessary for AFREZZA, if it is approved, to ensure that the benefits of the drug outweigh:

- the risk of respiratory difficulty immediately post-inhalation, especially in patients with undiagnosed chronic lung disease;
- the risk of pulmonary function decline over time; and
- the potential risk of harm due to use by inappropriate patient populations, such as smokers and patients with chronic lung disease.

We expect to continue our discussions with the FDA regarding the REMS after we submit our response to the January 2011 Complete Response letter.

INVESTIGATIONAL CANCER THERAPIES

Our cancer immunotherapy program utilizes the body s immune system to help eradicate tumor cells. The immune system is a network of cells and organs that defends the body against infection and abnormal cells, such as tumor cells. A key element of the immune system is its ability to distinguish between healthy cells and foreign or diseased cells that do not belong in the body. The immune system accomplishes this task by recognizing distinctive molecules called epitopes on the surface of each cell as either normal or abnormal, and responding to them appropriately. Any substance capable of being recognized by the immune system is known as an antigen. An antigen can be all or part of a pathogenic organism or it can be a by-product of diseased cells. Certain specialized cells of the immune system (antigen-presenting cells or APC) sample antigens found in the body and present the epitopes associated with foreign antigens to other cells of the immune system, known as T cells, whose function is to destroy any cell that expresses the same epitope; this process is known as cell-mediated immunity. In this way, the immune system can launch a very specific response to infection or disease.

Our approach uses DNA- and peptide-based compounds that correspond to tumor-associated antigens that are expressed in a range of tumors. We select as target antigens molecules that either play a role in disease progression or that are very selectively expressed by tumor cells. A patient s immune system is first primed by DNA-based compounds, or plasmids, that are injected directly into the patient s lymph nodes. This is designed to sensitize the

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immune system to the tumor-associated antigens encoded by the plasmids. After a period of time, the patient s lymph nodes are then injected with synthetic peptides that are designed to boost or greatly amplify the immune response to the target antigens. The immune response is maintained by repeated immunization cycles. This prime-boost regimen is designed to provoke a potent cell-mediated immune response that destroys cancer cells along with the underlying blood supply to tumors.

The key features of our cancer immunotherapy program include the following:

- It is a targeted therapeutic approach that aims to redirect patients immune response to the tumor targets expressed by their cancer. The patients with a highest likelihood to benefit from this treatment can be identified by histological analysis of their tumors.
- It involves an innovative and potent vaccination approach comprising direct intra-lymphatic administration of the immunizing components using a prime-boost sequence that is designed to achieve optimal response.
- The selected target antigens are molecules that play a key role in tumor progression and migration and that display increased expression, or selective expression, in tumor cells. Moreover, they are expressed in a range of tumors.
- The immunizing components are off-the-shelf formulations of DNA and peptides containing excipients that are well recognized and generally regarded as safe. There is no need to harvest any material from patients tumors or cells in order to manufacture our immunotherapy products.

To date, we have evaluated two product candidates in clinical trials: MKC1106-PP and MKC1106-MT. MKC1106-PP consists of three components: a plasmid that encodes pharmacologically active elements from two tumor-associated antigens, known as PRAME and PSMA, and two synthetic peptides, one an analog of a PRAME epitope and the other an analog of a PSMA epitope. In addition to melanoma, PRAME is expressed in carcinomas such as prostate, lung, breast, ovarian, renal, pancreatic and colorectal. PSMA was originally isolated from prostate carcinoma cells and later shown to be expressed in the blood vessels that supply several types of carcinoma, including breast, lung, ovarian, pancreatic, renal and colorectal carcinoma and melanoma. MKC1106-MT consists of a plasmid that encodes portions of two antigens known as Melan-A and tyrosinase, and two synthetic peptides, one an analog of a Melan-A epitope and the other an analog of a tyrosinase epitope. Melan-A and tyrosinase are antigens commonly expressed by melanoma tumor cells.

In one study, MKC1106-PP was used to treat 26 advanced cancer patients with diverse tumor types, metastatic disease and/or progressive, refractory disease. Patients were evaluated after two therapeutic cycles of six weeks each and again after four therapeutic cycles, as applicable. Patients demonstrating a clinical response or no evidence of disease progression remained in the clinical trial and received up to six cycles of treatment over nine months. In all patients, the treatment was well tolerated with few and mild adverse events. The primary endpoint of this study was the determination of an immune response following the first or second cycle of treatment. Overall, 15 subjects had an immune response to the either the PRAME or PSMA antigens, or both. Ten subjects overall demonstrated no disease progression and continued treatment past the second treatment cycle. Of these ten subjects, five subjects had an immune response for at least two cycles of treatment, one subject had an immune response during the first treatment cycle only, and four subjects had no immune response. In connection with our restructuring in February 2011, clinical development activities for MKC1106-PP were halted to focus our resources on securing the approval of the NDA for AFREZZA, although we retained the key assets and intellectual property required to restart development activities for MKC1106-PP if and when we are able to do so.

In a separate study, 18 patients with advanced melanoma were treated with MKC1106-MT. Patients were evaluated after each therapeutic cycle of six weeks and those who demonstrated a clinical response or no evidence of disease progression remained in the clinical trial and received up to eight cycles of treatment over one year. Treatment with MKC1106-MT was well tolerated by all patients. An endpoint of this study was the determination of an immune response following the first or second cycle of treatment. Overall, nine subjects had an immunologic response to the either the Melan A or tyrosinase antigens. Of these subjects, two subjects showed objective tumor responses. Of the remaining nine subjects with no or undetermined immune response, four subjects achieved an objective tumor response.

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In October 2010, we initiated a Phase 2 study of MKC1106-MT involving up to 44 patients with advanced melanoma that is confined to the skin, subcutaneous tissue or lymph nodes. The primary end-point of this open-label, non-randomized study is to evaluate objective tumor response. Clinical efficacy will also be assessed using measures of time-to-progression, progression-free survival and overall survival. We do not expect to obtain results from this study until the second half of 2012.

Cancer Drug Discovery

Our drug discovery effort is directed at a biochemical signaling pathway known as the unfolded protein response, or UPR, which is a response to stress or changes in cellular conditions during which proteins cease to function correctly. The UPR is intended to restore the normal function of the cell and preserve its viability, by halting protein production while molecular chaperones remove the improperly folded proteins. When cellular stress continues for an extended period of time, the role of the UPR changes from restoring normal function to initiating programmed cell death or apoptosis. In this manner, the improperly functioning cell is removed from the body.

However, in myeloma cells and possibly other malignancies, the UPR is not properly regulated. In these cells, an enzyme known as inositol-requiring enzyme-1, or IRE-1 , activates the X-box binding protein-1 gene, or XBP-1, thus enhancing molecular chaperone activity and protein degradation. The result is that tumor cells escape apoptosis, proliferate and invade vital organs in cancer patients, and/or confer resistance to other therapeutic means that induce cellular stress, including chemotherapy, radiotherapy and anti-angiogenic drugs.

Multiple myeloma, the second most prevalent blood cancer after non-Hodgkin s lymphoma, is a key focus of our IRE-1 program. This disease results in excessive abnormal cells as a result of transformation of normal B-cells (B-lymphocytes) into malignant plasma cells.

Using our proprietary IRE-1 assay, we have identified novel compounds that selectively antagonize IRE-1 *in vitro* and consequently down-regulates XBP-1 activity in tumor cells and animal models. We are currently undertaking nonclinical studies in order to position a compound for clinical trials.

OUR STRATEGY

Our primary objective is to secure the approval of the NDA for AFREZZA by the FDA, and our resources are focused on the activities necessary to pursue this objective. In February 2011, we implemented a restructuring to streamline our operations, reduce our operating expenses and extend our cash runway. We expect that we will require additional financial resources in order to continue the development of AFREZZA and to support our other ongoing activities. In addition to traditional financing transactions, such as the sale of equity and/or debt securities, we intend to explore opportunities to generate additional financial resources through the entry into one or more strategic business collaborations. Specifically, we intend to:

Seek a development and commercialization partner for AFREZZA. We intend to pursue potential collaboration opportunities with large pharmaceutical companies in the United States, Europe and elsewhere in order to provide the financial and operational resources to develop, commercialize, market and sell AFREZZA. We have not licensed or transferred any of our rights to this product or to our platform technology.

Out-license our proprietary Technosphere formulation technology for the delivery of active pharmaceutical ingredients. We believe that additional Technosphere formulations of active pharmaceutical ingredients have the potential to demonstrate clinical advantages over existing therapeutic options in a variety of therapeutic areas. We intend to pursue opportunities to out-license our technology to pharmaceutical companies that are in need of alternative formulations for their proprietary active pharmaceutical ingredients.

Pursue transactional opportunities for our investigational cancer therapies. We are currently conducting a Phase 2 clinical trial of one of our investigational cancer immunotherapy products. As this program and the

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cancer drug discovery program reach upcoming milestones that are expected to increase the perceived value of these programs, we intend to pursue opportunities to enter into transactions with potential partners or acquirers.

SALES AND MARKETING

Our efforts to date have primarily been directed at developing pharmaceutical products for a number of different markets. We currently have no sales or distribution capabilities and have no experience as a company in marketing or selling pharmaceutical products. However, we have built a small marketing team and are engaged in the planning and market research activities that would normally be undertaken to support the late-stage development of a pharmaceutical product.

In order to commercially market any of our products, we need either to develop an internal sales team, continue to expand our marketing infrastructure or collaborate with third parties who have greater sales and marketing capabilities and have access to potentially large markets. Although we believe that establishing our own sales and marketing organizations in North America would have substantial advantages, we recognize that this may not be practical for some of our products and that collaborating with companies with established sales and marketing capabilities in a particular market or markets may be a more effective alternative for some products. To date, we have retained worldwide commercialization rights for all of our product candidates, including AFREZZA. We intend to pursue potential collaboration opportunities to assist us in the commercialization of AFREZZA in the United States and other major markets.

MANUFACTURING AND SUPPLY

We formulate and fill the AFREZZA Inhalation Powder into plastic cartridges and blister package the cartridges in our Danbury facility. We believe that our Danbury facility has enough capacity to satisfy the initial commercial demand for AFREZZA, although the facility includes expansion space that will allow production capacity to be increased based on anticipated needs during the initial years of commercialization. The quality management systems of our facility were certified to be in conformance with the ISO 13485 and ISO 9001 standards. In addition, our facility underwent a successful pre-approval inspection by the FDA during the fall of 2009. A portion of this pre-approval inspection was related to our ability to fill and package cartridges for the MedTone inhaler. We anticipate that our facility may need to undergo another successful pre-approval inspection related to our ability to fill and package cartridges for the next-generation inhaler before the FDA is able to approve the NDA for AFREZZA.

Currently, our insulin inventory is from two sources. In November 2007, we entered into a long-term supply agreement with N.V. Organon, or Organon, now a subsidiary of Merck & Co., Inc., pursuant to which Organon would manufacture and supply specified quantities of recombinant human insulin to us. Under the terms of this supply agreement, we had the right to terminate the agreement upon 30 days advance written notice to Organon if the FDA fails to approve AFREZZA. In connection with the January 2011 Complete Response letter that we received from the FDA, on February 8, 2011, we gave 30 days written notice to Organon to terminate the supply agreement effective March 10, 2011. As a result of the termination of the agreement. Organon is not entitled to make (and we are not obliged to accept) any deliveries of insulin for which a delivery date under a purchase order has not yet passed, which includes all purchase orders previously placed for 2011 shipments. However, pursuant to the terms of the supply agreement, we may be required to pay Organon a termination fee if Organon is unable to sell certain quantities of insulin to other parties under commercially viable terms within 12 months after termination. While we cannot determine at this time the amount of the termination fee, if any, that we may have to pay to Organon, we estimate that the maximum amount of the termination fee is approximately $40.1 million based on the applicable exchange rate and purchase price at the time the termination notice was sent. We must rely on our insulin supplier to maintain compliance with relevant regulatory requirements including current Good Manufacturing Practices, or cGMP.

In June 2009, we acquired a quantity of bulk insulin from Pfizer Manufacturing Frankfurt GmbH, a subsidiary of Pfizer Inc., or Pfizer, as well as Pfizer s rights under a license to manufacture insulin for pulmonary delivery. In addition, we acquired an option to purchase additional insulin inventory, in whole or in part, at a specified price, to the extent it remains available.

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We are in the process of qualifying a manufacturer to supply us with our next-generation inhaler and the corresponding cartridges. We rely on our manufacturers to comply with relevant regulatory requirements, including compliance with Quality System Regulations, or QSRs.

Currently, we purchase the raw material from which we produce Technosphere particles from a major chemical manufacturer with facilities in Europe and North America. We also have the capability of manufacturing this chemical ourselves in our Danbury facility, which is treated as a back-up facility. Like us, our third-party manufacturers are subject to extensive governmental regulation.

INTELLECTUAL PROPERTY AND PROPRIETARY TECHNOLOGY

Our success will depend in large measure on our ability to obtain and enforce our intellectual property rights, effectively maintain our trade secrets and avoid infringing the proprietary rights of third parties. Our policy is to file patent applications on what we deem to be important technological developments that might relate to our product candidates or methods of using our product candidates and to seek intellectual property protection in the United States, Europe, Japan and selected other jurisdictions for all significant inventions. We have obtained, are seeking, and will continue to seek patent protection on the compositions of matter, methods and devices flowing from our research and development efforts. We have also in-licensed certain technology.

Our Technosphere drug delivery platform, including AFREZZA, enjoys patent protection relating to the particles, their manufacture, and their use for pulmonary delivery of drugs. We have additional patent coverage relating to the treatment of diabetes using AFREZZA. We have been granted patent coverage for our inhaler and cartridges in the form in which our insulin product will be sold to the consumer. We have additional pending patent applications, and expect to file further applications, relating to the drug delivery platform, methods of manufacture, the AFREZZA product and its use, and other Technosphere-based products, inhalers and inhaler cartridges. Overall, we own 102 issued utility patents, 74 issued design patents and over 240 pending applications in the United States and selected jurisdictions around the world related to our Technosphere platform. These include composition and method of treatment patents providing protection for AFREZZA that will remain in force into 2020, and patents on our inhaler and inhaler cartridges that will remain in force into 2023.

In addition, we own or have in-licensed intellectual property relating to several drug targets of interest in the treatment of cancer and other fields. Patents and patent applications in this area are drawn to drug screening methods, methods of treatment, and chemical structures of inhibitors of these targets. Our cancer immunotherapy program is built on proprietary methods for the selection, design and administration of epitopes, as well as the plasmids and peptides that are the active ingredients of our product candidates. Overall, we own 55 issued patents and over 230 pending applications in the United States and selected jurisdictions around the world related to our immunotherapy program.

The fields of pulmonary drug delivery and cancer therapies are crowded and a substantial number of patents have been issued in these fields. In addition, because patent positions can be highly uncertain and frequently involve complex legal and factual questions, the breadth of claims obtained in any application or the enforceability of issued patents cannot be confidently predicted. Further, there can be substantial delays in commercializing pharmaceutical products, which can partially consume the statutory period of exclusivity through patents.

In addition, the coverage claimed in a patent application can be significantly reduced before a patent is issued, either in the United States or abroad. Statutory differences in patentable subject matter may limit the protection we can obtain on some of our inventions outside of the United States. For example, methods of treating humans are not patentable in many countries outside of the United States. These and other issues may limit the patent protection we will be able to secure internationally. Consequently, we do not know whether any of our pending or future patent applications will result in the issuance of patents or, to the extent patents have been issued or will be issued, whether these patents will be subjected to further proceedings limiting their scope, will provide significant proprietary protection or competitive advantage, or will be circumvented or invalidated. Furthermore, patents already issued to us or our pending applications may become subject to disputes that could be resolved against us. In addition, patent applications in the United States filed before November 29, 2000 are currently maintained in secrecy until the patent issues, although in certain countries, including the United States, for applications filed on or after November 29, 2000, applications are generally published 18 months after the application s priority date. In any event, because

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publication of discoveries in scientific or patent literature often trails behind actual discoveries, we cannot be certain that we were the first inventor of the subject matter covered by our pending patent applications or that we were the first to file patent applications on such inventions.

Although we own a number of domestic and foreign patents and patent applications relating to our Technosphere-based investigational products and our cancer products under development, we have identified certain third-party patents having claims relating to pulmonary insulin delivery that may trigger an allegation of infringement upon the commercial manufacture and sale of AFREZZA. We have also identified third-party patents disclosing methods and compositions of matter related to cancer vaccines that also may trigger an allegation of infringement upon the commercial manufacture and sale of our cancer immunotherapy. We believe that we are not infringing any valid claims of any patent owned by a third party. However, if a court were to determine that our inhaled insulin product or cancer immunotherapies were infringing any of these patent rights, we would have to establish with the court that these patents were invalid in order to avoid legal liability for infringement of these patents. Proving patent invalidity can be difficult because issued patents are presumed valid. Therefore, in the event that we are unable to prevail in an infringement or invalidity action we will either have to acquire the third-party patents outright or seek a royalty-bearing license. Royalty-bearing licenses effectively increase costs and therefore may materially affect product profitability. Furthermore, if the patent holder refuses to either assign or license us the infringed patents, it may be necessary to cease manufacturing the product entirely and/or design around the patents. In either event, our business would be harmed and our profitability could be materially adversely impacted. If third parties file patent applications, or are issued patents claiming technology also claimed by us in pending applications, we may be required to participate in interference proceedings in the United States Patent and Trademark Office, or USPTO, to determine priority of invention. We may be required to participate in interference proceedings involving our issued patents and pending applications.

We also rely on trade secrets and know-how, which are not protected by patents, to maintain our competitive position. We require our officers, employees, consultants and advisors to execute proprietary information and invention and assignment agreements upon commencement of their relationships with us. These agreements provide that all confidential information developed or made known to the individual during the course of our relationship must be kept confidential, except in specified circumstances. These agreements also provide that all inventions developed by the individual on behalf of us must be assigned to us and that the individual will cooperate with us in connection with securing patent protection on the invention if we wish to pursue such protection. There can be no assurance, however, that these agreements will provide meaningful protection for our inventions, trade secrets or other proprietary information in the event of unauthorized use or disclosure of such information.

We also execute confidentiality agreements with outside collaborators. However, disputes may arise as to the ownership of proprietary rights to the extent that outside collaborators apply technological information to our projects that are developed independently by them or others, or apply our technology to outside projects, and there can be no assurance that any such disputes would be resolved in our favor. In addition, any of these parties may breach the agreements and disclose our confidential information or our competitors might learn of the information in some other way. If any trade secret, know-how or other technology not protected by a patent were to be disclosed to or independently developed by a competitor, our business, results of operations and financial condition could be adversely affected.

COMPETITION

The pharmaceutical and biotechnology industries are highly competitive and characterized by rapidly evolving technology and intense research and development efforts. We expect to compete with companies, including the major international pharmaceutical companies, and other institutions that have substantially greater financial, research and development, marketing and sales capabilities and have substantially greater experience in undertaking preclinical and clinical testing of products, obtaining regulatory approvals and marketing and selling biopharmaceutical products. We will face competition based on, among other things, product efficacy and safety, the timing and scope of regulatory approvals, product ease of use and price.

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Diabetes Treatments

We believe that AFREZZA has important competitive advantages in the delivery of insulin when compared with currently known alternatives. However, new drugs or further developments in alternative drug delivery methods may provide greater therapeutic benefits, or comparable benefits at lower cost, than AFREZZA. There can be no assurance that existing or new competitors will not introduce products or processes competitive with or superior to our product candidates.

We have set forth below more detailed information about certain of our competitors. The following is based on information currently available to us.

Rapid-acting (Injected) Insulin

Currently, there is no approved insulin product that is absorbed into the bloodstream as rapidly as AFREZZA, i.e., reaching peak levels within 12 to 14 minutes after administration. There are several formulations of rapid-acting insulin analogs that claim to reach peak insulin levels within 30 to 90 minutes after injection. The principal products in this category are Humalog®, which was developed by Eli Lilly & Company, or Lilly, NovoLog®, which was developed by Novo Nordisk A/S, or Novo Nordisk, and Apidra®, which was developed by sanofi-aventis.

Several insulin products in development are reported to have a time-action profile that is more rapid than that of the currently available rapid-acting insulin analogs. Halozyme Therapeutics, Inc. is conducting Phase 2 clinical studies to evaluate the safety and efficacy of a formulation of human insulin or an insulin analog that is co-administered with human hyaluronidase enzyme. This enzyme temporarily degrades a naturally occurring, space-filling substance that is a major component of normal tissues throughout the body, thereby facilitating the penetration and diffusion of insulin that is injected under the skin.

Biodel, Inc. submitted an NDA for Linjeta , its proprietary diluent that is combined with human insulin to create a rapid-acting insulin formulation. In October 2010, Biodel received a Complete Response letter from the FDA requesting that the company conduct two Phase 3 clinical trials, one in patients with type 1 diabetes and the other in patients with type 2 diabetes, to establish the efficacy and safety of Linjeta.

Novo Nordisk is conducting Phase 1 clinical studies of NN1218, an insulin analog that is intended to provide faster onset of action than the currently available rapid-acting insulin analogs.

Inhaled Insulin Delivery Systems

In January 2006, Exubera®, developed by Pfizer in collaboration with Nektar Therapeutics, was approved for the treatment of adults with type 1 and type 2 diabetes. Exubera® was slow to gain market acceptance and, in October 2007, Pfizer announced that it was discontinuing the product. In September 2008, we announced a collaboration agreement with Pfizer pursuant to which certain patients with a continuing medical need for inhaled insulin were transitioned to AFREZZA on a compassionate use basis. Pfizer subsequently withdrew the NDA for Exubera from the FDA.

In January 2008, Novo Nordisk announced that it was halting development of its inhaled insulin product, having reached the conclusion that the product did not have adequate commercial potential. Notwithstanding the termination of this program, Novo Nordisk stated that it intended to increase research and development activities targeted at inhalation systems for long-acting formulations of insulin and GLP-1.

In March 2008, Lilly announced that it too was terminating the development of its AIR® inhaled insulin system. Lilly stated that this decision resulted from increasing uncertainties in the regulatory environment and after a thorough evaluation of the evolving commercial and clinical potential of its product compared to existing medical therapies.

In January 2011, Dance Pharma announced that it will develop an inhaled insulin product based on aerosol technology licensed to Dance Pharma by Aerogen Ltd.

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Non-insulin Medications

We expect that AFREZZA will compete with currently available non-insulin medications for type 2 diabetes. These products include the following:

Sulfonylureas, also called oral hypoglycemic agents, prompt the pancreas to secrete insulin. This class of drugs is most effective in individuals whose pancreas still have some working pancreas cells.

Meglitinides are taken with meals and reduce the elevation in blood glucose that generally follows eating. If these drugs are not taken with meals, blood glucose will drop dramatically and inappropriately.

Biguanides lower blood glucose by improving the sensitivity of cells to insulin (*i.e.*, by diminishing insulin resistance).

Thiazolidinedione improves the uptake of glucose by cells in the body.

Alpha-glucosidase inhibitors lower the amount of glucose absorbed from the intestines, thereby reducing the rise in blood glucose that occurs after a meal.

Inhibitors of dipeptidyl peptidase IV are a class of drugs that work by blocking the degradation of GLP-1, which is a naturally occurring incretin.

Incretin mimetics work by several mechanisms including stimulating the pancreas to secrete insulin when blood glucose levels are high.

Cancer Treatments

For many types of cancer, chemotherapy remains a significant component of the treatment regimen. Increasingly, however, drugs and antibodies that specifically target the abnormal mechanisms of proliferation, differentiation and invasion of malignant cells are being used to treat cancer. One such cancer therapy is Rituxan® (rituximab), an antibody marketed in the United States by Biogen IDEC Inc. and Genentech, Inc., or Genentech, a wholly-owned member of the Roche Group, or Roche, and by Roche in the rest of the world. Genentech and Roche have also partnered to market two other successful antibodies: Avastin® (bevacizumab) and Herceptin® (trastuzumab). Erbitux® (cetuximab) is another antibody approved for use in metastatic colon cancer and squamous cell carcinoma of the head and neck. This antibody is marketed domestically by ImClone Systems Inc., a wholly-owned subsidiary of Lilly, and Bristol-Myers Squibb Company and elsewhere by Merck KGaA.

The armamentarium of cancer treatments has been strengthened in recent years by several drugs that target specific molecular aberrations in tumor cells. One such drug is Gleevec®, developed and marketed by Novartis AG, which was initially approved for use in chronic myeloid leukemia. The drug has subsequently been approved for use in additional types of cancer. Velcade®, developed by Millenium Pharmaceuticals, Inc., a wholly owned subsidiary of Takeda Pharmaceutical Company Limited, and Ortho Biotech Inc., now Centocor Ortho Biotech Inc., acts by inhibiting protein degradation, thereby inducing apoptosis. It was initially approved for use in multiple myeloma; its label now includes an indication for mantle cell lymphoma.

Our cancer products may face competition from the products described above as well as from other brands. In addition, our cancer immunotherapy products may face direct competition from one or more therapeutic cancer vaccines that may be approved in the coming years. Although there have been a number of notable failures recently among immunotherapy products in development, a few approaches continue to show potential:

Provenge®, developed by Dendreon Corporation, is a vaccine composed of autologous APC that are loaded with an antigen (prostate acid phosphatase) from prostate tumor cells then re-injected into patients. In April 2010, the FDA approved Provenge for the treatment of asymptomatic or minimally symptomatic metastatic castrate resistant (hormone refractory) prostate cancer.

MAGE-A3 is a tumor-specific antigen that is expressed in a large variety of cancers but not in normal cells. GlaxoSmithKline plc is evaluating a cancer vaccine that combines MAGE-A3, delivered as a purified recombinant protein, with certain immunostimulating compounds that are intended to increase the anti-tumor immune response. This investigational product is being evaluated in Phase 3 clinical trials for the treatment of non-small cell lung cancer and melanoma.

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Rindopepimut (CDX-110) is an immunotherapy being developed by Celldex, Inc. Rindopepimut targets a mutated form of epidermal growth factor receptor that is present in multiple cancer types and is currently being evaluated for the treatment of glioblastoma multiforme in a Phase 2 clinical trial.

GOVERNMENT REGULATION AND PRODUCT APPROVAL

The FDA and comparable regulatory agencies in state, local and foreign jurisdictions impose substantial requirements upon the clinical development, manufacture and marketing of medical devices and new drug and biologic products. These agencies, through regulations that implement the Federal Food, Drug, and Cosmetic Act, as amended, or FDCA, and other regulations, regulate research and development activities and the development, testing, manufacture, labeling, storage, shipping, approval, recordkeeping, advertising, promotion, sale and distribution of such products. In addition, if our products are marketed abroad, they also are subject to export requirements and to regulation by foreign governments. The regulatory approval process is generally lengthy, expensive and uncertain. Failure to comply with applicable FDA and other regulatory requirements can result in sanctions being imposed on us or the manufacturers of our products, including hold letters on clinical research, civil or criminal fines or other penalties, product recalls, or seizures, or total or partial suspension of production or injunctions, refusals to permit products to be imported into or exported out of the United States, refusals of the FDA to grant approval of drugs or to allow us to enter into government supply contracts, withdrawals of previously approved marketing applications and criminal prosecutions.

The steps typically required before an unapproved new drug or biologic product for use in humans may be marketed in the United States include:

Preclinical studies that include laboratory evaluation of product chemistry and formulation, as well as animal studies to assess the potential safety and efficacy of the product. Certain preclinical tests must be conducted in compliance with good laboratory practice regulations. Violations of these regulations can, in some cases, lead to invalidation of the studies, or requiring such studies to be repeated. In some cases, long-term preclinical studies are conducted while clinical studies are ongoing.

Submission to the FDA of an investigational new drug application, or IND, which must become effective before human clinical trials may commence. The results of the preclinical studies are submitted to the FDA as part of the IND. Unless the FDA objects, the IND becomes effective 30 days following receipt by the FDA.

Approval of clinical protocols by independent institutional review boards, or IRBs, at each of the participating clinical centers conducting a study. The IRBs consider, among other things, ethical factors, the potential risks to individuals participating in the trials and the potential liability of the institution. The IRB also approves the consent form signed by the trial participants.

Adequate and well-controlled human clinical trials to establish the safety and efficacy of the product. Clinical trials involve the administration of the drug to healthy volunteers or to patients under the supervision of a qualified medical investigator according to an approved protocol. The clinical trials are conducted in accordance with protocols that detail the objectives of the study, the parameters to be used to monitor participant safety and efficacy or other criteria to be evaluated. Each protocol is submitted to the FDA as part of the IND. Human clinical trials are typically conducted in the following four sequential phases that may overlap or be combined:

In Phase 1, the drug is initially introduced into a small number of individuals and tested for safety, dosage tolerance, absorption, metabolism, distribution and excretion. Phase 1 clinical trials are often conducted in healthy human volunteers and such cases do not provide evidence of efficacy. In the case of severe or life-threatening diseases, the initial human testing is often conducted in patients rather than healthy volunteers. Because these patients already have the target disease, these studies may provide initial evidence of efficacy that would traditionally be obtained in Phase 2 clinical trials. Consequently, these types of trials are frequently referred to as Phase 1/2 clinical trials. The FDA receives reports on the progress of each phase of clinical testing and it may require the modification, suspension or termination of clinical trials if it concludes that an unwarranted risk is presented to patients or healthy volunteers.

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Phase 2 involves clinical trials in a limited patient population to further identify any possible adverse effects and safety risks, to determine the efficacy of the product for specific targeted diseases and to determine dosage tolerance and optimal dosage.

Phase 3 clinical trials are undertaken to further evaluate dosage, clinical efficacy and to further test for safety in an expanded patient population at geographically dispersed clinical study sites. Phase 3 clinical trials usually include a broader patient population so that safety and efficacy can be substantially established. Phase 3 clinical trials cannot begin until Phase 2 evaluation demonstrates that a dosage range of the product may be effective and has an acceptable safety profile.

Phase 4 clinical trials are performed if the FDA requires, or a company pursues, additional clinical trials after a product is approved. These clinical trials may be made a condition to be satisfied after a drug receives approval. The results of Phase 4 clinical trials can confirm the effectiveness of a product candidate and can provide important safety information to augment the FDA s voluntary adverse drug reaction reporting system.

Concurrent with clinical trials and preclinical studies, companies also must develop information about the chemistry and physical characteristics of the drug and finalize a process for manufacturing the product in accordance with drug cGMP requirements. The manufacturing process must be capable of consistently producing quality batches of the product and the manufacturer must develop methods for testing the quality, purity, and potency of the final products. Additionally, appropriate packaging must be selected and tested and chemistry stability studies must be conducted to demonstrate that the product does not undergo unacceptable deterioration over its shelf-life.

Submission to the FDA of an NDA, or Biologics License Application, or BLA, based on the clinical trials. The results of product development, preclinical studies, and clinical trials are submitted to the FDA in the form of an NDA or BLA for approval of the marketing and commercial shipment of the product. Under the Pediatric Research Equity Act of 2003, NDAs are required to include an assessment, generally based on clinical study data, of the safety and efficacy of drugs for all relevant pediatric populations. The statute provides for waivers or deferrals in certain situations but we can make no assurances that such situations will apply to us or our product candidates.

Medical products containing a combination of new drugs, biological products, or medical devices are regulated as combination products in the United States. A combination product generally is defined as a product comprised of components from two or more regulatory categories (*e.g.*, drug/device, device/biologic, drug/biologic). Each component of a combination product is subject to the requirements established by the FDA for that type of component, whether a new drug, biologic, or device. In order to facilitate pre-market review of combination products, the FDA designates one of its centers to have primary jurisdiction for the pre-market review and regulation of the overall product. The determination whether a product is a combination product or two separate products is made by the FDA on a case-by-case basis. The FDA considers AFREZZA to be a drug-device combination product, so the review of our NDA for AFREZZA involves reviews within the Division of Metabolism and Endocrinology Products and the Division of Pulmonary and Allergy Products, both within the Center for Drug Evaluation and Research, as well as review within the Center for Devices and Radiological Health, the Center within the FDA that reviews Medical Devices. The Division of Metabolic and Endocrine Products is the lead group and obtains consulting reviews from the other two FDA groups.

The testing and approval process requires substantial time, effort and financial resources. Data that we submit are subject to varying interpretations, and the FDA and comparable regulatory authorities in foreign jurisdictions may not agree that our product candidates have been shown to be safe and effective. We cannot be certain that any approval of our products will be granted on a timely basis, if at all. If any of our products are approved for marketing by the FDA, we will be subject to continuing regulation by the FDA, including record-keeping requirements, reporting of adverse experiences with the product, submitting other periodic reports, drug sampling and distribution requirements, notifying the FDA and gaining its approval of certain manufacturing or labeling changes, and complying with certain electronic records and signature requirements. Prior to and following approval, if granted, all manufacturing sites are subject to inspection by the FDA and other national regulatory bodies and

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must comply with cGMP, QSR and other requirements enforced by the FDA and other national regulatory bodies through their facilities inspection program. Foreign manufacturing establishments must comply with similar regulations. In addition, our drug-manufacturing facilities located in Danbury and the facilities of our insulin supplier, the supplier(s) of our Technosphere material and the supplier(s) of our inhaler and cartridges are subject to federal registration and listing requirements and, if applicable, to state licensing requirements. Failure, including those of our suppliers, to obtain and maintain applicable federal registrations or state licenses, or to meet the inspection criteria of the FDA or the other national regulatory bodies, would disrupt our manufacturing processes and would harm our business. In complying with standards set forth in these regulations, manufacturers must continue to expend time, money and effort in the area of production and quality control to ensure full compliance. Currently, we believe we are operating under all of the necessary guidelines and permits.

As a drug-device combination, we currently expect that our inhaler will be approved, if at all, as part of the NDA for AFREZZA. However, numerous device regulatory requirements still apply to the device part of the drug-device combination. These include:

product labeling regulations;
general prohibition against promoting products for unapproved or off-label uses;
corrections and removals (*e.g.*, recalls);
establishment registration and device listing;
general prohibitions against the manufacture and distribution of adulterated and misbranded devices; and

the Medical Device Reporting regulation, which requires that manufacturers report to the FDA if their device may have caused or contributed to a death or serious injury or malfunctioned in a way that would likely cause or contribute to a death or serious injury if it were to recur.

Further, the company we contract with to manufacture our inhaler and cartridges will be subject to the QSR, which requires manufacturers to follow elaborate design, testing, control, documentation and other quality assurance procedures during the manufacturing process of medical devices, among other requirements.

Failure to adhere to regulatory requirements at any stage of development, including the preclinical and clinical testing process, the review process, or at any time afterward, including after approval, may result in various adverse consequences. These consequences include action by the FDA or another national regulatory body that has the effect of delaying approval or refusing to approve a product; suspending or withdrawing an approved product from the market; seizing or recalling a product; or imposing criminal penalties against the manufacturer. In addition, later discovery of previously unknown problems may result in restrictions on a product, its manufacturer, or the NDA holder, or market restrictions through labeling changes or product withdrawal. Also, new government requirements may be established or current government requirements may be changed at any time, which could delay or prevent regulatory approval of our products under development. For example, healthcare reform legislation currently being considered in Congress could provide the FDA and other federal agencies with greater authority to consider the comparative effectiveness of products and to control costs of public spending on prescription drugs and biologics. We cannot predict the likelihood, nature or extent of adverse governmental regulation that might arise from future legislative or administrative action, either in the United States or abroad.

In addition, the FDA imposes a number of complex regulations on entities that advertise and promote drugs, which include, among other requirements, standards for and regulations of direct-to-consumer advertising, off-label promotion, industry sponsored scientific and educational activities, and promotional activities involving the Internet. The FDA has very broad enforcement authority under the FDCA, and failure to comply with these regulations can result in penalties, including the issuance of a warning letter directing us to correct deviations from FDA standards, including corrective advertising to healthcare providers, a requirement that future advertising and promotional materials be pre-cleared by the FDA, and state and federal civil and criminal investigations and prosecutions.

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Products manufactured in the United States and marketed outside the United States are subject to certain FDA regulations, as well as regulation by the country in which the products are to be sold. We also would be subject to foreign regulatory requirements governing clinical trials and drug product sales if products are studied or marketed abroad. Whether or not FDA approval has been obtained, approval of a product by the comparable regulatory authorities of foreign countries usually must be obtained prior to the marketing of the product in those countries. The approval process varies from jurisdiction to jurisdiction and the time required may be longer or shorter than that required for FDA approval.

Product development and approval within this regulatory framework take a number of years, involve the expenditure of substantial resources and are uncertain. Many drug products ultimately do not reach the market because they are not found to be safe or effective or cannot meet the FDA s other regulatory requirements. In addition, there can be no assurance that the current regulatory framework will not change or that additional regulation will not arise at any stage of our product development that may affect approval, delay the submission or review of an application or require additional expenditures by us. There can be no assurance that we will be able to obtain necessary regulatory clearances or approvals on a timely basis, if at all, for any of our product candidates under development, and delays in receipt or failure to receive such clearances or approvals, the loss of previously received clearances or approvals, or failure to comply with existing or future regulatory requirements could have a material adverse effect on our business and results of operations.

Under European Union regulatory systems, marketing authorizations may be submitted either under a centralized or decentralized procedure. The centralized procedure provides for the grant of a single marketing authorization that is valid for all European Union member states. The decentralized procedure provides for mutual recognition of national approval decisions. Under this latter procedure, the holder of a national marketing authorization may submit an application to the remaining member states. Within 90 days of receiving the application and assessment report, each member state must decide whether to recognize approval. We plan to choose the appropriate route of European regulatory filing in an attempt to accomplish the most rapid regulatory approvals. For example, diabetes medication is required to be submitted under the centralized procedure. However, the chosen regulatory strategy may not secure regulatory approvals or approvals of the chosen product indications. In addition, these approvals, if obtained, may take longer than anticipated.

In addition to the foregoing, we are subject to numerous federal, state and local laws relating to such matters as laboratory practices, the experimental use of animals, the use and disposal of hazardous or potentially hazardous substances, controlled drug substances, privacy of individually identifiable healthcare information, safe working conditions, manufacturing practices, environmental protection and fire hazard control. Further, if a drug product is reimbursed by Medicare, Medicaid or other federal or state health care programs, sales, marketing and scientific/educational grant programs must comply with the Medicare-Medicaid Anti-Fraud and Abuse Act, as amended, the False Claims Act, also as amended, and similar state laws. If a drug product is reimbursed by Medicare or Medicaid, pricing and rebate programs must comply with, as applicable, the Medicaid rebate requirements of the Omnibus Budget Reconciliation Act of 1990, as amended, and the Medicare Prescription Drug Improvement and Modernization Act of 2003. Additionally, the Patient Protection and Affordable Care Act, as amended by the Health Care and Education Affordability Reconciliation Act, or collectively the PPACA, enacted in March 2010, substantially changes the way healthcare is financed by both governmental and private insurers. Among other cost containment measures, the PPACA establishes: an annual, nondeductible fee on any entity that manufactures or imports certain branded prescription drugs and biologic agents; a new Medicare Part D coverage gap discount program; and a new formula that increases the rebates a manufacturer must pay under the Medicaid Drug Rebate Program. In the future, there may continue to be additional proposals relating to the reform of the U.S. health care system, some of which could further limit the prices we are able to charge for our products, or the amounts of reimbursement available for our products. If drug products are made available to authorized users of the Federal Supply Schedule of the General Services Administration, additional laws and requirements apply. All of these activities are also potentially subject to federal and state consumer protection and unfair competition laws. We may incur significant costs to comply with those laws and regulations now or in the future.

For additional information regarding the regulatory approval of AFREZZA, see discussion under the heading Regulatory Approval Status beginning on page 5 of this report.

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Patent Restoration and Marketing Exclusivity

The Drug Price Competition and Patent Term Restoration Act of 1984, known as the Hatch-Waxman Amendments to the Federal Food, Drug, and Cosmetic Act, permits the FDA to approve abbreviated new drug applications, or ANDAs, for generic versions of innovator drugs and also provides certain patent restoration and market exclusivity protections to innovator drug manufacturers. The ANDA process permits competitor companies to obtain marketing approval for a new drug with the same active ingredient for the same uses, dosage form and strength as an innovator drug but does not require the conduct and submission of preclinical or clinical studies demonstrating safety and efficacy for that product. Instead of providing completely new safety and efficacy data, the ANDA applicant only needs to submit manufacturing information and clinical data demonstrating that the copy is bioequivalent to the innovator s product in order to gain marketing approval from the FDA.

Another type of marketing application allowed by the Hatch-Waxman Amendments, a Section 505(b)(2) application, may be permitted where a company does not own or have a right to reference all the data required for approval. Section 505(b)(2) applications are often submitted for drug products that contain the same active ingredient as those in first approved drug products and where additional studies are required for approval, such as for changes in routes of administration or dosage forms.

Once an NDA is approved, the product covered thereby becomes a listed drug which can, in turn, be cited by potential competitors in support of approval of an ANDA or a 505(b)(2) application.

The Hatch-Waxman Amendments provide for a period of three years exclusivity following approval of a listed drug that contains previously approved active ingredients but is approved in a new dosage, dosage form, route of administration or combination, or for a new use, the approval of which was required to be supported by new clinical trials conducted by or for the sponsor. During this period of exclusivity, the FDA cannot grant effective approval of an ANDA or a 505(b)(2) application based on that listed drug.

The Hatch-Waxman Amendments also provide a period of five years exclusivity following approval of a drug containing no previously approved active ingredients. During this period of exclusivity, ANDAs or 505(b)(2) applications based upon those drugs cannot be submitted unless the submission accompanies a challenge to a listed patent, in which case the submission may be made four years following the original product approval.

Additionally, in the event that the sponsor of the listed drug has informed the FDA of patents covering its listed drug and FDA lists those patents in the Orange Book, applicants submitting an ANDA or a 505(b)(2) application referencing that drug are required to certify whether they intend to market their generic products prior to expiration of those patents. If an ANDA applicant certifies that it believes one or more listed patents is invalid or not infringed, it is required to provide notice of its filing to the NDA sponsor and the patent holder. If either party then initiates a suit for patent infringement against the ANDA sponsor within 45 days of receipt of the notice, the FDA cannot grant effective approval of the ANDA until either 30 months has passed or there has been a court decision holding that the patent in question is invalid or not infringed. If the ANDA applicant certifies that it does not intend to market its generic product before some or all listed patents on the listed drug expire, then the FDA cannot grant effective approval of the ANDA until those patents expire. The first ANDA applicant submitting substantially complete applications certifying that listed patents for a particular product are invalid or not infringed may qualify for a period of 180 days after a court decision of invalidity or non-infringement or after it begins marketing its product, whichever occurs first. During this 180 day period, subsequently submitted ANDAs cannot be granted effective approval.

Pediatric exclusivity, if granted, provides an additional six months of market exclusivity in the United States for new or currently marketed drugs if certain pediatric studies requested by the FDA are completed by the applicant and the applicant has other existing patent or exclusivity protection for the drug. To obtain this additional six months of exclusivity, it would be necessary for us to first receive a written request from the FDA to conduct pediatric studies and then to conduct the requested studies according to a previously agreed timeframe and submit the report of the study. There can be no assurances that we would receive a written request from the FDA and if so that we would complete the studies in accordance with the requirements for this six-month exclusivity. The current pediatric exclusivity provision is scheduled to end on October 1, 2012, and there can be no assurances that it will be reauthorized.

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EMPLOYEES

As of December 31, 2010, we had 436 full-time employees. 47 of these employees were engaged in research and development, 155 in manufacturing, 132 in clinical, regulatory affairs and quality assurance and 102 in administration, finance, management, information systems, marketing, corporate development and human resources. 55 of these employees had a Ph.D. degree and/or M.D. degree and were engaged in activities relating to research and development, manufacturing, quality assurance and business development. A significant percentage of our operating expenses relates to research and development totaling $112.3 million in 2010, $156.3 million in 2009 and $250.4 million in 2008.

On February 10, 2011, we announced that we had implemented a restructuring to streamline our operations, reduce our operating expenses, extend our cash runway and focus our resources on securing the FDA s approval of the NDA for AFREZZA. In connection with the restructuring, we reduced our total workforce by approximately 41 percent to 257 employees.

None of our employees is subject to a collective bargaining agreement. We believe relations with our employees are good.

SCIENTIFIC ADVISORS

We seek advice from a number of leading scientists and physicians on scientific, technical and medical matters. These advisors are leading scientists in the areas of pharmacology, chemistry, immunology and biology. Our scientific advisors are consulted regularly to assess, among other things:

- our research and development programs;
- the design and implementation of our clinical programs;
- our patent and publication strategies;
- market opportunities from a clinical perspective;
- new technologies relevant to our research and development programs; and
- specific scientific and technical issues relevant to our business.

Our diabetes program is supported by the following scientific advisors (and their primary affiliations):

Name	Primary Affiliation
Richard Bergenstal, MD	International Diabetes Center, Park Nicollet Institute
Geremia Bolli	University of Perugia
Alan D. Cherrington, PhD	Vanderbilt University Medical Center
David D Alessio, MD	University of Cincinnati
Steven Edelman, MD	University of California, San Diego
Alexander Fleming, MD	Kinexum Box LLC
Brian Frier, MD, FECP, BS	Edinburgh Royal Infirmary
Irl B. Hirsch, MD	University of Washington Medical Center
Lois Jovanovic, MD	Sansum Medical Research Institute
Daniel Lorber, MD	Diabetes Care & Information Center of New York
Sten Madsbad	Hvidovre University Hospital, Copenhagen
Chantal Mathieu, MD, PhD	Laboratorium voor Experimentele Geneeskunde en Endocrinologie
Mark Peyrot, MD	Loyola College Center
Daniel Porte, MD	University of California, San Diego
Julio Rosenstock, MD	Dallas Diabetes and Endocrinology Center

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Name	Primary Affiliation
Jesse Roth, MD, FACP	North Shore-Long Island Jewish Health System
Richard Rubin, PhD, CDE	Johns Hopkins University School of Medicine
Robert Sherwin, MD	Yale University School of Medicine
Jay Skyler, MD, MACP	University of Miami, Diabetes Research Institute

Our cancer program is supported by the following scientific advisors (and their primary affiliations):

Name	Primary Affiliation
Kenneth Anderson, M.D.	Dana Farber Cancer Institute, Boston
James Berenson, M.D.	Institute for Myeloma and Bone Cancer Research
Philippe Bey, Ph.D.	Pharmaceutical consultant
Bernard Fox, Ph.D.	Earle A. Chiles Research Institute
W. Martin Kast, Ph.D.	University of Southern California
Antoni Ribas, M.D.	University of California, Los Angeles
Frank Sicheri, Ph.D.	University of Toronto

EXECUTIVE OFFICERS

The following table sets forth our current executive officers and their ages as of December 31, 2010:

Name	Age	Position(s)
Alfred E. Mann	85	Chairman of the Board of Directors and Chief Executive Officer
Hakan S. Edstrom	60	President, Chief Operating Officer and Director
Matthew J. Pfeffer	53	Corporate Vice President and Chief Financial Officer
Juergen A. Martens, Ph.D.	55	Corporate Vice President, Technical Operations and Chief Technical Officer
Diane M. Palumbo	57	Corporate Vice President, Human Resources
Dr. Peter C. Richardson	51	Corporate Vice President and Chief Scientific Officer
David Thomson, Ph.D., J.D.	44	Corporate Vice President, General Counsel and Secretary

Alfred E. Mann has been one of our directors since April 1999, our Chairman of the Board since December 2001 and our Chief Executive Officer since October 2003. He founded and formerly served as Chairman and Chief Executive Officer of MiniMed, Inc., a publicly traded company focused on diabetes therapy and microinfusion drug delivery that was acquired by Medtronic, Inc. in August 2001. Mr. Mann also founded and, from 1972 through 1992, served as Chief Executive Officer of Pacesetter Systems, Inc. and its successor, Siemens Pacesetter, Inc., a manufacturer of cardiac pacemakers, now the Cardiac Rhythm Management Division of St. Jude Medical Corporation. Mr. Mann founded and since 1993, has served as Chairman and until January 2008, as Co-Chief Executive Officer of Advanced Bionics Corporation, a medical device manufacturer focused on neurostimulation to restore hearing to the deaf and to treat chronic pain and other neural deficits, that was acquired by Boston Scientific Corporation in June 2004. In January 2008, the former stockholders of Advanced Bionics Corporation repurchased certain segments from Boston Scientific Corporation and formed Advanced Bionics LLC for cochlear implants and Infusion Systems LLC for infusion pumps. Mr. Mann was non-executive Chairman of both entities. Advanced Bionics LLC was acquired by Sonova Holdings on December 30, 2009. Infusion Systems LLC was acquired by the Alfred E. Mann Foundation in February 2010. Mr. Mann has also founded and is non-executive Chairman of Second Sight Medical Products, Inc., which is developing a visual prosthesis for the blind; Bioness Inc., which is developing rehabilitation neurostimulation systems; Quallion LLC, which produces batteries for medical products and for the military and aerospace industries; and Stellar Microelectronics Inc., a supplier of electronic assemblies to the medical, military and aerospace industries. Mr. Mann also founded and is the managing member of PerQFlo, LLC, which is developing drug delivery systems. Mr. Mann is the managing member of the Alfred Mann Foundation and is also non-executive Chairman of Alfred Mann Institutes at the University of Southern California, AMI Purdue and AMI

Technion, and the Alfred Mann Foundation for Biomedical Engineering, which is establishing additional institutes at other research universities. Mr. Mann is also non-executive Chairman of the Southern California Biomedical Council and a Director of the Nevada Cancer Institute. Mr. Mann holds bachelor s and master s degrees in Physics from the University of California at Los Angeles, honorary doctorates from Johns Hopkins University,

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the University of Southern California, Western University and the Technion-Israel Institute of Technology and is a member of the National Academy of Engineering.

Hakan S. Edstrom has been our President and Chief Operating Officer since April 2001 and has served as one of our directors since December 2001. Mr. Edstrom was with Bausch & Lomb, Inc., a health care product company, from January 1998 to April 2001, advancing to the position of Senior Corporate Vice President and President of Bausch & Lomb, Inc. Americas Region. From 1981 to 1997, Mr. Edstrom was with Pharmacia Corporation, where he held various executive positions, including President and Chief Executive Officer of Pharmacia Ophthalmics Inc. Mr. Edstrom was educated in Sweden and holds a master s degree in Business Administration from the Stockholm School of Economics.

Matthew J. Pfeffer has been our Corporate Vice President and Chief Financial Officer since April 2008. Previously, Mr. Pfeffer served as Chief Financial Officer and Senior Vice President of Finance and Administration of VaxGen, Inc. from March 2006 until April 2008, with responsibility for finance, tax, treasury, human resources, IT, purchasing and facilities functions. Prior to VaxGen, Mr. Pfeffer served as CFO of Cell Genesys, Inc. During his nine year tenure at Cell Genesys, Mr. Pfeffer served as Director of Finance before being named CFO in 1998. Prior to that, Mr. Pfeffer served in a variety of financial management positions at other companies, including roles as Corporate Controller, Manager of Internal Audit and Manager of Financial Reporting. Mr. Pfeffer began his career at Price Waterhouse. Mr. Pfeffer serves on boards and advisory committees of the Biotechnology Industry Organization and the American Institute of Certified Public Accountants. Mr. Pfeffer has a bachelor s degree in Accounting from the University of California, Berkeley and is a Certified Public Accountant.

Juergen A. Martens, Ph.D. has been our Corporate Vice President of Operations and Chief Technology Officer since September 2005. From 2000 to August 2005, he was employed by Nektar Therapeutics, Inc., most recently as Vice President of Pharmaceutical Technology Development. Previously, he held technical management positions at Aerojet Fine Chemicals from 1998 to 2000 and at FMC Corporation from 1996 to 1998. From 1987 to 1996, Dr. Martens held a variety of management positions with increased responsibility in R&D, plant management, and business process development at Lonza, in Switzerland and in the United States. Dr. Martens holds a bachelor s degree in chemical engineering from the Technical College Mannheim/Germany, a bachelor s and master s degree in Chemistry and a doctorate in Physical Chemistry from the University of Marburg/Germany.

Diane M. Palumbo has been our Corporate Vice President of Human Resources since November 2004. From July 2003 to November 2004, she was President of her own human resources consulting company. From June 1991 to July 2003, Ms. Palumbo held various positions with Amgen, Inc., a California-based biopharmaceutical company, including Senior Director, Human Resources. In addition, Ms. Palumbo has held Human Resources positions with Unisys and Mitsui Bank Ltd. of Tokyo. She holds a master s degree in Business Administration from St. John s University, New York and a bachelor s degree, magna cum laude, also from St. John s University.

Dr. Peter C. Richardson has been our Corporate Vice President and Chief Scientific Officer since October 2005. From 1991 to October 2005, he was employed by Novartis Pharmaceuticals Corporation, which is the U.S. affiliate of Novartis AG, a world leader in healthcare, most recently as Senior Vice President, Global Head of Development Alliances. From 2003 until 2005, he was Senior Vice President and Head of Development of Novartis Pharmaceuticals KK Japan. He earlier practiced as an endocrinologist. Dr. Richardson holds a B.Med.Sci (Hons.) and a BM.BS (Hons.) from University of Nottingham Medical School; a MRCP (UK) from the Royal College of Physicians, UK; a Certificate in Pharmaceutical Medicine from Universities of Freibourg, Strasbourg and Basle; and a Diploma in Pharmaceutical Medicine from the Royal College of Physicians Faculty of Pharmaceutical Medicine.

David Thomson, Ph.D., J.D. has been our Corporate Vice President, General Counsel and Corporate Secretary since January 2002. Prior to joining us, he practiced corporate/commercial and securities law at the Toronto law firm of Davies Ward Phillips & Vineberg LLP. Earlier in his career, Dr. Thomson was a post-doctoral fellow at the Rockefeller University. Dr. Thomson obtained his bachelor s degree, master s degree and Ph.D. degree from Queens University and obtained his J.D. degree from the University of Toronto.

Executive officers serve at the discretion of our Board of Directors. There are no family relationships between any of our directors and executive officers.

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Item 1A. ***Risk Factors***

You should consider carefully the following information about the risks described below, together with the other information contained in this Annual Report before you decide to buy or maintain an investment in our common stock. We believe the risks described below are the risks that are material to us as of the date of this Annual Report. Additional risks and uncertainties that we are unaware of may also become important factors that affect us. If any of the following risks actually occur, our business, financial condition, results of operations and future growth prospects would likely be materially and adversely affected. In these circumstances, the market price of our common stock could decline, and you may lose all or part of the money you paid to buy our common stock.

RISKS RELATED TO OUR BUSINESS

We depend heavily on the successful development and commercialization of our lead product candidate, AFREZZA, which is not yet approved.

To date, we have not commercialized any product candidates. We have expended significant time, money and effort in the development of our lead product candidate, AFREZZA, which has not yet received regulatory approval and which may not be approved by the FDA in a timely manner, or at all. Our other product candidates are generally in early clinical or preclinical development. We anticipate that in the near term, our ability to generate revenues will depend solely on the successful development and commercialization of AFREZZA.

In a Complete Response letter received on January 18, 2011, the FDA requested that we conduct two clinical studies with the next-generation inhaler (one in patients with type 1 diabetes and one in patients with type 2 diabetes), with at least one study including a treatment group using the MedTone (model C) inhaler in order to obtain a head-to-head comparison of the pulmonary safety data for the two devices. The FDA also stated that after an adequate titration of study medication there should be at least 12 weeks of relatively stable insulin dosing at the end of the treatment period. We are scheduled to hold an End-of-Review meeting with the agency in mid-April to discuss the protocols for the two requested studies. As part of our briefing to the FDA, we have submitted the protocols for two studies that are designed to evaluate A1C levels after an adequate titration of AFREZZA followed by a relative stable insulin dose for at least 12 weeks We expect that data from these two studies, known as study 171 in type 1 patients and study 172 in type 2 patients, will form the basis of our response to the January 2011 Complete Response letter. We plan to work closely with the FDA in our effort to ensure that these clinical studies address the agency s requests. There can be no assurance that we will be able to satisfy all of the FDA s requirements or that the FDA will find our proposed approach to these and other future clinical studies acceptable. The FDA could also request that we conduct additional clinical trials to provide sufficient data for approval of the NDA. There can be no assurance that we will be able to satisfy all of the FDA s requirements or that the FDA will find our proposed approach to these and other future clinical studies acceptable. The FDA could also request that we conduct additional clinical trials to provide sufficient data for approval of the NDA. There can be no assurance that we will obtain approval of the NDA in a timely manner or at all.

We must receive the necessary approvals from the FDA and similar foreign regulatory agencies before AFREZZA can be marketed and sold in the United States or elsewhere. Even if we were to receive regulatory approval, we ultimately may be unable to gain market acceptance of AFREZZA for a variety of reasons, including the treatment and dosage regimen, potential adverse effects, the availability of alternative treatments and cost effectiveness. If we fail to commercialize AFREZZA, our business, financial condition and results of operations will be materially and adversely affected.

We have sought to develop our product candidates through our internal research programs. All of our product candidates will require additional research and development and, in some cases, significant preclinical, clinical and other testing prior to seeking regulatory approval to market them. Accordingly, these product candidates will not be commercially available for a number of years, if at all.

A significant portion of the research that we have conducted involves new and unproven compounds and technologies, including AFREZZA, Technosphere platform technology and immunotherapy product candidates. Even if our research programs identify candidates that initially show promise, these candidates may fail to progress to clinical development for any number of reasons, including discovery upon further research that these candidates have adverse effects or other characteristics that indicate they are unlikely to be effective. In addition, the clinical

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results we obtain at one stage are not necessarily indicative of future testing results. If we fail to successfully complete the development and commercialization of AFREZZA or develop or expand our other product candidates, or are significantly delayed in doing so, our business and results of operations will be harmed and the value of our stock could decline.

We have a history of operating losses, we expect to continue to incur losses and we may never become profitable.

We are a development stage company with no commercial products. All of our product candidates are still being developed, and all but AFREZZA are still in the early stages of development. Our product candidates will require significant additional development, clinical trials, regulatory clearances and additional investment before they can be commercialized. We cannot be certain when AFREZZA may be approved or if it will be approved.

We have never been profitable and, as of December 31, 2010, we had incurred a cumulative net loss of $1.8 billion. The cumulative net loss has resulted principally from costs incurred in our research and development programs, the write-off of goodwill and general operating expenses. We expect to make substantial expenditures and to incur increasing operating losses in the future in order to further develop and commercialize our product candidates, including costs and expenses to complete clinical trials, seek regulatory approvals and market our product candidates, including AFREZZA. This cumulative net loss may increase significantly as we continue development and clinical trial efforts.

Our losses have had, and are expected to continue to have, an adverse impact on our working capital, total assets and stockholders equity. As of December 31, 2010, we had a stockholders deficit of $185.5 million. Our ability to achieve and sustain profitability depends upon obtaining regulatory approvals for and successfully commercializing AFREZZA, either alone or with third parties. We do not currently have the required approvals to market any of our product candidates, and we may not receive them. We may not be profitable even if we succeed in commercializing any of our product candidates. As a result, we cannot be sure when we will become profitable, if at all.

If we fail to raise additional capital our financial condition and business would suffer.

It is costly to develop therapeutic product candidates and conduct clinical trials for these product candidates. Although we are currently focusing on AFREZZA as our lead product candidate, we had begun to conduct clinical trials for additional product candidates. Our existing capital resources will not be sufficient to support the expense of fully developing and commercializing AFREZZA or fully developing any of our other product candidates.

Based upon our current expectations, we believe that our existing capital resources, including the loan arrangement with The Mann Group LLC, an entity controlled by our principal stockholder. but excluding any proceeds to us from the common stock purchase agreement that we entered into with Seaside 88, LP, or Seaside, will enable us to continue planned operations through the fourth quarter of 2011. However, we cannot assure you that our plans will not change or that changed circumstances will not result in the depletion of our capital resources more rapidly than we currently anticipate. In any event, we plan to raise additional funds, whether through the sale of equity or debt securities, the entry into strategic business collaborations, the establishment of other funding facilities, licensing arrangements, asset sales or other means, or an increase in the borrowings available under the loan arrangement with our related party, in order to continue the development and commercialization of AFREZZA and other product candidates and to support our other ongoing activities. However, it may be difficult for us to raise additional funds through these planned measures. As of December 31, 2010, we had a stockholders deficit of $185.5 million which may raise concerns about our solvency and affect our ability to raise additional capital. The amount of additional funds we need will depend on a number of factors, including:

- the rate of progress and costs of our clinical trials and research and development activities, including costs of procuring clinical materials and operating our manufacturing facilities;
- our success in establishing strategic business collaborations and the timing and amount of any payments we might receive from any collaboration we are able to establish;
- actions taken by the FDA and other regulatory authorities affecting our products and competitive products;

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our degree of success in commercializing AFREZZA;
the emergence of competing technologies and products and other adverse market developments;
the timing and amount of payments we might receive from potential licensees;
the costs of preparing, filing, prosecuting, maintaining and enforcing patent claims and other intellectual property rights or defending against claims of infringement by others;
the level of our legal expenses, including those expenses associated with the securities class actions and derivative lawsuits filed against us and certain of our executive officers and directors and any settlement or damages payments associated with litigation;

the costs of the restructuring that we implemented following receipt of the Complete Response letter from the FDA in January 2011;
the costs of discontinuing projects and technologies;
the costs of decommissioning existing facilities, if we undertake such activities; and
the costs of performing additional clinical trials requested by the FDA.

We have raised capital in the past primarily through the sale of equity and debt securities. We may in the future pursue the sale of additional equity and/or debt securities, or the establishment of other funding facilities. In August 2010, we entered into the Seaside purchase agreement and the Mann purchase agreement for the sale and issuance by us of up to 36,400,000 shares of our common stock over a period of approximately 50 weeks. To date, we have issued and sold a total of 7.0 million shares to Seaside and The Mann Group under these agreements, and could issue and sell an additional 18.2 million shares under both agreements if we are able to satisfy the conditions precedent for sales of shares under these agreements, including the minimum price requirement. Issuances of additional debt or equity securities or the conversion of any of our currently outstanding convertible debt securities into shares of our common stock could impact the rights of the holders of our common stock and may dilute their ownership percentage. We anticipate that we will seek approval by our stockholders of an amendment to our certificate of incorporation to increase the authorized number of shares of our common stock to facilitate any future capital-raising transactions. Such a proposal would require approval by the holders of a majority of the outstanding shares of our common stock. If we were unable to obtain the requisite approval, our ability to raise additional capital by selling our equity securities would be constrained. Moreover, the establishment of other funding facilities may impose restrictions on our operations. These restrictions could include limitations on additional borrowing and specific restrictions on the use of our assets, as well as prohibitions on our ability to create liens, pay dividends, redeem our stock or make investments.

We also may seek to raise additional capital by pursuing opportunities for the licensing or sale of certain intellectual property and other assets. We cannot offer assurances, however, that any strategic collaborations, sales of securities or sales or licenses of assets will be available to us on a timely basis or on acceptable terms, if at all. We may be required to enter into relationships with third parties to develop or commercialize products or technologies that we otherwise would have sought to develop independently, and any such relationships may not be on terms as commercially favorable to us as might otherwise be the case.

In the event that sufficient additional funds are not obtained through strategic collaboration opportunities, sales of securities, credit facilities, licensing arrangements and/or asset sales on a timely basis, we may be required to reduce expenses through the delay, reduction or curtailment of our projects, including AFREZZA commercialization, or further reduction of costs for facilities and administration. Moreover, if we do not obtain such additional funds, there will be substantial doubt about our ability to continue as a going concern and increased risk of insolvency and loss of investment to the holders of our securities. As of the date hereof, we have not obtained a solvency opinion or otherwise conducted a valuation of our properties to determine whether our debts exceed the fair value of our property within the meaning of applicable solvency laws. If we are or become

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insolvent, investors in our stock may lose the entire value of their investment.

Deteriorating global economic conditions may have an adverse impact on the loan facility with an entity controlled by our principal stockholder, which we currently cannot predict.

As widely reported, financial markets in the United States, Europe and Asia have been experiencing a period of unprecedented turmoil and upheaval characterized by extreme volatility and declines in security prices, severely diminished liquidity and credit availability, inability to access capital markets, the bankruptcy, failure, collapse or sale of various financial institutions and an unprecedented level of intervention from the United States federal government and other governments. We cannot predict the impact of these events on the loan facility with The Mann Group. If we are unable to draw on this financial resource, our business and financial condition will be adversely affected.

If we do not achieve our projected development and commercialization goals in the timeframes we announce and expect, our business would be harmed and the market price of our common stock could decline.

For planning purposes, we estimate the timing of the accomplishment of various scientific, clinical, regulatory and other product development goals, which we sometimes refer to as milestones. These milestones may include the commencement or completion of scientific studies and clinical trials and the submission of regulatory filings. From time to time, we publicly announce the expected timing of some of these milestones. All of these milestones are based on a variety of assumptions. The actual timing of the achievement of these milestones can vary dramatically from our estimates, in many cases for reasons beyond our control, depending on numerous factors, including:

- the rate of progress, costs and results of our clinical trial and research and development activities, which will be impacted by the level of proficiency and experience of our clinical staff;
- our ability to identify and enroll patients who meet clinical trial eligibility criteria;
- our ability to access sufficient, reliable and affordable supplies of components used in the manufacture of our product candidates, including insulin and other materials for AFREZZA;
- the costs of expanding and maintaining manufacturing operations, as necessary;
- the extent of scheduling conflicts with participating clinicians and clinical institutions;
- the receipt of approvals by our competitors and by us from the FDA and other regulatory agencies;
- our ability to enter into sales and marketing collaborations for AFREZZA; and
- other actions by regulators.

In addition, if we do not obtain sufficient additional funds through sales of securities, strategic collaborations or the license or sale of certain of our assets on a timely basis, we may be required to reduce expenses by delaying, reducing or curtailing our development of AFREZZA. If we fail to commence or complete, or experience delays in or are forced to curtail, our proposed clinical programs or otherwise fail to adhere to our projected development goals in the timeframes we announce and expect (or within the timeframes expected by analysts or investors), our business and results of operations will be harmed and the market price of our common stock will decline.

We face substantial competition in the development of our product candidates and may not be able to compete successfully, and our product candidates may be rendered obsolete by rapid technological change.

A number of established pharmaceutical companies have or are developing technologies for the treatment of diabetes. We also face substantial competition for the development of our other product candidates.

Many of our existing or potential competitors have, or have access to, substantially greater financial, research and development, production, and sales and marketing resources than we do and have a greater depth and number of

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experienced managers. As a result, our competitors may be better equipped than we are to develop, manufacture, market and sell competing products. In addition, gaining favorable reimbursement is critical to the success of AFREZZA. Many of our competitors have existing infrastructure and relationships with managed care organizations and reimbursement authorities which can be used to their advantage.

The rapid rate of scientific discoveries and technological changes could result in one or more of our product candidates becoming obsolete or noncompetitive. Our competitors may develop or introduce new products that render our technology and AFREZZA less competitive, uneconomical or obsolete. Our future success will depend not only on our ability to develop our product candidates but to improve them and keep pace with emerging industry developments. We cannot assure you that we will be able to do so.

We also expect to face increasing competition from universities and other non-profit research organizations. These institutions carry out a significant amount of research and development in the areas of diabetes and cancer. These institutions are becoming increasingly aware of the commercial value of their findings and are more active in seeking patent and other proprietary rights as well as licensing revenues.

If we fail to enter into a strategic collaboration with respect to AFREZZA, we may not be able to execute on our business model.

We have held extensive discussions with a number of pharmaceutical companies concerning a potential strategic business collaboration for AFREZZA. To date we have not reached an agreement on a collaboration with any of these companies. We cannot predict when, if ever, we could conclude an agreement with a partner. There can be no assurance that any such collaboration will be available to us on a timely basis or on acceptable terms. If we are not able to enter into a collaboration on terms that are favorable to us, we may be unable to undertake and fund product development, clinical trials, manufacturing and/or marketing activities at our own expense, which would delay or otherwise impede the commercialization of AFREZZA.

We will face similar challenges as we seek to develop our other product candidates. Our current strategy for developing, manufacturing and commercializing our other product candidates includes evaluating the potential for collaborating with pharmaceutical and biotechnology companies at some point in the drug development process and for these collaborators to undertake the advanced clinical development and commercialization of our product candidates. It may be difficult for us to find third parties that are willing to enter into collaborations on economic terms that are favorable to us, or at all. Failure to enter into a collaboration with respect to any other product candidate could substantially increase our requirements for capital and force us to substantially reduce our development effort.

If we enter into collaborative agreements with respect to AFREZZA and if our third-party collaborators do not perform satisfactorily or if our collaborations fail, development or commercialization of AFREZZA may be delayed and our business could be harmed.

We may enter into license agreements, partnerships or other collaborative arrangements to support the financing, development and marketing of AFREZZA. We may also license technology from others to enhance or supplement our technologies. These various collaborators may enter into arrangements that would make them potential competitors. These various collaborators also may breach their agreements with us and delay our progress or fail to perform under their agreements, which could harm our business.

If we enter into collaborative arrangements, we will have less control over the timing, planning and other aspects of our clinical trials, and the sale and marketing of AFREZZA and our other product candidates. We cannot offer assurances that we will be able to enter into satisfactory arrangements with third parties as contemplated or that any of our existing or future collaborations will be successful.

Continued testing of AFREZZA or our other product candidates may not yield successful results, and even if it does, we may still be unable to commercialize our product candidates.

Our research and development programs are designed to test the safety and efficacy of AFREZZA and our other product candidates through extensive nonclinical and clinical testing. We may experience numerous unforeseen

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events during, or as a result of, the testing process that could delay or prevent commercialization of AFREZZA or any of our other product candidates, including the following:

- safety and efficacy results for AFREZZA obtained in our nonclinical and previous clinical testing may be inconclusive or may not be predictive of results that we may obtain in our Affinity 1, Affinity 2 or other clinical trials or following long-term use, and we may as a result be forced to stop developing AFREZZA;
- the data collected from clinical trials of AFREZZA or our other product candidates may not reach statistical significance or otherwise be sufficient to support FDA or other regulatory approval;
- after reviewing test results, we or any potential collaborators may abandon projects that we previously believed were promising; and
- our product candidates may not produce the desired effects or may result in adverse health effects or other characteristics that preclude regulatory approval or limit their commercial use if approved.

Forecasts about the effects of the use of drugs, including AFREZZA, over terms longer than the clinical trials or in much larger populations may not be consistent with the clinical results. If use of AFREZZA results in adverse health effects or reduced efficacy or both, the FDA or other regulatory agencies may terminate our ability to market and sell AFREZZA, may narrow the approved indications for use or otherwise require restrictive product labeling or marketing, or may require further clinical trials, which may be time-consuming and expensive and may not produce favorable results.

As a result of any of these events, we, any collaborator, the FDA, or any other regulatory authorities, may suspend or terminate clinical trials or marketing of AFREZZA at any time. Any suspension or termination of our clinical trials or marketing activities may harm our business and results of operations and the market price of our common stock may decline.

If our suppliers fail to deliver materials and services needed for the production of AFREZZA in a timely and sufficient manner, or they fail to comply with applicable regulations, our business and results of operations would be harmed and the market price of our common stock could decline.

For AFREZZA to be commercially viable, we need access to sufficient, reliable and affordable supplies of insulin, our AFREZZA inhaler, the related cartridges and other materials. In June 2009, we purchased from Pfizer, a portion of its inventory of bulk insulin and acquired an option to purchase the remainder of Pfizer s insulin inventory, in whole or in part, at a specified price to the extent that Pfizer has not otherwise disposed of or used the retained insulin.

We obtain FDKP, the precursor raw material for AFREZZA, from a major multinational chemical manufacturer. We have completed a successful validation campaign of FDKP at commercial scale. We can also utilize our in-house chemical manufacturing plant for supplemental capacity. We believe our contract manufacturer has the capacity to supply our current clinical and future commercial requirements. We obtain our intended commercial AFREZZA inhaler and cartridges from a plastic molding company located in the United States.

We must rely on our suppliers to comply with relevant regulatory and other legal requirements, including the production of insulin in accordance with the FDA s current good manufacturing practices, or cGMP for drug products, and the production of the AFREZZA inhaler and related cartridges in accordance with Quality System Regulations, or QSR. The supply of any of these materials may be limited or any of the manufacturers may not meet relevant regulatory requirements, and if we are unable to obtain any of these materials in sufficient amounts, in a timely manner and at reasonable prices, or if we should encounter delays or difficulties in our relationships with manufacturers or suppliers, the development or manufacturing of AFREZZA may be delayed. Any such events could delay market introduction and subsequent sales of AFREZZA and, if so, our business and results of operations will be harmed and the market price of our common stock may decline.

We have never manufactured AFREZZA or any other product candidates in commercial quantities, and if we fail to develop an effective manufacturing capability for our product candidates or to engage third-party manufacturers with this capability, we may be unable to commercialize these products.

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We use our Danbury facility to formulate AFREZZA, fill plastic cartridges with AFREZZA, blister package the cartridges, place the blister packs into foil bags and package three bags plus two inhalers and the package insert as units in 90-unit boxes (and single bag packs for trials). This facility has been qualified and undergone an inspection by the FDA in connection with our original NDA submission that sought approval of AFREZZA using the MedTone (model D) inhaler. We anticipate that our facility may need to undergo further inspection related to our ability to fill and package cartridges for the next-generation inhaler before we can be approved to manufacture commercially. The manufacture of pharmaceutical products requires significant expertise and capital investment, including the development of advanced manufacturing techniques and process controls. Manufacturers of pharmaceutical products often encounter difficulties in production, especially in scaling up initial production. These problems include difficulties with production costs and yields, quality control and assurance and shortages of qualified personnel, as well as compliance with strictly enforced federal, state and foreign regulations. If we engage a third-party manufacturer, we would need to transfer our technology to that third-party manufacturer and gain FDA approval, potentially causing delays in product delivery. In addition, our third-party manufacturer may not perform as agreed or may terminate its agreement with us.

Additionally, when we manufacture commercial material on a significantly larger production scale than the production scale for clinical trial materials, we are required by the FDA to establish that the results obtained from the clinical trials may reasonably be extrapolated to such commercial material. We have submitted documentation to the FDA to show correlation to the clinical-scale production materials but can provide no assurance that approval will be obtained.

Any of these factors could cause us to delay or suspend clinical trials, regulatory submissions or required approvals of our product candidates, could entail higher costs and may result in our being unable to effectively commercialize our products. Furthermore, if we or a third-party manufacturer fail to deliver the required commercial quantities of any product on a timely basis, and at commercially reasonable prices and acceptable quality, and we were unable to promptly find one or more replacement manufacturers capable of production at a substantially equivalent cost, in substantially equivalent volume and quality on a timely basis, we would likely be unable to meet demand for such products and we would lose potential revenues.

We and certain of our executive officers and directors have been named as defendants in recently initiated securities class actions and a derivative lawsuit that could result in substantial costs and divert management s attention.

We are aware of lawsuits in which we, and certain of our executive officers, have been sued for alleged violations of federal securities laws related to alleged false and misleading statements regarding AFREZZA. We are also aware of a state derivative lawsuit that has been filed against certain of our directors and executive officers. We intend to engage in a vigorous defense of such litigation. If we are not successful in our defense of such litigation, we could be forced to make significant payments to or other settlements with our stockholders and their lawyers, and such payments or settlement arrangements could have a material adverse effect on our business, operating results or financial condition. Even if such claims are not successful, the litigation could result in substantial costs and significant adverse impact on our reputation and divert management s attention and resources, which could have a material adverse effect on our business, operating results or financial condition.

Our operations might be interrupted by the occurrence of a natural disaster or other catastrophic event.

We expect that at least for the foreseeable future, our manufacturing facility in Danbury, Connecticut will be the sole location for the manufacturing of AFREZZA. This facility and the manufacturing equipment we use would be costly to replace and could require substantial lead time to repair or replace. We depend on our facilities and on collaborators, contractors and vendors for the continued operation of our business, some of whom are located in Europe. Natural disasters or other catastrophic events, including interruptions in the supply of natural resources, political and governmental changes, severe weather conditions, wildfires and other fires, explosions, actions of animal rights activists, terrorist attacks, volcanic eruptions, earthquakes and wars could disrupt our operations or those of our collaborators, contractors and vendors. Even though we believe we carry commercially reasonable liability insurance and stage-appropriate business interruption insurance, and our contractors may carry liability insurance that protect us in certain events, we might suffer losses as a result of business interruptions that exceed the coverage available under

our and our contractors insurance policies or for which we or our contractors do not have

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coverage. For example, we are not insured against a terrorist attack. Any natural disaster or catastrophic event could have a significant negative impact on our operations and financial results. Moreover, any such event could delay our research and development programs and adversely affect, which may include stopping, our readiness for commercial production.

We deal with hazardous materials and must comply with environmental laws and regulations, which can be expensive and restrict how we do business.

Our research and development work involves the controlled storage and use of hazardous materials, including chemical, radioactive and biological materials. In addition, our manufacturing operations involve the use of a chemical that is stable and non-hazardous under normal storage conditions, but may form an explosive mixture under certain conditions. Our operations also produce hazardous waste products. We are subject to federal, state and local laws and regulations governing how we use, manufacture, store, handle and dispose of these materials. Moreover, the risk of accidental contamination or injury from hazardous materials cannot be completely eliminated, and in the event of an accident, we could be held liable for any damages that may result, and any liability could fall outside the coverage or exceed the limits of our insurance. Currently, our general liability policy provides coverage up to $1 million per occurrence and $2 million in the aggregate and is supplemented by an umbrella policy that provides a further $4 million of coverage; however, our insurance policy excludes pollution coverage and we do not carry a separate hazardous materials policy. In addition, we could be required to incur significant costs to comply with environmental laws and regulations in the future. Finally, current or future environmental laws and regulations may impair our research, development or production efforts.

When we purchased the facilities located in Danbury, Connecticut in 2001, there was a soil cleanup plan in process. As part of the purchase, we obtained an indemnification from the seller related to the remediation of the soil for all known environmental conditions that existed at the time the seller acquired the property. The seller was, in turn, indemnified for these known environmental conditions by the previous owner. We also received an indemnification from the seller for environmental conditions created during its ownership of the property and for environmental problems unknown at the time that the seller acquired the property. These additional indemnities are limited to the purchase price that we paid for the Danbury facilities.

During the construction of our expanded manufacturing facility, we completed the final stages of the soil cleanup plan in the third quarter of 2008, at a cost of approximately $2.25 million. We reached an agreement with the party responsible for their contribution to past clean-up costs and were reimbursed $1.625 million in July 2010. The responsible party has agreed to pay for or indemnify us for any future costs and expenses directly related to the final closure of the environmental remediation. If we are unable to collect these future costs and expenses, if any, from the responsible party, our business and results of operations may be harmed.

If we fail to enter into collaborations with third parties, we would be required to establish our own sales, marketing and distribution capabilities, which could impact the commercialization of our products and harm our business.

Our products are intended to be used by a large number of healthcare professionals who will require substantial education and support. For example, a broad base of physicians, including primary care physicians and endocrinologists, treat patients with diabetes. A large sales force will be required in order to educate these physicians about the benefits and advantages of AFREZZA and to provide adequate support for them. Therefore, we plan to enter into collaborations with one or more pharmaceutical companies to market, distribute and sell AFREZZA, if it is approved. If we fail to enter into collaborations, we would be required to establish our own direct sales, marketing and distribution capabilities. Establishing these capabilities can be time-consuming and expensive and would delay our ability to commercialize AFREZZA. Because we lack experience in selling pharmaceutical products to the diabetes market, we would be at a disadvantage compared to our potential competitors, all of whom have substantially more resources and experience than we do. For example, several other companies selling products to treat diabetes have existing sales forces in excess of 1,500 sales representatives. We, acting alone, would not initially be able to field a sales force as large as our competitors or provide the same degree of marketing support. Also, we would not be able to match our competitor s spending levels for pre-launch marketing preparation, including medical education. We cannot assure you that we will succeed in entering into acceptable collaborations,

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that any such collaboration will be successful or, if not, that we will successfully develop our own sales, marketing and distribution capabilities.

If any product that we may develop does not become widely accepted by physicians, patients, third-party payers and the healthcare community, we may be unable to generate significant revenue, if any.

AFREZZA and our other product candidates are new and unproven. Even if any of our product candidates obtain regulatory approval, they may not gain market acceptance among physicians, patients, third-party payers and the healthcare community. Failure to achieve market acceptance would limit our ability to generate revenue and would adversely affect our results of operations.

The degree of market acceptance of AFREZZA and our other product candidates will depend on many factors, including the:

- claims for which FDA approval can be obtained, including superiority claims;
- perceived advantages and disadvantages of competitive products;
- willingness of the healthcare community and patients to adopt new technologies;
- ability to manufacture the product in sufficient quantities with acceptable quality and cost;
- perception of patients and the healthcare community, including third-party payers, regarding the safety, efficacy and benefits compared to competing products or therapies;
- convenience and ease of administration relative to existing treatment methods;
- pricing and reimbursement relative to other treatment therapeutics and methods; and
- marketing and distribution support.

Because of these and other factors, any product that we may develop may not gain market acceptance, which would materially harm our business, financial condition and results of operations.

If third-party payers do not reimburse consumers for our products, our products might not be used or purchased, which would adversely affect our revenues.

Our future revenues and potential for profitability may be affected by the continuing efforts of governments and third-party payers to contain or reduce the costs of healthcare through various means. For example, in certain foreign markets the pricing of prescription pharmaceuticals is subject to governmental control. In the United States, there has been, and we expect that there will continue to be, a number of federal and state proposals to implement similar governmental controls. We cannot be certain what legislative proposals will be adopted or what actions federal, state or private payers for healthcare goods and services may take in response to any drug pricing reform proposals or legislation. Such reforms may make it difficult to complete the development and testing of AFREZZA and our other product candidates, and therefore may limit our ability to generate revenues from sales of our product candidates and achieve profitability. Further, to the extent that such reforms have a material adverse effect on the business, financial condition and profitability of other companies that are prospective collaborators for some of our product candidates, our ability to commercialize our product candidates under development may be adversely affected.

In the United States and elsewhere, sales of prescription pharmaceuticals still depend in large part on the availability of reimbursement to the consumer from third-party payers, such as governmental and private insurance plans. Third-party payers are increasingly challenging the prices charged for medical products and services. In addition, because each third-party payer individually approves reimbursement, obtaining these approvals is a time-consuming and costly process. We would be required to provide scientific and clinical support for the use of any product to each third-party payer separately with no assurance that approval would be obtained. This process could delay the market acceptance of any product and could have a negative effect on our future revenues and operating

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results. Even if we succeed in bringing one or more products to market, we cannot be certain that any such products would be considered cost-effective or that reimbursement to the consumer would be available, in which case our business and results of operations would be harmed and the market price of our common stock could decline.

If product liability claims are brought against us, we may incur significant liabilities and suffer damage to our reputation.

The testing, manufacturing, marketing and sale of AFREZZA and our other product candidates expose us to potential product liability claims. A product liability claim may result in substantial judgments as well as consume significant financial and management resources and result in adverse publicity, decreased demand for a product, injury to our reputation, withdrawal of clinical trial volunteers and loss of revenues. We currently carry worldwide liability insurance in the amount of $10 million. We believe these limits are reasonable to cover us from potential damages arising from current and previous clinical trials of AFREZZA. In addition, we carry local policies per trial in each country in which we conduct clinical trials that require us to carry coverage based on local statutory requirements. We intend to obtain product liability coverage for commercial sales in the future if AFREZZA is approved. However, we may not be able to obtain insurance coverage that will be adequate to satisfy any liability that may arise, and because insurance coverage in our industry can be very expensive and difficult to obtain, we cannot assure you that we will be able to obtain sufficient coverage at an acceptable cost, if at all. If losses from such claims exceed our liability insurance coverage, we may ourselves incur substantial liabilities. If we are required to pay a product liability claim our business and results of operations would be harmed and the market price of our common stock may decline.

If we lose any key employees or scientific advisors, our operations and our ability to execute our business strategy could be materially harmed.

In order to commercialize our product candidates successfully, we will be required to expand our work force, particularly in the areas of manufacturing, clinical trials management, regulatory affairs, business development, and sales and marketing. These activities will require the addition of new personnel, including management, and the development of additional expertise by existing personnel. We face intense competition for qualified employees among companies in the biotechnology and biopharmaceutical industries. Our success depends upon our ability to attract, retain and motivate highly skilled employees. We may be unable to attract and retain these individuals on acceptable terms, if at all.

The loss of the services of any principal member of our management and scientific staff could significantly delay or prevent the achievement of our scientific and business objectives. All of our employees are at will and we currently do not have employment agreements with any of the principal members of our management or scientific staff, and we do not have key person life insurance to cover the loss of any of these individuals. Replacing key employees may be difficult and time-consuming because of the limited number of individuals in our industry with the skills and experience required to develop, gain regulatory approval of and commercialize our product candidates successfully.

We have relationships with scientific advisors at academic and other institutions to conduct research or assist us in formulating our research, development or clinical strategy. These scientific advisors are not our employees and may have commitments to, and other obligations with, other entities that may limit their availability to us. We have limited control over the activities of these scientific advisors and can generally expect these individuals to devote only limited time to our activities. Failure of any of these persons to devote sufficient time and resources to our programs could harm our business. In addition, these advisors are not prohibited from, and may have arrangements with, other companies to assist those companies in developing technologies that may compete with our product candidates.

If our Chairman and Chief Executive Officer is unable to devote sufficient time and attention to our business, our operations and our ability to execute our business strategy could be materially harmed.

Alfred Mann, our Chairman and Chief Executive Officer, is involved in many other business and charitable activities. As a result, the time and attention Mr. Mann devotes to the operation of our business varies, and he may not expend the same time or focus on our activities as other, similarly situated chief executive officers. If Mr. Mann

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is unable to devote the time and attention necessary to running our business, we may not be able to execute our business strategy and our business could be materially harmed.

If our internal controls over financial reporting are not considered effective, our business and stock price could be adversely affected.

Section 404 of the Sarbanes-Oxley Act of 2002 requires us to evaluate the effectiveness of our internal controls over financial reporting as of the end of each fiscal year, and to include a management report assessing the effectiveness of our internal controls over financial reporting in our annual report on Form 10-K for that fiscal year. Section 404 also requires our independent registered public accounting firm to attest to, and report on, our internal controls over financial reporting.

Our management, including our Chief Executive Officer and Chief Financial Officer, does not expect that our internal controls over financial reporting will prevent all errors and all fraud. A control system, no matter how well designed and operated, can provide only reasonable, not absolute, assurance that the control system s objectives will be met. Further, the design of a control system must reflect the fact that there are resource constraints, and the benefits of controls must be considered relative to their costs. Because of the inherent limitations in all control systems, no evaluation of controls can provide absolute assurance that all control issues and instances of fraud involving a company have been, or will be, detected. The design of any system of controls is based in part on certain assumptions about the likelihood of future events, and we cannot assure you that any design will succeed in achieving its stated goals under all potential future conditions. Over time, controls may become inadequate because of changes in conditions or deterioration in the degree of compliance with policies or procedures. Because of the inherent limitations in a cost-effective control system, misstatements due to error or fraud may occur and not be detected. We cannot assure you that we or our independent registered public accounting firm will not identify a material weakness in our internal controls in the future. A material weakness in our internal controls over financial reporting would require management and our independent registered public accounting firm to evaluate our internal controls as ineffective. If our internal controls over financial reporting are not considered effective, we may experience a loss of public confidence, which could have an adverse effect on our business and on the market price of our common stock.

RISKS RELATED TO REGULATORY APPROVALS

Our product candidates must undergo rigorous nonclinical and clinical testing and we must obtain regulatory approvals, which could be costly and time-consuming and subject us to unanticipated delays or prevent us from marketing any products.

Our research and development activities, as well as the manufacturing and marketing of our product candidates, including AFREZZA, are subject to regulation, including regulation for safety, efficacy and quality, by the FDA in the United States and comparable authorities in other countries. FDA regulations and the regulations of comparable foreign regulatory authorities are wide-ranging and govern, among other things:

- product design, development, manufacture and testing;
- product labeling;
- product storage and shipping;
- pre-market clearance or approval;
- advertising and promotion; and
- product sales and distribution.

Clinical testing can be costly and take many years, and the outcome is uncertain and susceptible to varying interpretations. We cannot be certain if or when the FDA might request additional studies, under what conditions such studies might be requested, or what the size or length of any such studies might be. The clinical trials of our

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product candidates may not be completed on schedule, the FDA or foreign regulatory agencies may order us to stop or modify our research, or these agencies may not ultimately approve any of our product candidates for commercial sale. The data collected from our clinical trials may not be sufficient to support regulatory approval of our various product candidates, including AFREZZA. Even if we believe the data collected from our clinical trials are sufficient, the FDA has substantial discretion in the approval process and may disagree with our interpretation of the data. Our failure to adequately demonstrate the safety and efficacy of any of our product candidates would delay or prevent regulatory approval of our product candidates, which could prevent us from achieving profitability.

The requirements governing the conduct of clinical trials and manufacturing and marketing of our product candidates, including AFREZZA, outside the United States vary widely from country to country. Foreign approvals may take longer to obtain than FDA approvals and can require, among other things, additional testing and different clinical trial designs. Foreign regulatory approval processes include essentially all of the risks associated with the FDA approval processes. Some of those agencies also must approve prices of the products. Approval of a product by the FDA does not ensure approval of the same product by the health authorities of other countries. In addition, changes in regulatory policy in the United States or in foreign countries for product approval during the period of product development and regulatory agency review of each submitted new application may cause delays or rejections.

The process of obtaining FDA and other required regulatory approvals, including foreign approvals, is expensive, often takes many years and can vary substantially based upon the type, complexity and novelty of the products involved. We are not aware of any precedent for the successful commercialization of products based on our technology. In January 2006, the FDA approved the first pulmonary insulin product, Exubera. This approval has had an impact on and notwithstanding the voluntary withdrawal of the product from the market by its manufacturer could still impact the development and registration of AFREZZA in different ways. For example, Exubera may be used as a reference for safety and efficacy evaluations of AFREZZA, and the approval standards set for Exubera may be applied to other products that follow, including AFREZZA.

The FDA has advised us that it will regulate AFREZZA as a combination product because of the complex nature of the system that includes the combination of a new drug (AFREZZA) and a new medical device (the inhaler used to administer the insulin). The FDA indicated that the review of our NDA for AFREZZA will involve several separate review groups of the FDA including: (1) the Metabolic and Endocrine Drug Products Division; (2) the Pulmonary Drug Products Division; and (3) the Center for Devices and Radiological Health, which reviews medical devices. The Metabolic and Endocrine Drug Products Division is the lead group and obtains consulting reviews from the other two FDA groups. We can make no assurances at this time about what impact FDA review by multiple groups will have on the approvability of our product or that we will obtain approval of the NDA in a timely manner or at all.

Also, questions that have been raised about the safety of marketed drugs generally, including pertaining to the lack of adequate labeling, may result in increased cautiousness by the FDA in reviewing new drugs based on safety, efficacy, or other regulatory considerations and may result in significant delays in obtaining regulatory approvals. Such regulatory considerations may also result in the imposition of more restrictive drug labeling or marketing requirements as conditions of approval, which may significantly affect the marketability of our drug products. FDA review of AFREZZA as a combination product may lengthen the product development and regulatory approval process, increase our development costs and delay or prevent the commercialization of AFREZZA. Our product candidates that are currently in development for the treatment of cancer also face similar obstacles and costs.

We have only limited experience in filing and pursuing applications necessary to gain regulatory approvals, which may impede our ability to obtain timely approvals from the FDA or foreign regulatory agencies, if at all.

We will not be able to commercialize AFREZZA or any other product candidates until we have obtained regulatory approval. Until we prepared and submitted our NDA for AFREZZA, we had no experience as a company in late-stage regulatory filings, such as preparing and submitting NDAs, which may place us at risk of delays, overspending and human resources inefficiencies. Any delay in obtaining, or inability to obtain, regulatory approval could harm our business.

If we do not comply with regulatory requirements at any stage, whether before or after marketing approval is obtained, we may be subject to criminal prosecution, fined or forced to remove a product from the market or

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experience other adverse consequences, including restrictions or delays in obtaining regulatory marketing approval.

Even if we comply with regulatory requirements, we may not be able to obtain the labeling claims necessary or desirable for product promotion. We may also be required to undertake post-marketing trials. In addition, if we or other parties identify adverse effects after any of our products are on the market, or if manufacturing problems occur, regulatory approval may be withdrawn and a reformulation of our products, additional clinical trials, changes in labeling of, or indications of use for, our products and/or additional marketing applications may be required. If we encounter any of the foregoing problems, our business and results of operations will be harmed and the market price of our common stock may decline.

Even if we obtain regulatory approval for our product candidates, such approval may be limited and we will be subject to stringent, ongoing government regulation.

Even if regulatory authorities approve any of our product candidates, they could approve less than the full scope of uses or labeling that we seek or otherwise require special warnings or other restrictions on use or marketing or could require potentially costly post-marketing follow-up clinical trials. Regulatory authorities may limit the segments of the diabetes population to which we or others may market AFREZZA or limit the target population for our other product candidates. Based on currently available clinical studies, we believe that AFREZZA may have certain advantages over currently approved insulin products including its approximation of the natural early insulin secretion normally seen in healthy individuals following the beginning of a meal. Nonetheless, there are no assurances that these or any other advantages of AFREZZA will be agreed to by the FDA or otherwise included in product labeling or advertising and, as a result, AFREZZA may not have our expected competitive advantages when compared to other insulin products.

The manufacture, marketing and sale of any of our product candidates will be subject to stringent and ongoing government regulation. The FDA may also withdraw product approvals if problems concerning the safety or efficacy of a product appear following approval. We cannot be sure that FDA and United States Congressional initiatives pertaining to ensuring the safety of marketed drugs or other developments pertaining to the pharmaceutical industry will not adversely affect our operations.

We also are required to register our establishments and list our products with the FDA and certain state agencies. We and any third-party manufacturers or suppliers must continually adhere to federal regulations setting forth requirements, known as cGMP (for drugs) and QSR (for medical devices), and their foreign equivalents, which are enforced by the FDA and other national regulatory bodies through their facilities inspection programs. If our facilities, or the facilities of our manufacturers or suppliers, cannot pass a preapproval plant inspection, the FDA will not approve the marketing of our product candidates. In complying with cGMP and foreign regulatory requirements, we and any of our potential third-party manufacturers or suppliers will be obligated to expend time, money and effort in production, record-keeping and quality control to ensure that our products meet applicable specifications and other requirements. QSR requirements also impose extensive testing, control and documentation requirements. State regulatory agencies and the regulatory agencies of other countries have similar requirements. In addition, we will be required to comply with regulatory requirements of the FDA, state regulatory agencies and the regulatory agencies of other countries concerning the reporting of adverse events and device malfunctions, corrections and removals (*e.g.*, recalls), promotion and advertising and general prohibitions against the manufacture and distribution of adulterated and misbranded devices. Failure to comply with these regulatory requirements could result in civil fines, product seizures, injunctions and/or criminal prosecution of responsible individuals and us. Any such actions would have a material adverse effect on our business and results of operations.

Our suppliers will be subject to FDA inspection before the agency approves an NDA for AFREZZA.

When we are required to find a new or additional supplier of insulin, we will be required to evaluate the new supplier s ability to provide insulin that meets regulatory requirements, including cGMP requirements as well as our specifications and quality requirements, which would require significant time and expense and could delay the manufacturing and future commercialization of AFREZZA. We also depend on suppliers for other materials that comprise AFREZZA, including our AFREZZA inhaler and cartridges. Each supplier must comply with relevant regulatory requirements including QSR, and is subject to inspection by the FDA. There can be no assurance, in the

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conduct of an inspection of any of our suppliers, that the agency would find that the supplier substantially complies with the QSR or cGMP requirements, where applicable. If we or any potential third-party manufacturer or supplier fails to comply with these requirements or comparable requirements in foreign countries, regulatory authorities may subject us to regulatory action, including criminal prosecutions, fines and suspension of the manufacture of our products.

Reports of side effects or safety concerns in related technology fields or in other companies clinical trials could delay or prevent us from obtaining regulatory approval or negatively impact public perception of our product candidates.

At present, there are a number of clinical trials being conducted by us and other pharmaceutical companies involving insulin delivery systems. If we discover that AFREZZA is associated with a significantly increased frequency of adverse events, or if other pharmaceutical companies announce that they observed frequent adverse events in their trials involving insulin therapies, we could encounter delays in the timing of our clinical trials or difficulties in obtaining approval of AFREZZA. As well, the public perception of AFREZZA might be adversely affected, which could harm our business and results of operations and cause the market price of our common stock to decline, even if the concern relates to another company s products or product candidates.

There are also a number of clinical trials being conducted by other pharmaceutical companies involving compounds similar to, or competitive with, our other product candidates. Adverse results reported by these other companies in their clinical trials could delay or prevent us from obtaining regulatory approval or negatively impact public perception of our product candidates, which could harm our business and results of operations and cause the market price of our common stock to decline.

RISKS RELATED TO INTELLECTUAL PROPERTY

If we are unable to protect our proprietary rights, we may not be able to compete effectively, or operate profitably.

Our commercial success depends, in large part, on our ability to obtain and maintain intellectual property protection for our technology. Our ability to do so will depend on, among other things, complex legal and factual questions, and it should be noted that the standards regarding intellectual property rights in our fields are still evolving. We attempt to protect our proprietary technology through a combination of patents, trade secrets and confidentiality agreements. We own a number of domestic and international patents, have a number of domestic and international patent applications pending and have licenses to additional patents. We cannot assure you that our patents and licenses will successfully preclude others from using our technologies, and we could incur substantial costs in seeking enforcement of our proprietary rights against infringement. Even if issued, the patents may not give us an advantage over competitors with alternative technologies.

Moreover, the issuance of a patent is not conclusive as to its validity or enforceability and it is uncertain how much protection, if any, will be afforded by our patents. A third party may challenge the validity or enforceability of a patent after its issuance by various proceedings such as oppositions in foreign jurisdictions or re-examinations in the United States. If we attempt to enforce our patents, they may be challenged in court where they could be held invalid, unenforceable, or have their breadth narrowed to an extent that would destroy their value.

We also rely on unpatented technology, trade secrets, know-how and confidentiality agreements. We require our officers, employees, consultants and advisors to execute proprietary information and invention and assignment agreements upon commencement of their relationships with us. We also execute confidentiality agreements with outside collaborators. There can be no assurance, however, that these agreements will provide meaningful protection for our inventions, trade secrets, know-how or other proprietary information in the event of unauthorized use or disclosure of such information. If any trade secret, know-how or other technology not protected by a patent were to be disclosed to or independently developed by a competitor, our business, results of operations and financial condition could be adversely affected.

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If we become involved in lawsuits to protect or enforce our patents or the patents of our collaborators or licensors, we would be required to devote substantial time and resources to prosecute or defend such proceedings.

Competitors may infringe our patents or the patents of our collaborators or licensors. To counter infringement or unauthorized use, we may be required to file infringement claims, which can be expensive and time-consuming. In addition, in an infringement proceeding, a court may decide that a patent of ours is not valid or is unenforceable, or may refuse to stop the other party from using the technology at issue on the grounds that our patents do not cover its technology. A court may also decide to award us a royalty from an infringing party instead of issuing an injunction against the infringing activity. An adverse determination of any litigation or defense proceedings could put one or more of our patents at risk of being invalidated or interpreted narrowly and could put our patent applications at risk of not issuing.

Interference proceedings brought by the U.S. Patent and Trademark Office may be necessary to determine the priority of inventions with respect to our patent applications or those of our collaborators or licensors. Litigation or interference proceedings may fail and, even if successful, may result in substantial costs and be a distraction to our management. We may not be able, alone or with our collaborators and licensors, to prevent misappropriation of our proprietary rights, particularly in countries where the laws may not protect such rights as fully as in the United States. We may not prevail in any litigation or interference proceeding in which we are involved. Even if we do prevail, these proceedings can be very expensive and distract our management.

Furthermore, because of the substantial amount of discovery required in connection with intellectual property litigation, there is a risk that some of our confidential information could be compromised by disclosure during this type of litigation. In addition, during the course of this kind of litigation, there could be public announcements of the results of hearings, motions or other interim proceedings or developments. If securities analysts or investors perceive these results to be negative, the market price of our common stock may decline.

If our technologies conflict with the proprietary rights of others, we may incur substantial costs as a result of litigation or other proceedings and we could face substantial monetary damages and be precluded from commercializing our products, which would materially harm our business.

Over the past three decades the number of patents issued to biotechnology companies has expanded dramatically. As a result it is not always clear to industry participants, including us, which patents cover the multitude of biotechnology product types. Ultimately, the courts must determine the scope of coverage afforded by a patent and the courts do not always arrive at uniform conclusions.

A patent owner may claim that we are making, using, selling or offering for sale an invention covered by the owner s patents and may go to court to stop us from engaging in such activities. Such litigation is not uncommon in our industry.

Patent lawsuits can be expensive and would consume time and other resources. There is a risk that a court would decide that we are infringing a third party s patents and would order us to stop the activities covered by the patents, including the commercialization of our products. In addition, there is a risk that we would have to pay the other party damages for having violated the other party s patents (which damages may be increased, as well as attorneys fees ordered paid, if infringement is found to be willful), or that we will be required to obtain a license from the other party in order to continue to commercialize the affected products, or to design our products in a manner that does not infringe a valid patent. We may not prevail in any legal action, and a required license under the patent may not be available on acceptable terms or at all, requiring cessation of activities that were found to infringe a valid patent. We also may not be able to develop a non-infringing product design on commercially reasonable terms, or at all.

Moreover, certain components of AFREZZA and/or our cancer vaccines may be manufactured outside the United States and imported into the United States. As such, third parties could file complaints under 19 U.S.C. Section 337(a)(1)(B), or a 337 action, with the International Trade Commission, or the ITC. A 337 action can be expensive and would consume time and other resources. There is a risk that the ITC would decide that we are infringing a third party s patents and either enjoin us from importing the infringing products or parts thereof into the United States or set a bond in an amount that the ITC considers would offset our competitive advantage from the

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continued importation during the statutory review period. The bond could be up to 100% of the value of the patented products. We may not prevail in any legal action, and a required license under the patent may not be available on acceptable terms, or at all, resulting in a permanent injunction preventing any further importation of the infringing products or parts thereof into the United States. We also may not be able to develop a non-infringing product design on commercially reasonable terms, or at all.

Although we own a number of domestic and foreign patents and patent applications relating to AFREZZA and cancer vaccine products under development, we have identified certain third-party patents having claims relating to pulmonary insulin delivery that may trigger an allegation of infringement upon the commercial manufacture and sale of AFREZZA, as well as third-party patents disclosing methods of use and compositions of matter related to cancer vaccines that also may trigger an allegation of infringement upon the commercial manufacture and sale of our cancer immunotherapy. If a court were to determine that our insulin products or cancer therapies were infringing any of these patent rights, we would have to establish with the court that these patents were invalid or unenforceable in order to avoid legal liability for infringement of these patents. However, proving patent invalidity or unenforceability can be difficult because issued patents are presumed valid. Therefore, in the event that we are unable to prevail in a non-infringement or invalidity action we will have to either acquire the third-party patents outright or seek a royalty-bearing license. Royalty-bearing licenses effectively increase production costs and therefore may materially affect product profitability. Furthermore, should the patent holder refuse to either assign or license us the infringed patents, it may be necessary to cease manufacturing the product entirely and/or design around the patents, if possible. In either event, our business would be harmed and our profitability could be materially adversely impacted.

Furthermore, because of the substantial amount of discovery required in connection with intellectual property litigation, there is a risk that some of our confidential information could be compromised by disclosure during this type of litigation. In addition, during the course of this kind of litigation, there could be public announcements of the results of hearings, motions or other interim proceedings or developments. If securities analysts or investors perceive these results to be negative, the market price of our common stock may decline.

In addition, patent litigation may divert the attention of key personnel and we may not have sufficient resources to bring these actions to a successful conclusion. At the same time, some of our competitors may be able to sustain the costs of complex patent litigation more effectively than we can because they have substantially greater resources. An adverse determination in a judicial or administrative proceeding or failure to obtain necessary licenses could prevent us from manufacturing and selling our products or result in substantial monetary damages, which would adversely affect our business and results of operations and cause the market price of our common stock to decline.

We may not obtain trademark registrations for our potential trade names.

We have not selected trade names for some of our product candidates; therefore, we have not filed trademark registrations for all of our potential trade names for our product candidates in all jurisdictions, nor can we assure that we will be granted registration of those potential trade names for which we have filed. Although we intend to defend any opposition to our trademark registrations, no assurance can be given that any of our trademarks will be registered in the United States or elsewhere or that the use of any of our trademarks will confer a competitive advantage in the marketplace. Furthermore, even if we are successful in our trademark registrations, the FDA has its own process for drug nomenclature and its own views concerning appropriate proprietary names. It also has the power, even after granting market approval, to request a company to reconsider the name for a product because of evidence of confusion in the marketplace. We cannot assure you that the FDA or any other regulatory authority will approve of any of our trademarks or will not request reconsideration of one of our trademarks at some time in the future.

RISKS RELATED TO OUR COMMON STOCK

Our stock price is volatile.

The stock market, particularly in recent years, has experienced significant volatility particularly with respect to pharmaceutical and biotechnology stocks, and this trend may continue. The volatility of pharmaceutical and biotechnology stocks often does not relate to the operating performance of the companies represented by the stock. Our business and the market price of our common stock may be influenced by a large variety of factors, including:

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- the progress and results of our clinical trials;
- general economic, political or stock market conditions;
- legislative developments;
- announcements by us or our competitors concerning clinical trial results, acquisitions, strategic alliances, technological innovations, newly approved commercial products, product discontinuations, or other developments;
- the availability of critical materials used in developing and manufacturing AFREZZA or other product candidates;
- developments or disputes concerning our patents or proprietary rights;
- the expense and time associated with, and the extent of our ultimate success in, securing regulatory approvals;
- announcements by us concerning our financial condition or operating performance;
- changes in securities analysts estimates of our financial condition or operating performance;
- general market conditions and fluctuations for emerging growth and pharmaceutical market sectors;
- the issuance and sale of our common stock pursuant to the Seaside purchase agreement and the Mann purchase agreement over the terms of these agreements;
- sales of large blocks of our common stock, including sales by our executive officers, directors and significant stockholders;
- the status of litigation against us and certain of our executive officers and directors;
- the existence of, and the issuance of shares of our common stock pursuant to, the share lending agreement and the short sales of our common stock effected in connection with the recently-completed sale of our 5.75% convertible notes due 2015; and
- discussion of AFREZZA, our other product candidates, competitors products, or our stock price by the financial and scientific press, the healthcare community and online investor communities such as chat rooms. In particular, statements about us and our investigational products that appear on interactive websites that permit users to generate content anonymously or under a pseudonym may be difficult to verify and statements attributed to company officials may, in fact, have originated elsewhere.

Any of these risks, as well as other factors, could cause the market price of our common stock to decline.

If other biotechnology and biopharmaceutical companies or the securities markets in general encounter problems, the market price of our common stock could be adversely affected.

Public companies in general and companies included on the Nasdaq Global Market in particular have experienced extreme price and volume fluctuations that have often been unrelated or disproportionate to the operating performance of those companies. There has been particular volatility in the market prices of securities of biotechnology and other life sciences companies, and the market prices of these companies have often fluctuated because of problems or successes in a given market segment or because investor interest has shifted to other segments. These broad market and industry factors may cause the market price of our common stock to decline, regardless of our operating performance. We have no control over this volatility and can only focus our efforts on our own operations, and even these may be affected due to the state of the capital markets.

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In the past, following periods of large price declines in the public market price of a company s securities, securities class action litigation has often been initiated against that company. Litigation of this type could result in substantial costs and diversion of management s attention and resources, which would hurt our business. Any adverse determination in litigation could also subject us to significant liabilities.

Our Chairman and Chief Executive Officer and principal stockholder can individually control our direction and policies, and his interests may be adverse to the interests of our other stockholders. After his death, his stock will be left to his funding foundations for distribution to various charities, and we cannot assure you of the manner in which those entities will manage their holdings.

At December 31, 2010, Mr. Mann beneficially owned approximately 39.2% of our outstanding shares of capital stock. By virtue of his holdings, Mr. Mann may be able to continue to effectively control the election of the members of our board of directors, our management and our affairs and prevent corporate transactions such as mergers, consolidations or the sale of all or substantially all of our assets that may be favorable from our standpoint or that of our other stockholders or cause a transaction that we or our other stockholders may view as unfavorable.

Subject to compliance with United States federal and state securities laws, Mr. Mann is free to sell the shares of our stock he holds at any time. Upon his death, we have been advised by Mr. Mann that his shares of our capital stock will be left to the Alfred E. Mann Medical Research Organization, or AEMMRO, and AEM Foundation for Biomedical Engineering, or AEMFBE, not-for-profit medical research foundations that serve as funding organizations for Mr. Mann s various charities, including the Alfred Mann Foundation, or AMF, and the Alfred Mann Institutes at the University of Southern California, the Technion-Israel Institute of Technology, and Purdue University, and that may serve as funding organizations for any other charities that he may establish. The AEMMRO is a membership foundation consisting of six members, including Mr. Mann, his wife, three of his children and Dr. Joseph Schulman, the chief scientist of the AEMFBE. The AEMFBE is a membership foundation consisting of five members, including Mr. Mann, his wife, and the same three of his children. Although we understand that the members of AEMMRO and AEMFBE have been advised of Mr. Mann s objectives for these foundations, once Mr. Mann s shares of our capital stock become the property of the foundations, we cannot assure you as to how those shares will be distributed or how they will be voted.

The future sale of our common stock or the conversion of our senior convertible notes into common stock could negatively affect our stock price.

As of December 31, 2010, we had 127,793,178 shares of common stock outstanding. Substantially all of these shares are available for public sale, subject in some cases to volume and other limitations or delivery of a prospectus. If our common stockholders sell substantial amounts of common stock in the public market, or the market perceives that such sales may occur, the market price of our common stock may decline. Likewise the issuance of additional shares of our common stock upon the conversion of some or all of our senior convertible notes could adversely affect the trading price of our common stock. In addition, the existence of these notes may encourage short selling of our common stock by market participants. Furthermore, if we were to include in a company-initiated registration statement shares held by our stockholders pursuant to the exercise of their registration rights, the sale of those shares could impair our ability to raise needed capital by depressing the price at which we could sell our common stock.

On August 10, 2010, we entered into the Seaside purchase agreement and the Mann purchase agreement, which together provide for the sale and issuance by us of up to 36,400,000 shares of our common stock over a period of approximately 50 weeks. As of December 31, 2010, we issued and sold a total of 4,200,000 shares under these agreements. The future issuance of shares of our common stock pursuant to these two agreements, or the expectation that these issuances will occur, may further depress the price of our common stock.

In addition, we will need to raise substantial additional capital in the future to fund our operations. If we raise additional funds by issuing equity securities or additional convertible debt, the market price of our common stock may decline and our existing stockholders may experience significant dilution.

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We have reserved for future issuance substantially all of our authorized but unissued shares of common stock, which may impair our ability to conduct future financing and other transactions.

Our certificate of incorporation currently authorizes us to issue up to 200,000,000 shares of common stock and 10,000,000 shares of preferred stock. As of December 31, 2010, we had a total of 72,206,822 shares of common stock that were authorized but unissued. We have reserved substantially all of our authorized but unissued shares for future issuance pursuant to outstanding equity awards, our equity plans, our 3.75% senior convertible notes due 2013, our 5.75% senior convertible notes due 2015 and the Seaside purchase agreement and Mann purchase agreement. As a result, our ability to issue shares of common stock other than pursuant to existing arrangements will be limited until such time, if ever, that we are able to amend our certificate of incorporation to further increase our authorized shares of common stock or shares currently reserved for issuance otherwise become available (for example, due to the termination of the underlying agreement to issue the shares).

If we are unable to enter into new arrangements to issue shares of our common stock or securities convertible or exercisable into shares of our common stock, our ability to complete equity-based financings or other transactions that involve the potential issuance of our common stock or securities convertible or exercisable into our common stock, will be limited. In lieu of issuing common stock or securities convertible into our common stock in any future equity financing transactions, we may need to issue some or all of our authorized but unissued shares of preferred stock, which would likely have superior rights, preferences and privileges to those of our common stock, or we may need to issue debt that is not convertible into shares of our common stock, which may require us to grant security interests in our assets and property and/or impose covenants upon us that restrict our business. If we are unable to issue additional shares of common stock or securities convertible or exercisable into our common stock, our ability to enter into strategic transactions such as acquisitions of companies or technologies, may also be limited. If we propose to amend our certificate of incorporation to increase our authorized shares of common stock, such a proposal would require the approval by the holders of a majority of our outstanding shares of common stock, and we cannot assure you that such a proposal would be adopted. If we are unable to complete financing, strategic or other transactions due to our inability to issue additional shares of common stock or securities convertible or exercisable into our common stock, our financial condition and business prospects may be materially harmed.

Anti-takeover provisions in our charter documents and under Delaware law could make an acquisition of us, which may be beneficial to our stockholders, more difficult and may prevent attempts by our stockholders to replace or remove our current management.

We are incorporated in Delaware. Certain anti-takeover provisions under Delaware law and in our certificate of incorporation and amended and restated bylaws, as currently in effect, may make a change of control of our company more difficult, even if a change in control would be beneficial to our stockholders. Our anti-takeover provisions include provisions such as a prohibition on stockholder actions by written consent, the authority of our board of directors to issue preferred stock without stockholder approval, and supermajority voting requirements for specified actions. In addition, we are governed by the provisions of Section 203 of the Delaware General Corporation Law, which generally prohibits stockholders owning 15% or more of our outstanding voting stock from merging or combining with us in certain circumstances. These provisions may delay or prevent an acquisition of us, even if the acquisition may be considered beneficial by some of our stockholders. In addition, they may frustrate or prevent any attempts by our stockholders to replace or remove our current management by making it more difficult for stockholders to replace members of our board of directors, which is responsible for appointing the members of our management.

Because we do not expect to pay dividends in the foreseeable future, you must rely on stock appreciation for any return on your investment.

We have paid no cash dividends on any of our capital stock to date, and we currently intend to retain our future earnings, if any, to fund the development and growth of our business. As a result, we do not expect to pay any cash dividends in the foreseeable future, and payment of cash dividends, if any, will also depend on our financial condition, results of operations, capital requirements and other factors and will be at the discretion of our board of directors. Furthermore, we may in the future become subject to contractual restrictions on, or prohibitions against, the payment of dividends. Accordingly, the success of your investment in our common stock will likely depend entirely upon any

future appreciation. There is no guarantee that our common stock will appreciate or maintain its current price. You could lose the entire value of your investment in our common stock.

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Item 1B. ***Unresolved Staff Comments***

None.

Item 2. ***Properties***

In 2001, we acquired a facility in Danbury, Connecticut that included two buildings comprising approximately 190,000 square feet encompassing 17.5 acres. In September 2008, we completed the construction of approximately 140,000 square feet of new manufacturing space providing us with two buildings totaling approximately 328,000 square feet, housing our research and development, administrative and manufacturing functions, primarily for AFREZZA, filling and packaging. We believe the Danbury facility will have sufficient space to satisfy potential commercial demand for the launch of AFREZZA and, with the expansion completed, the first few years thereafter for AFREZZA and other AFREZZA-related products.

We own and occupy approximately 142,000 square feet of laboratory, office and warehouse space in Valencia, California. The facility contains our principal executive offices and houses our research and development laboratories for our cancer and other programs. We also use this facility to provide support for the development of our AFREZZA programs.

We lease approximately 23,000 square feet of office space in Paramus, New Jersey pursuant to a lease that expires in May 2012.

Item 3. ***Legal Proceedings***

On November 23, 2010, John Arditi, our former Senior Director GCP Regulatory Affairs, filed a Demand for Arbitration against us and three employees our Chief Scientific Officer, our Vice President World Wide Regulatory Affairs, and our Chief Financial Officer claiming that we terminated his employment in retaliation for his purported reporting of alleged unlawful practices in connection with our clinical trials. Mr. Arditi has asserted claims for violation of the New Jersey Conscientious Employee Protection Act, wrongful discharge, breach of contract, breach of the implied covenant of good faith and fair dealing, defamation and intentional infliction of emotional distress. Mr. Arditi is seeking, among other relief, compensatory and punitive damages and counsel fees, costs and interest. Before Mr. Arditi filed his arbitration demand, we had completed an internal investigation and retained an independent outside firm to conduct an independent investigation of Mr. Arditi s claims. Neither investigation found any basis for his claims. We believe the allegations made by Mr. Arditi are without merit and we intend to defend against them vigorously.

Following the receipt by us of the Complete Response letter from the FDA regarding the NDA for AFREZZA in January 2011 and the subsequent decline of the price of our common stock, several complaints were filed in the U.S. District Court for the Central District of California against us and certain of our officers and directors on behalf of certain purchasers of our common stock. The complaints include claims asserted under Sections 10(b) and 20(a) of the Exchange Act and have been brought as purported shareholder class actions. In general, the complaints allege that we and certain of our officers and directors violated federal securities laws by making materially false and misleading statements regarding our business and prospects for AFREZZA, thereby artificially inflating the price of our common stock. The plaintiffs are seeking unspecified monetary damages and other relief. The complaints have been transferred to a single court and consolidated for all purposes. We expect the court to appoint a lead plaintiff and lead counsel and to order the lead plaintiff to file a consolidated complaint. We will vigorously defend against the claims advanced.

In February 2011, a shareholder derivative complaint was filed in the Superior Court of California for the County of Los Angeles against our directors and certain of our officers. The complaints in the shareholder derivative action allege breaches of fiduciary duties by the defendants and other violations of law. In general, the complaint alleges that our directors and certain of our officers caused or allowed for the dissemination of materially false and misleading statements regarding our business and prospects for AFREZZA, thereby artificially inflating the price of our common stock. The plaintiffs are seeking unspecified monetary damages and other relief, including reforms to our corporate governance and internal procedures. We will vigorously defend against the claims advanced.

Item 4. ***(Removed and Reserved)***

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PART II

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

Common Stock Market Price

Our common stock has been traded on the Nasdaq Global Market under the symbol MNKD since July 28, 2004. The following table sets forth for the quarterly periods indicated, the high and low sales prices for our common stock as reported by the Nasdaq Global Market.

	High	Low
Year ended December 31, 2009		
First quarter	$ 4.09	$2.00
Second quarter	$ 9.25	$3.35
Third quarter	$12.30	$6.62
Fourth quarter	$ 9.94	$5.02
Year ended December 31, 2010		
First quarter	$11.12	$6.35
Second quarter	$ 7.33	$4.76
Third quarter	$ 7.36	$5.50
Fourth quarter	$ 9.23	$5.07

The closing sales price of our common stock on the Nasdaq Global Market was $3.86 on February 18, 2011 and there were 192 registered holders of record as of that date.

Performance Measurement Comparison

The material in this section is not soliciting material, is not deemed filed with the SEC and shall not be incorporated by reference by any general statement incorporating by reference this Annual Report on Form 10-K into any of our filings under the Securities Act of 1933, as amended, or the Securities Act, or the Exchange Act of 1934, as amended, or the Exchange Act, except to the extent we specifically incorporate this section by reference.

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Performance Measurement Comparison

The following graph illustrates a comparison of the cumulative total stockholder return (change in stock price plus reinvested dividends) of our common stock with (i) the Nasdaq Composite Index and (ii) the Nasdaq Biotechnology Index. The comparisons in the graph are required by the SEC and are not intended to forecast or be indicative of possible future performance of our common stock.

Assumes a $100 investment, on December 31, 2005, in (i) our common stock, (ii) the securities comprising the Nasdaq Composite Index and (iii) the securities comprising the Nasdaq Biotechnology Index.

Dividend Policy

We have never declared or paid any cash dividends on our common stock. We currently intend to retain all available funds and any future earnings for use in the operation and expansion of our business. Accordingly, we do not anticipate paying any cash dividends on our common stock in the foreseeable future. Any future determination to pay dividends will be at the discretion of our board of directors.

Recent Sales of Unregistered Securities

The following list sets forth information regarding all securities sold by us during the fiscal year ended December 31, 2010 without registration under the Securities Act:

(1) On October 20, 2010, we issued 700,000 shares of our common stock to The Mann Group, an entity controlled by our principal stockholder.

(2) On December 15, 2010, we issued 700,000 shares of our common stock to The Mann Group.

(3) On December 29, 2010, we issued 700,000 shares of our common stock to The Mann Group.

The aggregate purchase price of the above transactions was approximately $16.7 million, which was paid by cancelling an equal amount of the outstanding principal under an existing $350.0 million revolving loan arrangement provided by The Mann Group. The offers, sales, and issuances of the securities described above were

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deemed to be exempt from registration under the Securities Act in reliance on Section 4(2) of the Securities Act and/or Rule 506 of Regulation D in that the issuance of securities to the accredited investors did not involve a public offering. The Mann Group was an accredited investor under Rule 501 of Regulation D. The Mann Group acquired the securities for investment only and not with a view to or for sale in connection with any distribution thereof and appropriate legends were affixed to the securities issued in these transactions.

Item 6. ***Selected Financial Data***

The following selected consolidated financial data should be read in conjunction with our consolidated financial statements and notes thereto and with Management s Discussion and Analysis of Financial Condition and Results of Operations, which are included elsewhere in this Annual Report on Form 10-K.

	Year Ended December 31,				
Statement of Operations Data:	**2006**	**2007**	**2008**	**2009**	**2010**
	(In thousands, except per share amounts)				
Revenue	$ 100	$ 10	$ 20	$	$ 93
Operating expenses:					
Research and development	191,796	256,844	250,442	156,331	112,279
General and administrative	42,001	50,523	55,343	53,447	40,312
Total operating expenses	233,797	307,367	305,785	209,778	152,591
Loss from operations	(233,697)	(307,357)	(305,765)	(209,778)	(152,498)
Other income (expense)	208	(197)	(62)	51	(725)
Interest expense on note payable to principal stockholder	(1,511)		(12)	(5,679)	(10,249)
Interest expense on senior convertible notes	(222)	(3,408)	(2,327)	(4,768)	(7,128)
Interest income	4,679	17,775	5,129	70	40
Loss before provision for income taxes	(230,543)	(293,187)	(303,037)	(220,104)	(170,560)
Income taxes	(5)	(3)	(2)		
Net loss applicable to common stockholders	$ (230,548)	$ (293,190)	$ (303,039)	$ (220,104)	$ (170,560)
Basic and diluted net loss per share	$ (4.52)	$ (3.66)	$ (2.98)	$ (2.07)	$ (1.50)
Shares used to compute basic and diluted net loss per share	50,970	80,038	101,561	106,534	113,672

	December 31,				
Balance Sheet Data:	**2006**	**2007**	**2008**	**2009**	**2010**
	(In thousands)				
Cash, cash equivalents and marketable securities	$ 436,479	$ 368,285	$ 46,492	$ 32,494	$ 70,431
Working capital	404,588	311,154	503	8,813	55,820
Total assets	539,737	543,443	282,459	247,397	277,256
Other liabilities	24	24			

Senior convertible notes	111,267	111,761	112,253	112,765	209,335
Note payable to related party			30,000	165,000	235,319
Deficit accumulated during the development stage	(787,849)	(1,081,039)	(1,384,078)	(1,604,182)	(1,774,742)
Total stockholders equity (deficit)	383,487	364,100	86,734	(59,221)	(185,532)

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

The following discussion of our financial condition and results of operations should be read in conjunction with our consolidated financial statements and notes thereto included in this Annual Report on Form 10-K.

OVERVIEW

We are a biopharmaceutical company focused on the discovery, development and commercialization of therapeutic products for diseases such as diabetes and cancer. Our lead product candidate, AFREZZA (insulin human [rDNA origin]) Inhalation Powder, is an ultra rapid-acting insulin therapy that is in late-stage clinical investigation for the treatment of adults with type 1 or type 2 diabetes for the control of hyperglycemia.

We are a development stage enterprise and have incurred significant losses since our inception in 1991. As of December 31, 2010, we have incurred a cumulative net loss of $1.8 billion and a stockholders deficit of $185.5 million. To date, we have not generated any product revenues and have funded our operations primarily through the sale of equity securities and convertible debt securities and borrowings under a loan arrangement provided by our principal stockholder. As discussed below in Liquidity and Capital Resources, if we are unable to obtain additional funding in the future, there will be substantial doubt about our ability to continue as a going concern.

We have held extensive discussions with a number of pharmaceutical companies concerning a potential strategic business collaboration for AFREZZA. We cannot predict when, if ever, we could conclude an agreement with a partner. There can be no assurance that any such collaboration will be available to us on a timely basis or on acceptable terms, if at all.

We do not expect to record sales of any product prior to regulatory approval and commercialization of AFREZZA. We currently do not have the required approvals to market any of our product candidates, and we may not receive such approvals. We may not be profitable even if we succeed in commercializing any of our product candidates. We expect to make substantial expenditures and to incur additional operating losses as we:

- continue the clinical development of AFREZZA for the treatment of diabetes;
- seek regulatory approval to sell AFREZZA in the United States and other markets; and
- pursue development and commercialization collaborations with other companies, if available on commercially reasonable terms.

Our business is subject to significant risks, including but not limited to the risks inherent in our ongoing clinical trials and the regulatory approval process, the results of our research and development efforts, competition from other products and technologies and uncertainties associated with obtaining and enforcing patent rights.

RESEARCH AND DEVELOPMENT EXPENSES

Our research and development expenses consist mainly of costs associated with the clinical trials of our product candidates that have not yet received regulatory approval for marketing and for which no alternative future use has been identified. This includes the salaries, benefits and stock-based compensation of research and development personnel, raw materials, such as insulin purchases, laboratory supplies and materials, facility costs, costs for consultants and related contract research, licensing fees, and depreciation of laboratory equipment. We track research and development costs by the type of cost incurred. We partially offset research and development expenses with the recognition of estimated amounts receivable from the State of Connecticut pursuant to a program under which we can exchange qualified research and development income tax credits for cash. Included in research and development expenses for the year ended December 31, 2010 were purchases of insulin totaling $16.3 million.

Our research and development staff conducts our internal research and development activities, which include research, product development, clinical development, manufacturing and related activities. This staff is located in our facilities in Valencia, California; Paramus, New Jersey; and Danbury, Connecticut. We expense research and development costs as we incur them.

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Clinical development timelines, likelihood of success and total costs vary widely. We are focused primarily on advancing AFREZZA through regulatory filings.

At this time, due to the risks inherent in the clinical trial process and given the early stage of development of our product candidates other than AFREZZA, we are unable to estimate with any certainty the costs that we will incur in the continued development of our product candidates for commercialization. The costs required to complete the development of AFREZZA will be largely dependent on the cost and efficiency of our clinical trial operations and discussions with the FDA regarding its requirements.

GENERAL AND ADMINISTRATIVE EXPENSES

Our general and administrative expenses consist primarily of salaries, benefits and stock-based compensation for administrative, finance, business development, human resources, legal and information systems support personnel. In addition, general and administrative expenses include professional service fees and business insurance costs.

CRITICAL ACCOUNTING POLICIES

We have based our discussion and analysis of our financial condition and results of operations on our financial statements, which have been prepared in accordance with accounting principles generally accepted in the United States. The preparation of these financial statements requires us to make estimates and judgments that affect the reported amounts of assets, liabilities and expenses. We evaluate our estimates and judgments on an ongoing basis. We base our estimates on historical experience and on various assumptions that we believe to be reasonable under the circumstances, the results of which form the basis for making estimates of expenses such as stock option expenses and judgments about the carrying values of assets and liabilities. Actual results may differ from these estimates under different assumptions or conditions. The significant accounting policies that are critical to the judgments and estimates used in the preparation of our financial statements are described in more detail below.

Impairment of long-lived assets

Assessing long-lived assets for impairment requires us to make assumptions and judgments regarding the carrying value of these assets. We evaluate long-lived assets for impairment whenever events or changes in circumstances indicate that the carrying value of an asset may not be recoverable. The assets are considered to be impaired if we determine that the carrying value may not be recoverable based upon our assessment of the following events or changes in circumstances:

- significant changes in our strategic business objectives and utilization of the assets;
- a determination that the carrying value of such assets cannot be recovered through undiscounted cash flows;
- loss of legal ownership or title to the assets;
- a significant adverse change in legal factors or in the business climate that could affect the value of a long-lived asset (asset group), including an adverse action or assessment by a regulator; or
- the impact of significant negative industry or economic trends.

If we believe our assets to be impaired, the impairment we recognize is the amount by which the carrying value of the assets exceeds the fair value of the assets. Any write-downs would be treated as permanent reductions in the carrying amount of the asset and an operating loss would be recognized. In addition, we base the useful lives and related amortization or depreciation expense on our estimate of the useful lives of the assets. If a change were to occur in any of the above-mentioned factors or estimates, our reported results could materially change.

To date, we have had recurring operating losses, and the recoverability of our long-lived assets is contingent upon executing our business plan. If we are unable to execute our business plan, we may be required to write down the value of our long-lived assets in future periods.

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Clinical trial expenses

Our clinical trial accrual process seeks to account for expenses resulting from our obligations under contract with vendors, consultants, and clinical site agreements in connection with conducting clinical trials. The financial terms of these contracts are subject to negotiations which vary from contract to contract and may result in payment flows that do not match the periods over which materials or services are provided to us under such contracts. Our objective is to reflect the appropriate trial expenses in our financial statements by matching period expenses with period services and efforts expended. We account for these expenses according to the progress of the trial as measured by patient progression and the timing of various aspects of the trial. We determine accrual estimates through discussions with internal clinical personnel and outside service providers as to the progress or state of completion of trials, or the services completed. Service provider status is then compared to the contractual obligated fee to be paid for such services. During the course of a clinical trial, we adjust our rate of clinical expense recognition if actual results differ from our estimates. In the event that we do not identify certain costs that have begun to be incurred or we underestimate or overestimate the level of services performed or the costs of such services, our reported expenses for a period would be too low or too high. The date on which certain services commence, the level of services performed on or before a given date and the cost of the services are often judgmental. We make these judgments based upon the facts and circumstances known to us in accordance with generally accepted accounting principles.

Stock-based compensation

We account for stock-based compensation in accordance with Financial Accounting Standards Board (FASB) Accounting Standards Codification (ASC) 718 (ASC 718) *Compensation- Stock Compensation*, previously FASB Statement No. 123R, *Accounting for Stock-Based Compensation*. ASC 718 requires all share-based payments to employees, including grants of stock options, restricted stock units, performance-based awards and the compensatory elements of employee stock purchase plans, to be recognized in the income statement based upon the fair value of the awards at the grant date. We use the Black-Scholes option valuation model to estimate the grant date fair value of employee stock options and the compensatory elements of employee stock purchase plans. Restricted stock units are valued based on the market price on the grant date. We evaluate stock awards with performance conditions as to the probability that the performance conditions will be met and estimate the date at which the performance conditions will be met in order to properly recognize stock-based compensation expense over the requisite service period.

Accounting for income taxes

We must make management judgments when determining our provision for income taxes, our deferred tax assets and liabilities and any valuation allowance recorded against our net deferred tax assets. At December 31, 2010, we have established a valuation allowance of $633.9 million against all of our net deferred tax asset balance, due to uncertainties related to our deferred tax assets as a result of our history of operating losses. The valuation allowance is based on our estimates of taxable income by jurisdiction in which we operate and the period over which our deferred tax assets will be recoverable. In the event that actual results differ from these estimates or we adjust these estimates in future periods, we may need to change the valuation allowance, which could materially impact our financial position and results of operations.

RESULTS OF OPERATIONS

Years ended December 31, 2010 and 2009

Revenues

During the year ended December 31, 2010 we recognized $93,000 in revenue, and during the year ended December 31, 2009, we recognized no revenue under a license agreement. We do not anticipate sales of any product prior to regulatory approval and commercialization of AFREZZA.

Research and Development Expenses

The following table provides a comparison of the research and development expense categories for the years ended December 31, 2010 and 2009 (dollars in thousands):

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	Year Ended December 31,			
	2010	2009	$ Change	% Change
Clinical	$ 23,558	$ 44,163	$ (20,605)	(47)%
Manufacturing	67,146	82,116	(14,970)	(18)%
Research	14,034	19,259	(5,225)	(27)%
Research and development tax credit	(385)	(1,322)	937	(71)%
Stock-based compensation expense	7,926	12,115	(4,189)	(35)%
Research and development expenses	$ 112,279	$ 156,331	$ (44,052)	(28)%

The decrease in research and development expenses for the year ended December 31, 2010, as compared to the year ended December 31, 2009, was primarily due to decreased costs associated with the clinical development of AFREZZA, including decreased raw material purchases and clinical supplies costs, offset by a loss on disposal of approximately $12.8 million in manufacturing expense related to the abandonment of MedTone specific assets, which would no longer be used as we pursue the commercialization of the next-generation device in 2010, reduced salary-related and other research costs as a result of a reduction in force that we implemented in April 2009 and decreased stock-based compensation expense related to reduced number of restricted stock units vesting in 2010 as compared to 2009. We anticipate that our research and development expenses will increase in 2011 as a result of costs associated with the clinical studies and other development activities in our effort to address the FDA s requests in the Complete Response letter received on January 18, 2011.

The research and development tax credit recognized for the years ended December 31, 2010 and 2009 partially offsets our research and development expenses. The State of Connecticut provides an opportunity to exchange certain research and development income tax credit carryforwards for cash in exchange for forgoing the carryforward of the research and development credits. Estimated amounts receivable under the program are recorded as a reduction of research and development expenses. During the years ended December 31, 2010 and 2009, research and development expenses were offset by $0.4 million and $1.3 million, respectively, in connection with the program. The decrease in the offset of research and development expenses resulted from reduced spending in Connecticut.

General and Administrative Expenses

The following table provides a comparison of the general and administrative expense categories for the years ended December 31, 2010 and 2009 (dollars in thousands):

	Year Ended December 31,			
	2010	2009	$ Change	% Change
Salaries, employee related and other general expenses	$ 34,658	$ 45,343	$ (10,685)	(24)%
Stock-based compensation expense	5,654	8,104	(2,450)	(30)%
General and administrative expenses	$ 40,312	$ 53,447	$ (13,135)	(25)%

The decrease in general and administrative expenses for the year ended December 31, 2010, as compared to the year ended December 31, 2009, was primarily due to decreased salary related costs resulting from the April 2009 reduction in force as well as non-recurrence of costs related to the Pfizer transaction during the first half of 2009 and decreased professional fees related to market studies conducted in 2009. Additionally, stock-based compensation expense decreased as a result of reduced number of restricted stock units vesting in 2010 as compared to 2009. We expect general and administrative expenses to decrease in 2011 as a result of the reduction of force implemented in February 2011.

Other Income (Expense)

Other expense for the year ended December 31, 2010 increased, as compared to the year ended December 31, 2009, as we recognized a $0.6 million other-than-temporary impairment loss on our common stock investment due to the length of time and the extent to which the fair value has been less than the amortized cost basis. In addition, we recorded a loss of $1.6 million on the execution of quarterly window forward contracts, offset by a reimbursement of $1.6 million received in connection with a soil cleanup plan.

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Interest Income and Expense

Interest expense for the year ended December 31, 2010 increased due to the convertible notes issued in August 2010 and related amortization of the debt issuance costs. Interest expense for the year ended December 31, 2010 also included interest related to additional amounts borrowed under the loan agreement with our principal stockholder.

Years ended December 31, 2009 and 2008

Revenues

During the year ended December 31, 2009 we recognized no revenue, and during the year ended December 31, 2008, we recognized $20,000 in revenue under a license agreement.

Research and Development Expenses

The following table provides a comparison of the research and development expense categories for the years ended December 31, 2009 and 2008 (dollars in thousands):

	Year Ended December 31,			
	2009	2008	$ Change	% Change
Clinical	$ 44,163	$ 114,922	$ (70,759)	(62)%
Manufacturing	82,116	92,935	(10,819)	(12)%
Research	19,259	30,081	(10,822)	(36)%
Research and development tax credit	(1,322)	(1,846)	524	(28)%
Stock-based compensation expense	12,115	14,350	(2,235)	(16)%
Research and development expenses	$ 156,331	$ 250,442	$ (94,111)	(38)%

The decrease in research and development expenses for the year ended December 31, 2009, as compared to the year ended December 31, 2008, was primarily due to decreased costs associated with the clinical development of AFREZZA as we completed our pivotal AFREZZA trials during 2008, including decreased raw material purchases and clinical supplies costs, offset by a loss on disposal of approximately $12.8 million in manufacturing expense related to the abandonment of MedTone specific assets. The decrease in research expenses reflects reduced salary-related and other research costs as a result of a reduction in force that we implemented in April 2009.

The research and development tax credit recognized for the years ended December 31, 2009 and 2008 partially offsets our research and development expenses. The State of Connecticut provides an opportunity to exchange certain research and development income tax credit carryforwards for cash in exchange for forgoing the carryforward of the research and development credits. Estimated amounts receivable under the program are recorded as a reduction of research and development expenses. During the years ended December 31, 2009 and 2008, research and development expenses were offset by $1.3 million and $1.8 million, respectively, in connection with Connecticut s income tax credit carryforward exchange program.

General and Administrative Expenses

The following table provides a comparison of the general and administrative expense categories for the years ended December 31, 2009 and 2008 (dollars in thousands):

	Year Ended December 31,			
	2009	2008	$ Change	% Change
Salaries, employee related and other general expenses	$ 45,343	$ 44,900	$ 443	1%
Stock-based compensation expense	8,104	10,443	(2,339)	(22)%