IDERA PHARMACEUTICALS, INC.
Form 10-K
March 14, 2012
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UNITED STATES

SECURITIES AND EXCHANGE COMMISSION

Washington, D.C. 20549

FORM 10-K

(Mark One)

þ **ANNUAL REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934**
For the Fiscal Year Ended December 31, 2011

OR

¨ **TRANSITION REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934**
For the Transition Period from to

Commission File Number: 001-31918

IDERA PHARMACEUTICALS, INC.

(Exact name of Registrant as specified in its charter)

Delaware	**04-3072298**
(State or other jurisdiction of incorporation or organization)	**(I.R.S. Employer Identification No.)**
167 Sidney Street **Cambridge, Massachusetts**	**02139** **(Zip Code)**
(Address of principal executive offices)	

(617) 679-5500

(Registrant s telephone number, including area code)

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

Title of Class:	Name of Each Exchange on Which Registered
Common Stock, $.001 par value	**NASDAQ Global Market**

(Including Associated Preferred Stock Purchase Rights)

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

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

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

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

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 (§ 232.405 of this chapter) during the preceding 12 months (or for such shorter period that the registrant was required to submit and post such files). Yes þ No ¨

Indicate by check mark if disclosure of delinquent filers pursuant to Item 405 of Regulation S-K (§ 229.405) is not contained herein, and will not be contained, to the best of the registrant s knowledge, in definitive proxy or information statements incorporated by reference in Part III of this Form 10-K or any amendment to this Form 10-K. þ

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

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

The aggregate market value of the voting and non-voting common equity held by non-affiliates of the registrant was $50,613,000 based on the last sale price of the registrant s common stock as reported on the NASDAQ Global Market on June 30, 2011. As of February 15, 2012, the registrant had 27,637,007 shares of common stock outstanding.

DOCUMENTS INCORPORATED BY REFERENCE

Portions of the Registrant s Proxy Statement with respect to the Annual Meeting of Stockholders to be held on May 23, 2012 are incorporated by reference into Items 10, 11, 12, 13 and 14 of Part III of this Form 10-K.

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IDERA PHARMACEUTICALS, INC.

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FORWARD-LOOKING STATEMENTS

This Annual Report on Form 10-K contains forward-looking statements within the meaning of Section 27A of the Securities Act of 1933, as amended, and Section 21E of the Securities Exchange Act of 1934, as amended. All statements, other than statements of historical fact, included or incorporated in this report regarding our strategy, future operations, collaborations, intellectual property, financial position, future revenues, projected costs, prospects, plans, and objectives of management are forward-looking statements. The words believes, anticipates, estimates, plans, expects, intends, may, could, should, potential, likely, projects, continue, will, and would and similar expressions forward-looking statements, although not all forward-looking statements contain these identifying words. We cannot guarantee that we actually will achieve the plans, intentions or expectations disclosed in our forward-looking statements and you should not place undue reliance on our forward-looking statements. There are a number of important factors that could cause our actual results to differ materially from those indicated or implied by forward-looking statements. These important factors include those set forth below under Part I, Item 1A Risk Factors. These factors and the other cautionary statements made in this Annual Report on Form 10-K should be read as being applicable to all related forward-looking statements whenever they appear in this Annual Report on Form 10-K. In addition, any forward-looking statements represent our estimates only as of the date that this Annual Report on Form 10-K is filed with the Securities and Exchange Commission and should not be relied upon as representing our estimates as of any subsequent date. We do not assume any obligation to update any forward-looking statements. We disclaim any intention or obligation to update or revise any forward-looking statement, whether as a result of new information, future events or otherwise.

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PART I.

Item 1. ***Business***

Overview

We are a clinical stage biotechnology company engaged in the discovery and development of novel synthetic DNA- and RNA- based drug candidates. We are developing drug candidates that are designed to modulate immune responses mediated through Toll-like Receptors, or TLRs. We believe that the modulation of immune responses through TLRs provides a rationale for the development of drug candidates to treat a broad range of diseases. We are also evaluating gene silencing oligonucleotides, or GSOs, which inhibit the production of disease-associated proteins by targeting RNA. We believe that our GSO technology provides us with a platform from which drug candidates for diverse disease indications can be developed.

TLRs are specific receptors present in immune system cells. Using a chemistry-based approach, we have created synthetic DNA- and RNA-based compounds that are targeted to TLRs 3, 7, 8, and 9. A TLR agonist is a compound that stimulates an immune response through the targeted TLR. A TLR antagonist is a compound that blocks activation of an immune response through the targeted TLR. Drug candidates are compounds that we are developing and that have not been approved for any commercial use.

We are focusing our internal development efforts on TLR-targeted clinical candidates for autoimmune and inflammatory diseases and cancer, and on the advancement of our GSO technology platform. We are seeking to advance our TLR-targeted programs in infectious diseases, respiratory diseases, hematologic oncology, and the use of TLR3 agonists in vaccine adjuvant applications through collaborative alliances with pharmaceutical companies. We currently are collaborating with Merck Sharp & Dohme Corp. (formerly Merck & Co., Inc.), which is referred to herein as Merck, for the use of agonists of TLRs 7, 8, and 9 as vaccine adjuvants for cancer, infectious diseases, and Alzheimer s disease.

Autoimmune and Inflammatory Disease Program. We are developing IMO-3100, an antagonist of TLR7 and TLR9, for the treatment of psoriasis. We plan to conduct a Phase 2 clinical trial of IMO-3100 in adult patients with moderate to severe plaque psoriasis, randomized into three arms over a four-week treatment period, which we expect to initiate in the second quarter of 2012. In the trial, we plan to evaluate two dose levels of IMO-3100 and a concurrent placebo arm. In addition, we have selected IMO-8400, an antagonist of TLRs 7, 8, and 9, for development in the treatment of lupus. We are conducting nonclinical studies of IMO-8400 to support the submission of an Investigational New Drug Application, or IND, for IMO-8400. We expect to submit this IND to the United States Food and Drug Administration, or FDA, in the fourth quarter of 2012. We have evaluated IMO-3100 and IMO-8400 in preclinical models of several autoimmune diseases including psoriasis, lupus, rheumatoid arthritis, and multiple sclerosis. In these models, treatment with IMO-3100 or IMO-8400 was associated with improvement in a number of disease parameters.

Cancer Program. IMO-2055, an agonist of TLR9, is in clinical development for the treatment of cancer. In November 2011, we reacquired rights to IMO-2055 from Merck KGaA, Darmstadt, Germany, our former collaborator. We believe that IMO-2055 can be developed for use as an immune modifier in combination with targeted anticancer agents. Recently, we announced favorable data from a Phase 1b clinical trial of IMO-2055 in combination with erlotinib and bevacizumab in patients with advanced non-small cell lung cancer. We anticipate top-line data from a randomized Phase 2 clinical trial of IMO-2055 in combination with cetuximab in second-line patients with squamous cell carcinoma of the head and neck in the second quarter of 2012. We also expect to have top-line data from a Phase 1b clinical trial of IMO-2055 in combination with cetuximab and chemotherapy in patients with advanced colorectal cancer in the second quarter of 2012.

Gene Silencing Oligonucleotide Technology Platform. Our GSOs are single-stranded RNA or DNA constructs that are complementary to targeted mRNA sequences of therapeutic interest. In preclinical studies, our GSOs have inhibited in vivo gene expression without requiring a delivery enhancement technology.

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Additional Programs. In addition to our clinical programs in autoimmune and inflammatory diseases and in cancer, we have identified TLR drug candidates for applications in the treatment of infectious diseases, respiratory diseases and hematological malignancies, and TLR3 agonists for use as vaccine adjuvants. We are seeking to enter into collaborations with pharmaceutical companies to advance these applications.

Overview of the Human Immune System

The immune system protects the body by working through various mechanisms to recognize and eliminate bacteria, viruses and other infectious agents, referred to as pathogens, and abnormal cells such as cancer cells. These mechanisms initiate a series of signals resulting in stimulation of the immune system in response to the pathogens or abnormal cells. The activities of the immune system are undertaken by its two components: the innate immune system and the adaptive immune system.

The role of the innate immune system is to provide a rapid, non-specific response to a pathogen or to abnormal cells in the body and to activate the adaptive immune system. The innate immune system consists of specialized cells such as macrophages, dendritic cells and monocytes. When the body recognizes a pathogen, it activates cells of the innate immune system, resulting in a cascade of signaling events that cause the production of proteins such as cytokines to fight the infection caused by the pathogen. Unlike the antibodies and cellular responses produced by the adaptive immune system as described below, the proteins produced by the innate immune system are not pathogen-specific. Moreover, once the pathogen is eliminated and the infection is resolved, the innate immune system will not remember the pathogen.

In contrast to the innate immune system, the adaptive immune system provides a pathogen-specific response to an infection. The adaptive immune system does this through the recognition by certain immune cells of specific proteins, called antigens, which are part of the pathogen or abnormal cell. Signals produced by the innate immune system initiate this process. Upon recognition of an antigen, which could come from pathogens or from cancer cells, the adaptive immune system produces antibodies and antigen-specific immune cells that specifically detect and destroy cells that contain the antigen. This response is referred to as an antigen-specific immune response. An antigen-specific immune response normally takes several weeks to develop the first time. However, once developed, the adaptive immune system remembers the antigen. In this manner, if the pathogen again infects the body, the presence of the memory immunity will allow the adaptive immune system to respond again in a shorter period of time.

TLR-based Drug Discovery Technology

The human immune system is activated by recognizing pathogen-associated molecular patterns, or PAMPs. TLRs comprise a family of receptors that are known to recognize PAMPs. The different TLRs are expressed in various immune system cells and recognize different PAMPs. TLR9 is a receptor that specifically recognizes a PAMP that occurs in the DNA of bacteria and other pathogens, and compounds that mimic bacterial DNA. TLR3, TLR7, and TLR8 are receptors that recognize viral RNA and compounds that mimic viral RNA.

Based on our extensive experience in DNA and RNA chemistry, we are designing and creating novel synthetic DNA- and RNA-based compounds, which as a chemical class are called oligonucleotides. Some of our compounds are designed to be agonists of TLR3, 7, 8, or 9. Others of our compounds are designed to be antagonists to TLRs 7 and 8 or to TLRs 7, 8, and 9.

TLR7, TLR8, and TLR9 Antagonists

We have created novel classes of drug candidates that are designed to be antagonists of specific TLRs. Preclinical studies from independent researchers have suggested that TLR7 and TLR9 may play a role in some autoimmune and inflammatory diseases, and that TLR8 may contribute to regulation of TLR7. In cell-based experiments and animal models, our antagonist compounds have blocked immune stimulation mediated through

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TLR7 and TLR9, or through TLRs 7, 8, and 9. We have evaluated our antagonist drug candidates in preclinical mouse models of human autoimmune and inflammatory diseases including lupus, rheumatoid arthritis, multiple sclerosis, psoriasis, colitis, pulmonary inflammation, and hyperlipidemia. In these models, treatment with our antagonist drug candidates was associated with improvement in a number of disease parameters. IMO-3100, a dual antagonist of TLR7 and TLR9, is in clinical development for the treatment of psoriasis. IMO-8400, an antagonist of TLRs 7, 8, and 9, is our lead candidate for the treatment of lupus.

TLR9 Agonists

Drug candidates that are agonists of TLR9 and induce immune responses through TLR9 may be useful for the treatment or prevention of infectious diseases, cancer, and asthma and allergies, and may be used as vaccine adjuvants. We have created our TLR9 agonist candidates to activate specific cells of the immune system and produce cytokines and other proteins. These activated cells and the cytokines and other proteins they produce lead to stimulation of both the innate and the adaptive components of the immune system. Furthermore, in preclinical cell culture and animal model studies, we have shown that we can change the immunological activity of our TLR9 agonists by modifying the chemical structure of the molecule. We are using our ability to change immunological activity of our TLR9 agonists to create a growing portfolio of drug candidates that are potentially useful for treating or preventing different diseases. One of our TLR9 drug candidates is IMO-2055, which is in clinical development for the treatment of cancer.

TLR7 and TLR8 Agonists

We have created novel synthetic RNA-based compounds that are agonists of TLR7 or dual agonists of TLR7 and TLR8. These compounds are designed to mimic viral RNA. In preclinical studies in cell culture and animal models, these TLR7 and dual TLR7 and TLR8 agonists induced immune responses that we believe may be useful for to the treatment of cancer and infectious diseases and as vaccine adjuvants. We have studied a dual TLR7 and TLR8 agonist, which we refer to as IMO-4200, in preclinical models of hematological cancers. In preclinical models, we have observed antitumor activity of IMO-4200 as a monotherapy and in combination with selected targeted drugs currently approved for cancer treatment.

TLR3 Agonists

We have created a new class of double-stranded RNA-based compounds that act as agonists of TLR3, and are evaluating their potential use as vaccine adjuvants. Vaccines are composed of one or more antigens and one or more adjuvants in an appropriate formulation. The function of the adjuvants is to enhance immune recognition of the antigens and increase the ability of the immune system to make antigen-specific antibodies. In preclinical models, our TLR3 agonists elicited production of cytokines and other proteins. Additionally, our TLR3 agonists promoted increased production of antigen-specific antibodies and cytotoxic T cells compared to responses induced by the antigen alone in preclinical vaccination studies.

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Research and Development Programs

We are engaged in the evaluation of TLR-targeted drug candidates in multiple therapeutic areas. The following table summarizes the disease areas and the development status of our programs.

RESEARCH AND DEVELOPMENT PROGRAMS

Drug candidate(s)	Application	Development Status
Autoimmune and Inflammatory Diseases		
IMO-3100	Psoriasis	Phase 2 Clinical Trial Expected to be Initiated 2Q 2012
IMO-8400	Lupus	IND-enabling Development Ongoing
Cancer		
IMO-2055 plus cetuximab	Squamous Cell, Head and Neck	Phase 2 Clinical Trial
IMO-2055 plus erlotinib and bevacizumab	Non-small Cell Lung Cancer	Phase 1b Clinical Trial
IMO-2055 plus cetuximab and FOLFIRI	Colorectal Cancer	Phase 1b Clinical Trial
Vaccine Adjuvants		
TLR7, 8, and 9 agonists	Cancer, Infectious Diseases, Alzheimer s Disease	Research in Collaboration with Merck
TLR3 agonists	Infectious Diseases and Other Applications	Research
Gene Silencing Oligonucleotides	Inhibition of Gene Expression by Targeting RNA	Research

Cetuximab, erlotinib, and bevacizumab are marketed under the names Erbitux®, Tarceva®, and Avastin®, respectively.

Research and Development Programs

Autoimmune and Inflammatory Diseases

In autoimmune diseases such as lupus, psoriasis, and rheumatoid arthritis, the immune system forms autoantibodies to a molecule that is a normal part of the body. The autoantibodies may bind RNA, DNA, or complexes that contain RNA or DNA. Independent researchers have reported that TLR7 and TLR9 may recognize autoantibody complexes that contain RNA or DNA and induce further immune responses that include cytokine production, inflammation, and tissue damage. TLR8 may play a role in regulating the activity of TLR7. Independent researchers have also reported that patients with autoimmune diseases such as lupus, psoriasis, and rheumatoid arthritis have increased incidence of hyperlipidemia and other cardiovascular risk factors.

We have created DNA-based compounds that in preclinical studies act as antagonists of TLR7 and TLR9, such as IMO-3100, or as antagonists of TLRs 7, 8, and 9, such as IMO-8400. We believe that these antagonists may have application in the treatment of autoimmune diseases by inhibiting TLR7-, TLR8-, or TLR9-mediated responses to the autoantibody complexes that contain RNA or DNA and thereby interfering with the inflammatory disease progression caused by activation of the immune system.

We continue to evaluate our TLR antagonist drug candidates in various preclinical studies. We have shown that treatment with IMO-3100 was associated with improvement in a number of disease parameters in mouse models of psoriasis, lupus, arthritis, and other autoimmune and inflammatory diseases.

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In November 2009, we submitted to the FDA an IND for the clinical evaluation of IMO-3100 in autoimmune diseases. Since that time, we have conducted two Phase 1 clinical trials of IMO-3100. In a single-dose Phase 1 clinical trial in 36 healthy subjects, IMO-3100 was administered by subcutaneous injection at five dose levels. At each dose level, six subjects received IMO-3100. An additional six subjects received placebo treatment. In a four-week multiple dose trial in 24 healthy subjects, IMO-3100 was administered at either 0.64 mg/kg once per week or at 0.32 mg/kg twice per week, with eight subjects per regimen. Eight additional subjects received placebo injections. IMO-3100 was well tolerated at all dose levels in both trials. There were no treatment-related discontinuations or serious adverse events. Mild injection site reactions were the most frequent adverse event. In both trials, the intended target engagement of TLR7 and TLR9 was observed through inhibition of TLR7- and TLR9-mediated cytokine induction in peripheral blood mononuclear cells from study subjects following IMO-3100 treatment.

Following those Phase 1 clinical trials, we selected psoriasis as the initial autoimmune disease indication for further clinical evaluation of IMO-3100. In June 2011, we submitted a Phase 2 protocol to the FDA to conduct a 12-week clinical trial of IMO-3100 in patients with psoriasis. In July 2011, the FDA placed a clinical hold on the protocol that we had submitted. In October 2011, we submitted to FDA a new Phase 2 protocol to evaluate IMO-3100 in adult patients with moderate to severe plaque psoriasis, randomized into three arms, over a four-week treatment period. In December 2011, the FDA removed the clinical hold and we expect to initiate the four-week Phase 2 clinical trial in the second quarter of 2012. We plan to evaluate two dose levels of IMO-3100 and a concurrent placebo arm in the trial.

In addition to IMO-3100, we have selected IMO-8400, an antagonist of TLRs 7, 8, and 9, for development in the treatment of autoimmune diseases, with lupus as the initial disease indication. Currently we are conducting nonclinical studies to support submission of an IND for IMO-8400. We expect to submit the IND to the FDA in the fourth quarter of 2012. We have shown that treatment with IMO-8400 was associated with improvement in a number of disease parameters in mouse models of lupus, psoriasis, and arthritis. Specifically, in mouse models of lupus, IMO-8400 activity has been evidenced by increased survival, suppression of anti-DNA and anti-RNA antibodies and inflammatory cytokines, decreased tissue pathology, and improved renal function.

Cancer

The immune system is capable of recognizing cancer cells as abnormal cells, leading to an immune response. However, the body s immune response to cancer cells may be weak or absent. We believe that agonists of TLR7, TLR8, and TLR9 can enhance the body s immune response to cancer cells because TLRs are involved in stimulation of both innate and adaptive immunity.

IMO-2055, a TLR9 agonist, is our lead drug candidate for the treatment of cancer. In December 2007, we entered into an exclusive, worldwide license agreement with Merck KGaA to research, develop, and commercialize products containing our TLR9 agonists, including IMO-2055, for the treatment of cancer, excluding cancer vaccines. In July 2011, Merck KGaA informed us that, based on increased incidence of neutropenia and electrolyte imbalances reported in its Phase 1 trial of IMO-2055 in combination with cisplatin, 5-fluorouracil, and cetuximab in patients with first-line SCCHN, Merck KGaA had terminated the trial and re-evaluated its IMO-2055 clinical development program and, following such re-evaluation, had determined that it would not conduct further clinical development of IMO-2055. In November 2011, we regained global rights to IMO-2055 and our other TLR9 agonists, including preclinical lead drug candidates selected for further evaluation under the collaboration, for the treatment of cancer as part of an agreed-upon termination of our oncology collaboration with Merck KGaA.

During the collaboration period, Merck KGaA conducted clinical trials of IMO-2055 in combination with other anticancer agents in several cancer indications, including a Phase 1b trial of IMO-2055 in combination with erlotinib and bevacizumab in patients with advanced non-small cell lung cancer, or NSCLC, a Phase 1b clinical trial of IMO-2055 in combination with cetuximab and the chemotherapy regimen FOLFIRI in patients with advanced colorectal cancer, and an ongoing randomized Phase 2 trial of IMO-2055 in combination with cetuximab in patients with squamous cell carcinoma of the head and neck, or SCCHN. In January 2012, we

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announced favorable data from the Phase 1b clinical trial of IMO-2055 in combination with erlotinib and bevacizumab in patients with advanced NSCLC. In this trial, the combination of IMO-2055 with erlotinib and bevacizumab was well tolerated, and in the 33 patients who were evaluable for efficacy, the disease control rate was 79%. Median progression-free survival was 5.6 months and median overall survival was 16 months. These results compare favorably with recently published results of erlotinib plus bevacizumab in second-line treatment of patients with advanced NSCLC. We plan to present detailed results of the trial at an upcoming scientific meeting.

We anticipate top-line data from the ongoing Phase 2 clinical trial of IMO-2055 in combination with cetuximab in patients with SCCHN in the second quarter of 2012. In this study, 104 patients with SCCHN who had progressed on a cytotoxic therapy were randomized into two arms. In one arm, patients were treated with IMO-2055 at a dose of 0.32 mg/kg given once weekly subcutaneously in combination with weekly cetuximab. In the other arm of the study, patients were treated with cetuximab alone. The primary endpoint of the study is progression-free survival. Secondary outcome measures include overall response rate, disease control rate, overall survival, safety and tolerability in patients treated with IMO-2055 plus cetuximab compared to patients treated with cetuximab alone. In this study, crossover of the patients who progress on cetuximab alone is permitted to the combination arm of IMO-2055 plus cetuximab. The trial is being conducted at multiple centers in Europe and the United States.

We also expect to have in the second quarter of 2012 top-line data from the Phase 1b clinical trial of IMO-2055 in combination with cetuximab and the chemotherapy regimen FOLFIRI in patients with advanced colorectal cancer who have progressed following chemotherapy. The goal of this study was to establish a recommended Phase 2 dose of IMO-2055. Sixteen patients have been enrolled at three dose levels of IMO-2055 combined with cetuximab and FOLFIRI.

Clinical trials of IMO-2055 previously completed by us or by Merck KGaA include four Phase 1 clinical trials, of which two were in healthy subjects and two were in refractory cancer patients, and one Phase 2 clinical trial. The Phase 2 clinical trial was a monotherapy trial of IMO-2055 in patients with metastatic or recurrent clear cell renal cancer.

We plan to determine our next steps in the development of IMO-2055 after receiving the data from the Phase 2 clinical trial in SCCHN and from the Phase 1b clinical trial in colorectal cancer.

Vaccine Adjuvants TLR7, 8, and 9 Agonists

Vaccines are composed of one or more antigens and one or more adjuvants in an appropriate formulation. The function of the adjuvants is to enhance immune recognition of the antigens and increase the ability of the immune system to make antigen-specific antibodies.

In preclinical animal models, our TLR7, 8, and 9 agonists have shown adjuvant activity when combined with various types of antigens. Preclinical studies that we conducted with our TLR9 agonists and various antigens have shown improvements in several measures of antigen recognition, such as achievement of higher antibody levels, higher ratios of specific to nonspecific antibodies, and a reduction in the number of doses required to achieve effective antibody levels. We believe that agonists of TLRs 7, 8, and 9 have the potential to be used as adjuvants in vaccines.

In December 2006, we entered into a research collaboration with Merck Sharp & Dohme Corp., or Merck, and granted Merck an exclusive license to develop and commercialize our TLR7, 8, and 9 agonists by incorporating them in therapeutic and prophylactic vaccines being developed by Merck for cancer, infectious diseases, and Alzheimer s disease. The original term of the research collaboration was two years and Merck extended the research collaboration for two additional years to December 2010. During the four-year research collaboration period, multiple TLR agonists were created by us and evaluated by Merck against the criteria established in the license agreement. In January 2012, in accordance with the research collaboration, Merck selected multiple novel TLR7, 8, and 9 agonists for Merck s exclusive evaluation and use as vaccine adjuvants.

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Gene Silencing Oligonucleotides

Through our expertise in nucleic acid chemistry, we have designed and created a new class of molecules to inhibit gene expression. These gene silencing oligonucleotides, which we refer to as GSOs, are nucleic acid-based and represent a novel approach to selectively silence gene expression. We have studied our GSO compounds in multiple cell culture and animal models and observed potent gene silencing activity. We are actively engaged in preclinical research with our GSOs that is designed to explore their potential as research reagents and therapeutic agents.

In April 2011 we published a scientific paper in the Journal of Medicinal Chemistry describing the structure and gene silencing activity of our GSO compounds. In preclinical studies, we have demonstrated that our GSOs exert gene silencing activity in animals following systemic administration. Preclinical data also have shown that systemic delivery of GSOs targeted to the mRNA of apolipoprotein B and proprotein convertase subtilisin/kexin type 9, which are proteins associated with cardiovascular diseases, resulted in reduced serum total cholesterol and low-density-lipoprotein cholesterol in addition to reduced levels of the targeted mRNA and associated proteins. Additionally, in mouse models, systemic administration of GSOs showed significant specific gene-silencing activity with minimized induction of immune responses, as compared to other gene silencing approaches.

Additional Programs

In addition to our internal programs, we are seeking to advance our TLR-targeted programs in infectious diseases, hematologic oncology, respiratory diseases, and vaccine adjuvant applications only through partnerships with third parties.

Infectious Disease. Chronic HCV infection causes inflammation of the liver, which significantly increases the risk that a patient will develop liver failure or liver cancer. Recombinant interferon-alpha has been used as part of the standard of care treatment for chronic HCV infection. We and other independent researchers have shown in preclinical studies that TLR9 agonists induce many proteins, including natural interferon-alpha and other antiviral proteins.

IMO-2125, a synthetic DNA-based TLR9 agonist, was our lead candidate for the treatment of chronic hepatitis C virus, or HCV, infection. We conducted two Phase 1 clinical trials of IMO-2125 in patients with chronic HCV infection, one in patients with HCV who had not responded to prior treatment and one in combination with ribavirin, an antiviral medication approved for use in combination with interferon-alpha in the treatment of HCV infection, in treatment-naïve patients with genotype 1 chronic HCV infection. The primary objective of both trials was to assess the safety of IMO-2125. We also evaluated the effects of IMO-2125 on HCV RNA levels and on parameters of immune system activation. Data from both Phase 1 clinical trials have been presented in scientific meetings. During the third quarter of 2011, we re-assessed and prioritized our drug development programs and based on this prioritization, we discontinued further investment of internal resources on the development of IMO-2125 for the treatment of HCV.

Cancer. In addition to the use of TLR9 agonists in oncology applications, we selected IMO-4200 as a lead TLR7 and TLR8 agonist candidate for the treatment of hematological cancers. In preclinical models of lymphoma, IMO-4200 in combination with approved cancer treatments increased antitumor activity. We have conducted preclinical studies in mouse models combining IMO-4200 with ofatumumab, an anti-CD20 antibody, and, in separate experiments, with rituximab, an anti-CD20 antibody, plus a chemotherapy agent, fludarabine or bendamustine. In all of these combinations, IMO-4200 improved antitumor activity, increased survival, and enhanced the immunological mechanism of action of the antibody in preclinical models.

Respiratory Diseases. Asthma and allergy conditions are characterized by an imbalance of the immune system. Currently approved agents for the treatment of asthma and allergy conditions, including steroids and

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antibodies, are generally designed to suppress symptoms of asthmatic or allergic response. Our TLR9 agonists, by comparison, are designed to induce immune responses that could be useful in restoring immune system balance. In preclinical studies conducted by us and our collaborators, our TLR9 agonists caused improvements in multiple indices of allergic conditions. For example, in mouse models of allergy, our TLR9 agonists restored the balance of immunological activity, produced a higher ratio of specific versus non-specific antibodies, reduced the number of pulmonary immune cells that produce allergic inflammation, and improved lung function. IMO-2134 is our lead TLR9 agonist for asthma and allergies. The safety and pharmacodynamics of IMO-2134 have been evaluated in a Phase 1 clinical trial.

Vaccine Adjuvants. In addition to use of TLR7, 8, and 9 agonists as vaccine adjuvants, we also have created proprietary TLR3 agonists for potential use as vaccine adjuvants. In preclinical models, our TLR3 agonists stimulated immune responses, including promoting an increased production of antigen-specific antibodies and cytotoxic T cells as compared to responses induced by the antigen alone in preclinical vaccination studies.

Collaborative Alliances

An important part of our business strategy is to enter into research and development collaborations, licensing agreements, and other strategic alliances with biotechnology and pharmaceutical corporations that bring expertise and resources to the potential development and commercialization of drugs based on our technology. We were a party to a collaboration with Merck KGaA that was terminated in November 2011. We are currently party to a collaboration with Merck.

Merck KGaA

In December 2007, we entered into an exclusive, worldwide license agreement with Merck KGaA, Darmstadt, Germany, to research, develop and commercialize products containing our TLR9 agonists for the treatment of cancer, excluding cancer vaccines. Under the terms of the agreement, we granted Merck KGaA worldwide exclusive rights to our lead TLR9 agonists, IMO-2055 and IMO-2125, and to a specified number of novel follow-on TLR9 agonists to be identified by Merck KGaA and us under a research collaboration that ended in June 2010, for use in the treatment, cure and delay of the onset or progression of cancer in humans. Under the terms of the agreement:

- In February 2008, Merck KGaA paid us a $40.0 million upfront license fee in Euros of which we received $39.7 million due to foreign currency exchange rates;
- Merck KGaA agreed to reimburse future development costs for certain of our on-going IMO-2055 clinical trials, which we continued to conduct on behalf of Merck KGaA until September 2009;
- Merck KGaA agreed to pay us up to EUR 264 million in development, regulatory approval, and commercial success milestone payments if products containing our TLR9 agonist compounds are successfully developed and marketed for treatment, cure and/or delay of the onset or progression of cancer in humans; and
- Merck KGaA agreed to pay mid single-digit to low double-digit royalties on net sales of products containing our TLR9 agonists that are marketed.

In February 2009, we amended the license agreement with Merck KGaA so that we could initiate and conduct on behalf of Merck KGaA additional clinical trials of IMO-2055, until such time as Merck KGaA had filed an IND application with the FDA for IMO-2055 and assumed sponsorship of these trials. Under the amendment, Merck KGaA agreed to reimburse us for costs associated with any additional trials that we initiated and conducted. As of March 2010, Merck KGaA had assumed sponsorship of all clinical trials of IMO-2055 for the treatment of cancer and had taken responsibility for all further clinical development of IMO-2055 in the treatment of cancer, excluding vaccines.

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In November 2011, we and Merck KGaA entered into a termination agreement terminating the license agreement. Under the termination agreement,

- The license agreement was terminated and we regained all rights for developing TLR9 agonists for the treatment of cancer, including all rights to IMO-2055 and any follow-on TLR9 agonists;
- Merck KGaA agreed to continue to conduct the ongoing Phase 2 trial of IMO-2055 in combination with cetuximab and other specified related activities;
- We gained the rights to the data from the Phase 2 trial of IMO-2055 in combination with cetuximab, as well as to the data from the Phase 1 trials conducted in other cancer indications;
- We agreed to reimburse Merck KGaA a maximum of 1.8 million ($2.4 million at December 31, 2011) of Merck KGaA s costs for the third party contract research organization that is coordinating the ongoing Phase 2 trial of IMO-2055 in combination with cetuximab, payable in eleven installments comprised of ten monthly installments to be invoiced by Merck KGaA to us commencing on March 1, 2012 and a final payment payable by us to Merck KGaA upon Merck KGaA s completion of certain specified activities;
- We agreed to pay to Merck KGaA one-time 1.0 million ($1.3 million at December 31, 2011) milestone payments upon occurrence of each of the following milestones: (i) partnering of IMO-2055 between us and any third party, (ii) initiation of any Phase 2 or Phase 3 clinical trial for IMO-2055 and (iii) regulatory submission of IMO-2055 in any country; and
- Merck KGaA granted us an option to obtain a license to certain manufacturing and formulation know-how owned or developed by Merck KGaA under the License Agreement and to a Merck KGaA trademark. If we elect to exercise our option to either of these options, we will pay a low single digit royalty on net sales of IMO-2055, with respect to such licenses.

Merck Sharp & Dohme Corp. (Merck)

In December 2006, we entered into an exclusive license and research collaboration agreement with Merck to research, develop and commercialize vaccine products containing our TLR7, 8, and 9 agonists in the fields of cancer, infectious diseases and Alzheimer s disease. Under the terms of the agreement, we granted Merck worldwide exclusive rights to a number of our TLR7, 8, and 9 agonists for use in combination with Merck s therapeutic and prophylactic vaccines under development in the fields of cancer, infectious diseases, and Alzheimer s disease. There is no limit to the number of vaccines to which Merck can apply our agonists within these fields. We also agreed with Merck to engage in a two-year research collaboration to generate novel agonists targeting TLR7 and TLR8 and incorporating both Merck and the Company s chemistry for use in vaccines in the defined fields. Under the terms of the agreement, Merck extended the research collaboration for two additional years to December 2010. Under the terms of the agreement:

- Merck paid us a $20.0 million upfront license fee;
- Merck purchased $10.0 million of our common stock at $5.50 per share;
- Merck agreed to fund the research and development collaboration through its term;

Merck agreed to pay us milestone payments as follows:

up to $165.0 million if vaccines containing our TLR9 agonist compounds are successfully developed and marketed in each of the oncology, infectious disease and Alzheimer s disease fields;

up to $260.0 million if vaccines containing our TLR9 agonist compounds are successfully developed and marketed for follow-on indications in the oncology field and if vaccines containing our TLR7 or TLR8 agonists are successfully developed and marketed in each of the oncology, infectious disease, and Alzheimer s disease fields; and

if Merck develops and commercializes additional vaccines using our agonists, we would be entitled to receive additional milestone payments; and

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Merck agreed to pay us mid to upper single-digit royalties on net product sales of vaccines using our TLR agonist technology that are developed and marketed, with the royalty rates being dependent on disease indication and the TLR agonist employed.

Under the agreement, Merck is obligated to pay us royalties, on a product-by-product and country-by-country basis, until the later of the expiration of the patent rights licensed to Merck and the expiration of regulatory-based exclusivity for the vaccine product. If the patent rights and regulatory-based exclusivity expire in a particular country before the 10th anniversary of the product s first commercial sale in such country, Merck s obligation to pay us royalties will continue at a reduced royalty rate until such anniversary, except that Merck s royalty obligation will terminate upon the achievement of a specified market share in such country by a competing vaccine containing an agonist targeting the same toll-like receptor as that targeted by the agonist in the Merck vaccine. In addition, the applicable royalties may be reduced if Merck is required to pay royalties to third parties for licenses to intellectual property rights, which royalties exceed a specified threshold. Merck s royalty and milestone obligations may also be reduced if Merck terminates the agreement based on specified uncured material breaches by us.

Merck may terminate the collaborative alliance without cause upon 90 days written notice to us. Either party may terminate the collaborative alliance upon the other party s filing or institution of bankruptcy, reorganization, liquidation or receivership proceedings, or for a material breach if such breach is not cured within 60 days after delivery of written notice.

In January 2012, in accordance with the agreement, Merck selected multiple novel TLR7, 8, and 9 agonists for Merck s exclusive evaluation and use as vaccine adjuvants.

Antisense Technology

We have been a pioneer in the development of antisense technology. We now are using our antisense expertise and technology to validate potential targets in the TLR signaling pathway. Antisense compounds may assist us in identifying drug candidates. We have identified antisense compounds targeted to human TLRs 2, 3, 4, 5, 7, 8, and 9 and to the TLR-associated signaling protein MyD88. We are studying these antisense compounds for potential applications in multiple disease indications.

We also believe that our antisense technology may be useful to pharmaceutical and biotechnology companies that are seeking to develop drug candidates that down-regulate gene targets discovered by, or proprietary to, such companies. Antisense drug candidates are designed to bind to RNA targets through hybridization, and decrease production of the specific protein encoded by the target RNA. We believe that drugs based on antisense technology may be more effective and cause fewer side effects than conventional drugs in applications with well-defined RNA targets because antisense drugs are designed to intervene in a highly specific fashion in the production of proteins, rather than after the proteins are made.

We have licensed specified rights related to antisense technology to certain parties. We also have in-licensed certain rights related to antisense technology.

Out-licenses. In 2001 we entered into an agreement with Isis Pharmaceuticals, Inc., under which we granted Isis a license, with the right to sublicense, to our antisense chemistry and delivery patents and patent applications; and we retained the right to use these patents and applications in our own drug discovery and development efforts and in collaborations with third parties. Isis paid us $15.0 million in cash and issued 857,143 shares of its common stock having an aggregate fair market value on the dates on which title to the shares was received of $17.3 million and is required to pay us a mid double-digit percentage of specified sublicense income it receives from some types of sublicenses of our patents and patent applications. To date, we have received $0.3 million in sublicense income from Isis. Also under the agreement, we licensed from Isis specified antisense patents and patent applications, principally Isis suite of RNase H patents and patent

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applications. We also paid to Isis $0.7 million and issued 1,005,499 shares of common stock having a fair market value of approximately $1.2 million on the date of issuance for this license and are obligated to pay Isis an annual maintenance fee and low single-digit royalties on net sales of antisense products sold that are covered by Isis s patent rights. We have the right to use these patents and patent applications in our drug discovery and development efforts and in some types of third-party collaborations. To date, we have only paid Isis annual maintenance fees and have not paid any royalties. The agreement may be terminated for an uncured material breach by either party. The licenses granted under the Isis agreement terminate upon the last to expire of the patents and patent applications licensed under the agreement. We may terminate at any time the sublicense by Isis to us of the patents and patent applications.

In addition, we are party to two other license agreements involving the license of our antisense patents and patent applications for antisense chemistry and delivery and for specific gene targets, under which we typically are entitled to receive license fees, sublicensing income, research payments, payments upon achievement of developmental milestones, and royalties on product sales.

In-licenses. Our principal in-license related to antisense technology is with University of Massachusetts Medical Center for antisense chemistry and for certain gene targets. Under the terms of our license agreement with University of Massachusetts Medical Center, we are the worldwide, exclusive licensee under a number of U.S. issued patents and various patent applications owned by University of Massachusetts Medical Center relating to the chemistry of antisense oligonucleotides and their use. This license expires upon the expiration of the last to expire of the patents covered by the license. Under the agreement, we have agreed to pay a low single-digit royalty on net product sales, a low double-digit percentage of any sublicense license income we receive, and a small annual license maintenance fee. Since 1999, we have paid approximately $1.7 million to University of Massachusetts Medical Center under this license agreement.

Additionally, we have entered into five other royalty-bearing license agreements under which we have acquired rights to antisense related patents, patent applications, and technology. Under all of these in-licenses, we are obligated to pay low to mid single-digit royalties on our net sales of products or processes covered by a valid claim of a licensed patent or patent application. Under some of these in-licenses, we are required to pay a low double-digit percentage of any sublicense income. All of our in-licenses impose various commercialization, sublicensing, insurance, and other obligations on us, and our failure to comply with these requirements could result in termination of the in-licenses.

Academic and Research Collaborations

We have entered into research collaborations with scientists at leading academic research institutions. These research collaborations allow us to augment our internal research capabilities and obtain access to specialized knowledge and expertise.

In general, our research collaborations may require us to supply compounds and pay various amounts to support the research. Under these research agreements, if a collaborator, solely or jointly with us, creates any invention, we may own exclusively such invention, have an automatic paid-up, royalty-free non-exclusive license or have an option to negotiate an exclusive, worldwide, royalty-bearing license to such invention. Inventions developed solely by our scientists in connection with research collaborations are owned exclusively by us. These collaborative agreements are non-exclusive and may be terminated with limited notice.

Research and Development Expenses

For the years ended December 31, 2011, 2010 and 2009, we spent approximately $18.0 million, $24.2 million, and $18.6 million on research and development activities. In 2009, Merck KGaA sponsored approximately $3.1 million of our research and development activities. In 2009, Merck sponsored approximately $0.8 million of our research and development activities. Sponsored research and development activities were minimal in 2011 and 2010.

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Patents, Proprietary Rights and Trade Secrets

Our success depends in part on our ability to obtain and maintain proprietary protection for our drug candidates, technology and know-how, to operate without infringing the proprietary rights of others and to prevent others from infringing our proprietary rights. We use a variety of methods to seek to protect our proprietary position, including filing U.S. and foreign patent applications related to our proprietary technology, inventions and improvements that are important to the development of our business. We also rely on trade secrets, know-how, continuing technological innovation, and in-licensing opportunities to develop and maintain our proprietary position.

We have devoted and continue to devote a substantial amount of our resources into establishing intellectual property protection for:

Novel chemical entities that function as agonists of TLR3, 7, 8 or 9;

Novel chemical entities that function as antagonists of TLR7, 8 or 9; and

Use of our novel chemical entities and chemical modifications to treat and prevent a variety of diseases.

As of March 1, 2012, we owned 78 U.S. patents and U.S. patent applications and 256 patents and patent applications throughout the rest of the world for our TLR-targeted immune modulation technologies. These patents and patent applications include novel chemical compositions of matter and methods of use for our immune modulatory compounds, including IMO-2055, IMO-2125, IMO-2134, IMO 3100, IMO-4200, and IMO-8400. To date, all of our intellectual property covering immune modulatory compositions and methods of their use is based on discoveries made solely by us. These patents expire at various dates ranging from 2017 to 2031. With respect to IMO-3100, we have patent applications that cover the chemical composition of matter of IMO-3100 and methods of its use that, if issued, would expire at the earliest in 2026. With respect to IMO-2055, we have issued patents that cover the chemical composition of matter of IMO-2055 and methods of its use, including in combination with marketed cancer products, with the earliest composition claims expiring in 2023. With respect to IMO-8400, we have patent applications that cover the chemical composition of matter of IMO-8400 and methods of its use that, if issued, would expire at the earliest in 2031.

As of March 1, 2012, we also own four U.S. patent applications and one corresponding worldwide patent application for our GSO compounds and methods of their use. Patents issuing from these applications, if any, would expire at their earliest in 2030.

In addition to our TLR-targeted patent portfolio, we are the owner or hold licenses of patents and patent applications related to antisense technology. As of March 1, 2012, our antisense patent portfolio included 100 U.S. patents and patent applications and 163 patents and patent applications throughout the rest of the world. These antisense patents and patent applications include novel compositions of matter, the use of these compositions for various genes, sequences and therapeutic targets, and oral and other routes of administration. Some of the patents and patent applications in our antisense portfolio were in-licensed. These in-licensed patents expire at various dates ranging from 2012 to 2022.

Because patent applications in the United States and many foreign jurisdictions are typically not published until 18 months after filing, or in some cases not at all, and because publications of discoveries in the scientific literature often lag behind actual discoveries, we cannot be certain that we were the first to make the inventions claimed in each of our issued patents or pending patent applications, or that we were the first to file for protection of the inventions set forth in these patent applications.

Litigation may be necessary to defend against or assert claims of infringement, to enforce patents issued to us, to protect trade secrets or know-how owned by us, or to determine the scope and validity of the proprietary rights of others or to determine the appropriate term for an issued patent. In addition, the U.S. Patent and Trademark Office, or USPTO, may declare interference proceedings to determine the priority of inventions with

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respect to our patent applications or reexamination or reissue proceedings to determine if the scope of a patent should be narrowed. Litigation or any of these other proceedings could result in substantial costs to and diversion of effort by us, and could have a material adverse effect on our business, financial condition and results of operations. These efforts by us may not be successful.

In January 2010, we filed a lawsuit against the USPTO in the United States District Court for the District of Columbia. In light of recent decisions in that court and the Court of Appeals for the Federal Circuit, we believe the USPTO assigned a shorter patent term to some of our U.S. patents than was allowed by law. We filed the lawsuit to obtain a determination of the appropriate patent term for these patents.

We may rely, in some circumstances, on trade secrets and confidentiality agreements to protect our technology. Although trade secrets are difficult to protect, wherever possible, we use confidential disclosure agreements to protect the proprietary nature of our technology. We regularly implement confidentiality agreements with our employees, consultants, scientific advisors, and other contractors and collaborators. However, there can be no assurance that these agreements will not be breached, that we will have adequate remedies for any breach, or that our trade secrets and/or proprietary information will not otherwise become known or be independently discovered by competitors. To the extent that our employees, consultants or contractors use intellectual property owned by others in their work for us, disputes may also arise as to the rights in related or resulting know-how and inventions.

Government Regulation

Government authorities in the United States, at the federal, state and local level, and in other countries extensively regulate, among other things, the research, development, testing, manufacture, including any manufacturing changes, packaging, storage, recordkeeping, labeling, advertising, promotion, distribution, marketing, post-approval monitoring and reporting, import and export of pharmaceutical products, such as those we are developing.

United States drug approval process

In the United States, the FDA regulates drugs under the Federal Food, Drug, and Cosmetic Act, or FDCA, the Public Health Service Act and implementing regulations. The process of obtaining regulatory approvals and the subsequent compliance with appropriate federal, state, local and foreign statutes and regulations requires the expenditure of substantial time and financial resources. Failure to comply with the applicable United States requirements at any time during the product development process, approval process or after approval, may subject an applicant to a variety of administrative or judicial sanctions, such as the FDA s refusal to approve pending applications, withdrawal of an approval, imposition of a clinical hold, issuance of warning letters, product recalls, product seizures, total or partial suspension of production or distribution injunctions, fines, refusals of government contracts, restitution, disgorgement of profits or civil or criminal penalties.

The process required by the FDA before a drug may be marketed in the United States generally involves the following:

- completion of nonclinical laboratory tests, animal studies and formulation studies in compliance with the FDA s good laboratory practice, or GLP, regulations;
- submission to the FDA of an IND, which must become effective before human clinical trials may begin;
- approval by an independent institutional review board, or IRB, for each clinical site before each trial may be initiated;
- performance of adequate and well-controlled human clinical trials in accordance with good clinical practices, or GCP, to establish the safety and efficacy of the proposed drug for each indication;
- submission to the FDA of a new drug application, or NDA;

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satisfactory completion of an FDA advisory committee review, if applicable;

satisfactory completion of an FDA inspection of the manufacturing facility or facilities at which the product is produced to assess compliance with current good manufacturing practices, or cGMP, requirements and to assure that the facilities, methods and controls are adequate to preserve the drug s identity, strength, quality and purity; and

FDA review and approval of the NDA.

Nonclinical studies

Nonclinical studies include laboratory evaluation of product chemistry and formulation, as well as *in vitro* and animal studies to assess the potential for adverse events and in some cases to establish a rationale for therapeutic use. The conduct of nonclinical studies is subject to federal regulations and requirements, including GLP regulations for safety/toxicology studies. An IND sponsor must submit the results of the nonclinical tests, together with manufacturing information, analytical data, any available clinical data or literature and plans for clinical studies, among other things, to the FDA as part of an IND. Additional nonclinical testing, such as animal tests of reproductive adverse events and carcinogenicity, may continue after the IND is submitted. An IND automatically becomes effective 30 days after receipt by the FDA, unless before that time the FDA raises concerns or questions related to one or more proposed clinical trials and places the trial on clinical hold. In such a case, the IND sponsor and the FDA must resolve any outstanding concerns before the clinical trial can begin. As a result, submission of an IND may not result in the FDA allowing clinical trials to commence.

Clinical trials

Clinical trials involve the administration of the investigational new drug to human subjects under the supervision of qualified investigators in accordance with GCP requirements, which include, among other things, the requirement that all research subjects provide their informed consent in writing before their participation in any clinical trial. Clinical trials are conducted under written study protocols detailing, among other things, the objectives of the study, the parameters to be used in monitoring safety and the effectiveness criteria to be evaluated. A protocol for each clinical trial and any subsequent protocol amendments must be submitted to the FDA as part of the IND. In addition, an IRB for each institution participating in the clinical trial must review and approve the plan for any clinical trial before it commences at that institution, and the IRB must conduct continuing review. The IRB must review and approve, among other things, the study protocol and informed consent information to be provided to study subjects. An IRB must operate in compliance with FDA regulations. Information about certain clinical trials must be submitted within specific timeframes to the National Institutes of Health for public dissemination on their ClinicalTrials.gov website.

Human clinical trials are typically conducted in three sequential phases, which may overlap or be combined:

Phase 1: The drug is initially introduced into healthy human subjects or patients with the target disease or condition and tested for safety, dosage tolerance, absorption, metabolism, distribution, excretion and, if possible, to gain an early indication of its effectiveness.

Phase 2: The drug is administered to a limited patient population to identify possible adverse effects and safety risks, to preliminarily evaluate the efficacy of the product for specific targeted diseases and to determine dosage tolerance and optimal dosage.

Phase 3: The drug is administered to an expanded patient population in adequate and well-controlled clinical trials to generate sufficient data to statistically confirm the efficacy and safety of the product for approval, to establish the overall risk-benefit profile of the product and to provide adequate information for the labeling of the product.

Progress reports detailing the results of the clinical trials must be submitted at least annually to the FDA and more frequently if serious adverse events occur. Phase 1, Phase 2 and Phase 3 clinical trials may not be

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completed successfully within any specified period, or at all. Furthermore, the FDA or the sponsor may suspend or terminate a clinical trial at any time on various grounds, including a finding that the research subjects are being exposed to an unacceptable health risk. Similarly, an IRB can suspend or terminate approval of a clinical trial at its institution if the clinical trial is not being conducted in accordance with the IRB s requirements or if the drug has been associated with unexpected serious harm to patients.

Marketing approval

Assuming successful completion of the required clinical testing, the results of the nonclinical and clinical studies, together with detailed information relating to the product s chemistry, manufacture, controls and proposed labeling, among other things, are submitted to the FDA as part of an NDA requesting approval to market the product for one or more indications. Under federal law, the submission of most NDAs is additionally subject to a substantial application user fee, currently exceeding $1.8 million, and the sponsor of an approved NDA is also subject to annual product and establishment user fees, currently exceeding $98,000 per product and $520,000 per establishment. These fees are typically increased annually.

The FDA conducts a preliminary review of all NDAs within the first 60 days after submission before accepting them for filing to determine whether they are sufficiently complete to permit substantive review. The FDA may request additional information rather than accept an NDA for filing. In this event, the application must be resubmitted with the additional information. The resubmitted application is also subject to review before the FDA accepts it for filing. Once the submission is accepted for filing, the FDA begins an in-depth substantive review. The FDA has agreed to specified performance goals in the review of NDAs. Under these goals, the FDA has committed to review most such applications for non-priority products within 10 months, and most applications for priority review products, that is, drugs that the FDA determines represent a significant improvement over existing therapy, within six months. These performance goals likely will be extended by several months when the Prescription Drug User Fee Act is reauthorized in 2012. The review process may be extended by the FDA for three additional months to consider certain information or clarification regarding information already provided in the submission. The FDA may also refer applications for novel drugs or products that present difficult questions of safety or efficacy to an advisory committee, typically a panel that includes clinicians and other experts, for review, evaluation and a recommendation as to whether the application should be approved. The FDA is not bound by the recommendations of an advisory committee, but it considers such recommendations carefully when making decisions.

Before approving an NDA, the FDA typically will inspect the facility or facilities where the product is manufactured. The FDA will not approve an application unless it determines that the manufacturing processes and facilities are in compliance with cGMP requirements and adequate to assure consistent production of the product within required specifications. In addition, before approving an NDA, the FDA will typically inspect one or more clinical sites to assure compliance with GCP and integrity of the clinical data submitted.

The testing and approval process requires substantial time, effort and financial resources, and each may take many years to complete. Data obtained from clinical activities are not always conclusive and may be susceptible to varying interpretations, which could delay, limit or prevent regulatory approval. The FDA may not grant approval on a timely basis, or at all. We may encounter difficulties or unanticipated costs in our efforts to develop our product candidates and secure necessary governmental approvals, which could delay or preclude us from marketing our products.

After the FDA s evaluation of the NDA and inspection of the manufacturing facilities, the FDA may issue an approval letter or a complete response letter. An approval letter authorizes commercial marketing of the drug with specific prescribing information for specific indications. A complete response letter generally outlines the deficiencies in the submission and may require substantial additional testing or information in order for the FDA to reconsider the application. If and when those deficiencies have been addressed to the FDA s satisfaction in a resubmission of the NDA, the FDA will issue an approval letter. The FDA has committed to reviewing such

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resubmissions in two or six months depending on the type of information included. Even with submission of this additional information, the FDA ultimately may decide that the application does not satisfy the regulatory criteria for approval and refuse to approve the NDA.

Even if the FDA approves a product, it may limit the approved indications for use for the product, require that contraindications, warnings or precautions be included in the product labeling, require that post-approval studies, including Phase 4 clinical trials, be conducted to further assess a drug s safety after approval, require testing and surveillance programs to monitor the product after commercialization, or impose other conditions, including distribution restrictions or other risk management mechanisms, which can materially affect the potential market and profitability of the product. The FDA may prevent or limit further marketing of a product based on the results of post-market studies or surveillance programs. After approval, some types of changes to the approved product, such as adding new indications, manufacturing changes and additional labeling claims, are subject to further testing requirements and FDA review and approval.

Fast track designation

The FDA is required to facilitate the development and expedite the review of drugs that are intended for the treatment of a serious or life-threatening condition for which there is no effective treatment and which demonstrate the potential to address unmet medical needs for the condition. Under the fast track program, the sponsor of a new drug candidate may request the FDA to designate the product for a specific indication as a fast track product concurrent with or after the filing of the IND for the product candidate. The FDA must determine if the product candidate qualifies for fast track designation within 60 days after receipt of the sponsor s request.

In addition to other benefits, such as the ability to use surrogate endpoints and have greater interactions with the FDA, the FDA may initiate review of sections of a fast track product s NDA before the application is complete. This rolling review is available if the applicant provides and the FDA approves a schedule for the submission of the remaining information and the applicant pays applicable user fees. However, the FDA s time period goal for reviewing a fast track application does not begin until the last section of the NDA is submitted. In addition, the fast track designation may be withdrawn by the FDA if the FDA believes that the designation is no longer supported by data emerging in the clinical trial process.

Priority review

Under FDA policies, a product candidate may be eligible for priority review, or review within a six-month time frame from the time a complete application is received. Products regulated by the FDA s Center for Drug Evaluation and Research, or CDER, are eligible for priority review if they provide a significant improvement compared to marketed products in the treatment, diagnosis or prevention of a disease. A fast track designated product candidate would ordinarily meet the FDA s criteria for priority review.

Accelerated approval

Under the FDA s accelerated approval regulations, the FDA may approve a drug for a serious or life-threatening illness that provides meaningful therapeutic benefit to patients over existing treatments based upon a surrogate endpoint that is reasonably likely to predict clinical benefit. In clinical trials, a surrogate endpoint is a measurement of laboratory or clinical signs of a disease or condition that substitutes for a direct measurement of how a patient feels, functions or survives. Surrogate endpoints can often be measured more easily or more rapidly than clinical endpoints. A product candidate approved on this basis is subject to rigorous post-marketing compliance requirements, including the completion of Phase 4 or post-approval clinical trials to confirm the effect on the clinical endpoint. Failure to conduct required post-approval studies, or confirm a clinical benefit during post-marketing studies, would allow the FDA to withdraw the drug from the market on an expedited basis. All promotional materials for drug candidates approved under accelerated regulations are subject to prior review by the FDA.

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Orphan drugs

Under the Orphan Drug Act, the FDA may grant orphan drug designation to drugs intended to treat a rare disease or condition, which is generally defined as a disease or condition that affects fewer than 200,000 individuals in the United States. Orphan drug designation must be requested before submitting an NDA. After the FDA grants orphan drug designation, the generic identity of the drug and its potential orphan use are disclosed publicly by the FDA. Orphan drug designation does not convey any advantage in, or shorten the duration of, the regulatory review and approval process. The first NDA applicant to receive FDA approval for a particular active ingredient to treat a particular disease with FDA orphan drug designation is entitled to a seven-year exclusive marketing period in the United States for that product, for that indication. During the seven-year exclusivity period, the FDA may not approve any other applications to market the same drug for the same orphan indication, except in limited circumstances, such as a showing of clinical superiority to the product with orphan drug exclusivity in that it is shown to be safer, more effective or makes a major contribution to patient care. Orphan drug exclusivity does not prevent the FDA from approving a different drug for the same disease or condition, or the same drug for a different disease or condition. Among the other benefits of orphan drug designation are tax credits for certain research and a waiver of the NDA application user fee.

Pediatric information

Under the Pediatric Research Equity Act of 2003, as amended and reauthorized by the Food and Drug Administration Amendments Act of 2007, or the FDAAA, an NDA or supplement to an NDA must contain data that are adequate to assess the safety and effectiveness of the drug for the claimed indications in all relevant pediatric subpopulations, and to support dosing and administration for each pediatric subpopulation for which the product is safe and effective. The FDA may, on its own initiative or at the request of the applicant, grant deferrals for submission of some or all pediatric data until after approval of the product for use in adults, or full or partial waivers from the pediatric data requirements. Unless otherwise required by regulation, the pediatric data requirements do not apply to products with orphan drug designation.

The Hatch-Waxman Act

Abbreviated new drug applications

In seeking approval for a drug through an NDA, applicants are required to list with the FDA each patent with claims that cover the applicant s product or a method of using the product. Upon approval of a drug, each of the patents listed in the application for the drug is then published in the FDA s Approved Drug Products with Therapeutic Equivalence Evaluations, commonly known as the Orange Book. Drugs listed in the Orange Book can, in turn, be cited by potential competitors in support of approval of an abbreviated new drug application, or ANDA. Generally, an ANDA provides for marketing of a drug product that has the same active ingredients in the same strengths, dosage form and route of administration as the listed drug and has been shown to be bioequivalent through *in vitro* or *in vivo* testing or otherwise to the listed drug. ANDA applicants are not required to conduct or submit results of preclinical or clinical tests to prove the safety or effectiveness of their drug product, other than the requirement for bioequivalence testing. Drugs approved in this way are commonly referred to as generic equivalents to the listed drug, and can often be substituted by pharmacists under prescriptions written for the original listed drug.

The ANDA applicant is required to certify to the FDA concerning any patents listed for the approved product in the FDA s Orange Book, except for patents covering methods of use for which the ANDA applicant is not seeking approval. Specifically, the applicant must certify with respect to each patent that:

- the required patent information has not been filed;
- the listed patent has expired;
- the listed patent has not expired, but will expire on a particular date and approval is sought after patent expiration; or
- the listed patent is invalid, unenforceable or will not be infringed by the new product.

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A certification that the new product will not infringe the already approved product s listed patents or that such patents are invalid or unenforceable is called a Paragraph IV certification. If the applicant does not challenge the listed patents or indicate that it is not seeking approval of a patented method of use, the ANDA application will not be approved until all the listed patents claiming the referenced product have expired.

If the ANDA applicant has provided a Paragraph IV certification to the FDA, the applicant must also send notice of the Paragraph IV certification to the NDA and patent holders once the ANDA has been accepted for filing by the FDA. The NDA and patent holders may then initiate a patent infringement lawsuit in response to the notice of the Paragraph IV certification. The filing of a patent infringement lawsuit within 45 days after the receipt of a Paragraph IV certification automatically prevents the FDA from approving the ANDA until the earlier of 30 months, expiration of the patent, settlement of the lawsuit or a decision in the infringement case that is favorable to the ANDA applicant.

The ANDA also will not be approved until any applicable non-patent exclusivity period, such as exclusivity for obtaining approval of a new chemical entity, for the referenced product has expired. Federal law provides a period of five years following approval of a drug containing no previously approved active moiety during which ANDAs for generic versions of those drugs cannot be submitted unless the submission contains a Paragraph IV challenge to a listed patent, in which case the submission may be made four years following the original product approval. Federal law provides for a period of three years of exclusivity during which the FDA cannot grant effective approval of an ANDA if a listed drug contains a previously approved active moiety, but FDA requires as a condition of approval new clinical trials conducted by or for the sponsor. This three-year exclusivity period often protects changes to a previously approved drug product, such as a new dosage form, route of administration, combination or indication. Under the Best Pharmaceuticals for Children Act, federal law also provides that periods of patent and non-patent marketing exclusivity listed in the Orange Book for a drug may be extended by six months if the NDA sponsor conducts pediatric studies identified by the FDA in a written request. For written requests issued by the FDA after September 27, 2007, the date of enactment of the FDAAA, the FDA must grant pediatric exclusivity no later than nine months prior to the date of expiration of patent or non-patent exclusivity in order for the six-month pediatric extension to apply to that exclusivity period.

Section 505(b)(2) new drug applications

Most drug products obtain FDA marketing approval pursuant to an NDA or an ANDA. A third alternative is a special type of NDA, commonly referred to as a Section 505(b)(2) NDA, which enables the applicant to rely, in part, on the FDA s previous approval of a similar product, or published literature, in support of its application.

505(b)(2) NDAs often provide an alternate path to FDA approval for new or improved formulations or new uses of previously approved products. Section 505(b)(2) permits the filing of an NDA where at least some of the information required for approval comes from studies not conducted by or for the applicant and for which the applicant has not obtained a right of reference. If the 505(b)(2) applicant can establish that reliance on the FDA s previous approval is scientifically appropriate, it may eliminate the need to conduct certain preclinical or clinical studies of the new product. The FDA may also require companies to perform additional studies or measurements to support the change from the approved product. The FDA may then approve the new product candidate for all or some of the label indications for which the referenced product has been approved, as well as for any new indication sought by the Section 505(b)(2) applicant.

To the extent that the Section 505(b)(2) applicant is relying on studies conducted for an already approved product, the applicant is required to certify to the FDA concerning any patents listed for the approved product in the Orange Book to the same extent that an ANDA applicant would. As a result, approval of a 505(b)(2) NDA can be stalled until all the listed patents claiming the referenced product have expired, until any non-patent exclusivity, such as exclusivity for obtaining approval of a new chemical entity, listed in the Orange Book for the referenced product has expired, and, in the case of a Paragraph IV certification and subsequent patent infringement suit, until the earlier of 30 months, settlement of the lawsuit or a decision in the infringement case that is favorable to the Section 505(b)(2) applicant.

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Combination products

The FDA regulates combinations of products that cross FDA centers, such as drug, biologic or medical device components that are physically, chemically or otherwise combined into a single entity, as a combination product. The FDA center with primary jurisdiction for the combination product will take the lead in the premarket review of the product, with the other center consulting or collaborating with the lead center.

The FDA s Office of Combination Products, or OCP, determines which center will have primary jurisdiction for the combination product based on the combination product s primary mode of action. A mode of action is the means by which a product achieves an intended therapeutic effect or action. The primary mode of action is the mode of action that provides the most important therapeutic action of the combination product, or the mode of action expected to make the greatest contribution to the overall intended therapeutic effects of the combination product.

Often it is difficult for the OCP to determine with reasonable certainty the most important therapeutic action of the combination product. In those difficult cases, the OCP will consider consistency with other combination products raising similar types of safety and effectiveness questions, or which center has the most expertise to evaluate the most significant safety and effectiveness questions raised by the combination product.

A sponsor may use a voluntary formal process, known as a Request for Designation, when the product classification is unclear or in dispute, to obtain a binding decision as to which center will regulate the combination product. If the sponsor objects to that decision, it may request that the agency reconsider that decision.

Other regulatory requirements

Any drug manufactured or distributed by us pursuant to FDA approvals are subject to pervasive and continuing regulation by the FDA, including, among other things, requirements relating to recordkeeping, periodic reporting, product sampling and distribution, advertising and promotion and reporting of adverse experiences with the product. After approval, most changes to the approved product, such as adding new indications or other labeling claims are subject to prior FDA review and approval.

The FDA may impose a number of post-approval requirements as a condition of approval of an NDA. For example, the FDA may require post-marketing testing, including Phase 4 clinical trials, and surveillance to further assess and monitor the product s safety and effectiveness after commercialization. Regulatory approval of oncology products often requires that patients in clinical trials be followed for long periods to determine the overall survival benefit of the drug.

In addition, drug manufacturers and other entities involved in the manufacture and distribution of approved drugs are required to register their establishments with the FDA and state agencies, and are subject to periodic unannounced inspections by the FDA and these state agencies for compliance with cGMP requirements. Changes to the manufacturing process are strictly regulated and often require prior FDA approval before being implemented. FDA regulations also require investigation and correction of any deviations from cGMP and impose reporting and documentation requirements upon us and any third-party manufacturers that we may decide to use. Accordingly, manufacturers must continue to expend time, money and effort in the areas of production and quality control to maintain cGMP compliance.

Once an approval is granted, the FDA may withdraw the approval if compliance with regulatory requirements and standards is not maintained or if problems occur after the product reaches the market. Later discovery of previously unknown problems with a product, including adverse events of unanticipated severity or frequency, or with manufacturing processes, or failure to comply with regulatory requirements, may result in

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revisions to the approved labeling to add new safety information, imposition of post-market studies or clinical trials to assess new safety risks or imposition of distribution or other restrictions under a Risk Evaluation and Mitigation Strategy program. Other potential consequences include, among other things:

- restrictions on the marketing or manufacturing of the product, complete withdrawal of the product from the market or product recalls;
- fines, warning letters or holds on post-approval clinical trials;
- refusal of the FDA to approve pending applications or supplements to approved applications, or suspension or revocation of product license approvals;
- product seizure or detention, or refusal to permit the import or export of products; or
- consent decrees, injunctions or the imposition of civil or criminal penalties.

The FDA strictly regulates marketing, labeling, advertising and promotion of products that are placed on the market. Drugs may be promoted only for the approved indications and in accordance with the provisions of the approved label. The FDA and other agencies actively enforce the laws and regulations prohibiting the promotion of off label uses, and a company that is found to have improperly promoted off label uses may be subject to significant liability.

Additional provisions

Anti-kickback and false claims laws

In addition to FDA restrictions on marketing of pharmaceutical products, several other types of state and federal laws have been applied to restrict certain marketing practices in the pharmaceutical industry in recent years. These laws include anti-kickback statutes and false claims statutes. The federal healthcare program anti-kickback statute prohibits, among other things, knowingly and willfully offering, paying, soliciting or receiving remuneration to induce or in return for purchasing, leasing, ordering or arranging for the purchase, lease or order of any healthcare item or service reimbursable under Medicare, Medicaid or other federally financed healthcare programs. This statute has been interpreted to apply to arrangements between pharmaceutical manufacturers on the one hand and prescribers, purchasers and formulary managers on the other. Violations of the anti-kickback statute are punishable by imprisonment, criminal fines, civil monetary penalties and exclusion from participation in federal healthcare programs. Although there are a number of statutory exemptions and regulatory safe harbors protecting certain common activities from prosecution or other regulatory sanctions, the exemptions and safe harbors are drawn narrowly, and practices that involve remuneration intended to induce prescribing, purchases or recommendations may be subject to scrutiny if they do not qualify for an exemption or safe harbor.

Federal false claims laws prohibit any person from knowingly presenting, or causing to be presented, a false claim for payment to the federal government, or knowingly making, or causing to be made, a false statement to have a false claim paid. Recently, several pharmaceutical and other healthcare companies have been prosecuted under these laws for allegedly inflating drug prices they report to pricing services, which in turn were used by the government to set Medicare and Medicaid reimbursement rates, and for allegedly providing free product to customers with the expectation that the customers would bill federal programs for the product. In addition, certain marketing practices, including off-label promotion, may also violate false claims laws. The majority of states also have statutes or regulations similar to the federal anti-kickback law and false claims laws, which apply to items and services reimbursed under Medicaid and other state programs, or, in several states, apply regardless of the payor.

Physician drug samples

As part of the sales and marketing process, pharmaceutical companies frequently provide samples of approved drugs to physicians. The Prescription Drug Marketing Act, or the PDMA, imposes requirements and

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limitations upon the provision of drug samples to physicians, as well as prohibits states from licensing distributors of prescription drugs unless the state licensing program meets certain federal guidelines that include minimum standards for storage, handling and record keeping. In addition, the PDMA sets forth civil and criminal penalties for violations.

Foreign regulation

In order to market any product outside of the United States, we would need to comply with numerous and varying regulatory requirements of other countries regarding safety and efficacy and governing, among other things, clinical trials, marketing authorization, commercial sales and distribution of our products. Whether or not we obtain FDA approval for a product, we would need to obtain the necessary approvals by the comparable regulatory authorities of foreign countries before we can commence clinical trials or marketing of the product in those countries. The approval process varies from country to country and can involve additional product testing and additional administrative review periods. The time required to obtain approval in other countries might differ from and be longer than that required to obtain FDA approval. Regulatory approval in one country does not ensure regulatory approval in another, but a failure or delay in obtaining regulatory approval in one country may negatively impact the regulatory process in others.

New legislation and regulations

From time to time, legislation is drafted, introduced and passed in Congress that could significantly change the statutory provisions governing the testing, approval, manufacturing and marketing of products regulated by the FDA. For example, the FDAAA discussed above was enacted in 2007. In addition to new legislation, FDA regulations and policies are often revised or interpreted by the agency in ways that may significantly affect our business and our products. It is impossible to predict whether further legislative changes will be enacted or whether FDA regulations, guidance, policies or interpretations changed or what the effect of such changes, if any, may be.

Pharmaceutical coverage, pricing and reimbursement

Significant uncertainty exists as to the coverage and reimbursement status of any drug products for which we might obtain regulatory approval. Sales of any of our product candidates, if approved, will depend, in part, on the extent to which the costs of the products will be covered by third-party payors, including government health programs such as Medicare and Medicaid, commercial health insurers and managed care organizations. The process for determining whether a payor will provide coverage for a drug product may be separate from the process for setting the price or reimbursement rate that the payor will pay for the drug product once coverage is approved. Third-party payors may limit coverage to specific drug products on an approved list, or formulary, which might not include all of the approved drugs for a particular indication.

In order to secure coverage and reimbursement for any product that might be approved for sale, we may need to conduct expensive pharmacoeconomic studies in order to demonstrate the medical necessity and cost-effectiveness of the product, in addition to the costs required to obtain FDA or other comparable regulatory approvals. Our product candidates may not be considered medically necessary or cost-effective. A payor s decision to provide coverage for a drug product does not imply that an adequate reimbursement rate will be approved. Third-party reimbursement may not be sufficient to enable us to maintain price levels high enough to realize an appropriate return on our investment in product development.

The containment of healthcare costs has become a priority of federal, state and foreign governments, and the prices of drugs have been a focus in this effort. Third-party payors are increasingly challenging the prices

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charged for medical products and services and examining the medical necessity and cost-effectiveness of medical products and services, in addition to their safety and efficacy. If these third-party payors do not consider our products to be cost-effective compared to other available therapies, they may not cover our products after approval as a benefit under their plans or, if they do, the level of payment may not be sufficient to allow us to sell our products at a profit. The U.S. government, state legislatures and foreign governments have shown significant interest in implementing cost containment programs to limit the growth of government-paid health care costs, including price controls, restrictions on reimbursement and requirements for substitution of generic products for branded prescription drugs. Adoption of such controls and measures, and tightening of restrictive policies in jurisdictions with existing controls and measures, could limit payments for pharmaceuticals such as the drug candidates that we are developing and could adversely affect our net revenue and results.

Pricing and reimbursement schemes vary widely from country to country. Some countries provide that drug products may be marketed only after a reimbursement price has been agreed. Some countries may require the completion of additional studies that compare the cost-effectiveness of a particular product candidate to currently available therapies. For example, the European Union provides options for its member states to restrict the range of drug products for which their national health insurance systems provide reimbursement and to control the prices of medicinal products for human use. European Union member states may approve a specific price for a drug product or may instead adopt a system of direct or indirect controls on the profitability of the company placing the drug product on the market. Other member states allow companies to fix their own prices for drug products, but monitor and control company profits. The downward pressure on health care costs in general, particularly prescription drugs, has become very intense. As a result, increasingly high barriers are being erected to the entry of new products. In addition, in some countries, cross-border imports from low-priced markets exert competitive pressure that may reduce pricing within a country. There can be no assurance that any country that has price controls or reimbursement limitations for drug products will allow favorable reimbursement and pricing arrangements for any of our products.

The marketability of any products for which we might receive regulatory approval for commercial sale may suffer if the government and third-party payors fail to provide adequate coverage and reimbursement. In addition, an increasing emphasis on managed care in the United States has increased and we expect will continue to increase the pressure on drug pricing. Coverage policies, third-party reimbursement rates and drug pricing regulation may change at any time. In particular, the Patient Protection and Affordable Care Act was enacted in the United States in March 2010 and contains provisions that may reduce the profitability of drug products, including, for example, increased rebates for drugs sold to Medicaid programs, extension of Medicaid rebates to Medicaid managed care plans, mandatory discounts for certain Medicare Part D beneficiaries and annual fees based on pharmaceutical companies share of sales to federal health care programs. Even if favorable coverage and reimbursement status is attained for one or more products for which we receive regulatory approval, less favorable coverage policies and reimbursement rates may be implemented in the future.

Manufacturing

We do not currently own or operate manufacturing facilities for the production of clinical or commercial quantities of any of our drug candidates. We currently rely and expect to continue to rely on other companies for the manufacture of our drug candidates for preclinical and clinical development. We currently source our bulk drug manufacturing requirements from a limited number of contract manufacturers through the issuance of work orders on an as-needed basis. We depend and will continue to depend on our contract manufacturers to manufacture our drug candidates in accordance with cGMP regulations for use in clinical trials. We will ultimately depend on contract manufacturers for the manufacture of our products for commercial sale. Contract manufacturers are subject to extensive governmental regulation.

Under our collaborative agreement with Merck, Merck is responsible for manufacturing the drug candidates.

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Competition

We are developing our TLR-targeted drug candidates for use in the treatment of autoimmune and inflammatory diseases and cancer, and for use as vaccine adjuvants. For all of the disease areas in which we are developing potential therapies, there are many other companies, public and private, that are actively engaged in discovery, development, and commercializing products and technologies that may compete with our technologies and drug candidates and technology, including TLR targeted compounds as well as non-TLR targeted therapies.

Our principal competitors developing TLR-targeted compounds for autoimmune and inflammatory diseases include Dynavax Technologies Corporation, with its collaborator, GlaxoSmithKline plc., and for cancer treatment include Pfizer, Inc., and VentiRx Pharmaceuticals.

Merck s vaccines using our TLR7, 8 or 9 agonists as adjuvants may compete with vaccines using TLR agonists as adjuvants being developed or marketed by GlaxoSmithKline plc, Novartis, Dynavax Technologies Corporation, VaxInnate, Inc., Intercell AG, Cytos Biotechnology AG and Celldex Therapeutics, Inc.

Some of the potentially competitive products have been in development or commercialized for years, in some cases by large, well established pharmaceutical companies. Many of the marketed products have been accepted by the medical community, patients, and third-party payors. Our ability to compete may be affected by the previous adoption of such products by the medical community, patients, and third-party payors. Additionally, in some instances, insurers and other third-party payors seek to encourage the use of generic products, which makes branded products, such as our drug candidates, potentially less attractive, from a cost perspective, to buyers.

We recognize that other companies, including large pharmaceutical companies, may be developing or have plans to develop products and technologies that may compete with ours. Many of our competitors have substantially greater financial, technical, and human resources than we have. In addition, many of our competitors have significantly greater experience than we have in undertaking preclinical studies and human clinical trials of new pharmaceutical products, obtaining FDA and other regulatory approvals of products for use in health care and manufacturing, and marketing and selling approved products. Our competitors may discover, develop or commercialize products or other novel technologies that are more effective, safer or less costly than any that we are developing. Our competitors may also obtain FDA or other regulatory approval for their products more rapidly than we may obtain approval for ours.

We anticipate that the competition with our products and technologies will be based on a number of factors including product efficacy, safety, availability, and price. The timing of market introduction of our products and competitive products will also affect competition among products. We expect the relative speed with which we can develop products, complete the clinical trials, and approval processes and supply commercial quantities of the products to the market to be important competitive factors. Our competitive position will also depend upon our ability to attract and retain qualified personnel, to obtain patent protection or otherwise develop proprietary products or processes, and protect our intellectual property, and to secure sufficient capital resources for the period between technological conception and commercial sales.

Employees

As of March 1, 2012, we employed 26 individuals, 16 of whom are engaged in research and development and 16 of whom hold a Ph.D., M.D., or equivalent degree. None of our employees is covered by a collective bargaining agreement, and we consider relations with our employees to be good.

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Information Available on the Internet

Our internet address is www.iderapharma.com. The contents of our website are not part of this Annual Report on Form 10-K and our internet address is included in this document as an inactive textual reference. We make available free of charge through our web site our Annual Reports on Form 10-K, Quarterly Reports on Form 10-Q, Current Reports on Form 8-K and amendments to these reports filed or furnished pursuant to Section 12(a) or 15(d) of the Securities Exchange Act of 1934, as amended, as soon as reasonably practicable after we electronically file or furnish such materials to the Securities and Exchange Commission.

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Item 1A. ***RISK FACTORS.***

RISK FACTORS

Investing in our common stock involves a high degree of risk. You should carefully consider the risks and uncertainties described below in addition to the other information included or incorporated by reference in this Annual Report on Form 10-K before purchasing our common stock. If any of the following risks actually occurs, our business, financial condition or results of operations would likely suffer, possibly materially. In that case, the trading price of our common stock could fall, and you may lose all or part of the money you paid to buy our common stock.

Risks Relating to Our Financial Results and Need for Financing

We have incurred substantial losses and expect to continue to incur losses. We will not be successful unless we reverse this trend.

We have incurred losses in every year since our inception, except for 2002, 2008, and 2009 when our recognition of revenues under license and collaboration agreements resulted in our reporting net income for those years. As of December 31, 2011, we had an accumulated deficit of $375.4 million. Since January 1, 2001, we have primarily been involved in the development of our TLR pipeline. From January 1, 2001 through December 31, 2011, we incurred losses of $115.2 million. We incurred losses of $260.2 million prior to December 31, 2000 during which time we were primarily involved in the development of non-TLR targeted antisense technology. These losses, among other things, have had and will continue to have an adverse effect on our stockholders equity, total assets, and working capital.

We have never had any products of our own available for commercial sale and have received no revenues from the sale of drugs. To date, almost all of our revenues have been from collaborative and license agreements. We have devoted substantially all of our efforts to research and development, including clinical trials, and we have not completed development of any drug candidates. Because of the numerous risks and uncertainties associated with developing drugs, we are unable to predict the extent of any future losses, whether or when any of our drug candidates will become commercially available, or when we will become profitable, if at all. We expect to incur substantial operating losses in future periods.

We will need additional financing, which may be difficult to obtain. Our failure to obtain necessary financing or doing so on unattractive terms could adversely affect our research and development programs and other operations.

We will require substantial funds to conduct research and development, including preclinical testing and clinical trials of our drug candidates. We will also require substantial funds to conduct regulatory activities and to establish commercial manufacturing, marketing, and sales capabilities. We had cash and cash equivalents of $24.6 million at December 31, 2011. We believe that our existing cash and cash equivalents will be sufficient to fund our operations at least into the first quarter of 2013 based on our current operating plan. We will need to raise additional funds in order to operate our business beyond such time. If we proceed with the clinical development of IMO-3100 beyond the planned Phase 2 trial, of IMO-2055 beyond the ongoing Phase 2 trial or of any of our other compounds, including IMO-8400, we expect that the period of time that our current resources would be able to fund our operations could be significantly reduced.

We expect to seek additional funding through collaborations, the sale or license of assets or financings of equity or debt securities. We believe that the key factors that will affect our ability to obtain additional funding are:

- the results of our clinical and preclinical development programs, including the results of the planned Phase 2 trial of IMO-3100 and the results of the ongoing Phase 2 trial of IMO-2055;

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developments related to our existing strategic collaboration with Merck;

the cost, timing, and outcome of regulatory reviews;

competitive and potentially competitive products and technologies and investors receptivity to our drug candidates and the technology underlying them in light of competitive products and technologies;

the receptivity of the capital markets to financings by biotechnology companies generally and companies with drug candidates and technologies such as ours specifically; and

our ability to enter into additional strategic collaborations with biotechnology and pharmaceutical companies and the success of such collaborations.

Additional financing may not be available to us when we need it or may not be available to us on favorable terms. We could be required to seek funds through collaborative alliances or through other means that may require us to relinquish rights to some of our technologies, drug candidates or drugs that we would otherwise pursue on our own. In addition, if we raise additional funds by issuing equity securities, our then existing stockholders will experience dilution. The terms of any financing may adversely affect the holdings or the rights of existing stockholders. Debt financing, if available, may involve agreements that include covenants limiting or restricting our ability to take specific actions, such as incurring additional debt, making capital expenditures or declaring dividends, and are likely to include rights that are senior to the holders of our common stock. Any additional debt financing or equity that we raise may contain terms, such as liquidation and other preferences, or liens or other restrictions on our assets, which are not favorable to us or our stockholders. If we are unable to obtain adequate funding on a timely basis or at all, we may be required to terminate, modify or delay preclinical or clinical trials of one or more of our drug candidates, fail to establish or delay the establishment of manufacturing, sale or marketing capabilities, curtail research and development programs for new drug candidates and/or possibly relinquish rights to portions of our technology, drug candidates and/or products. For example, we significantly curtailed expenditures on our research and development programs during 1999 and 2000 because we did not have sufficient funds available to advance these programs at planned levels.

Risks Relating to Our Business, Strategy and Industry

We are depending heavily on the development of IMO-3100 and IMO-2055 and on our collaborative alliance with Merck. If we or our collaborator decides to terminate the development of any of our drug candidates, are unable to successfully develop and commercialize our drug candidates, or experience significant delays in doing so, our business may be materially harmed.

We have invested a significant portion of our time and financial resources in the development of our clinical stage lead drug candidates, IMO-3100 and IMO-2055. We anticipate that our ability to generate product revenues will depend heavily on the successful development and commercialization of IMO-3100, IMO-2055 and the drug candidates being developed under our collaboration with Merck. Our efforts, and the efforts of Merck, to develop and commercialize these compounds are at an early stage and are subject to many challenges. In 2011, we experienced setbacks with respect to our programs for IMO-3100, IMO-2125 and IMO-2055, including:

During the fourth quarter of 2010, we commenced additional nonclinical studies of IMO-3100 in light of some reversible immune responses that were observed in the 13 week nonclinical toxicology studies and that were inconsistent with observations made in our other nonclinical studies of IMO-3100. In June 2011, we submitted a Phase 2 protocol to the FDA to conduct a 12-week clinical trial of IMO-3100 in patients with psoriasis. In July 2011, the FDA placed a clinical hold on the protocol that we had submitted.

In April 2011, we chose to delay initiation of our planned 12-week Phase 2 randomized clinical trial of IMO-2125 plus ribavirin in treatment-naïve, genotype 1 HCV patients based on preliminary observations in an ongoing 26-week chronic nonclinical toxicology study of IMO-2125 in rodents. We subsequently completed a 39-week chronic nonclinical toxicology study of IMO-2125 in non-human primates in which

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there were no similar observations. During the third quarter of 2011, we re-assessed and prioritized our drug development programs, and determined to discontinue further investment of internal resources on the development of IMO-2125 for the treatment of HCV.

In July 2011, Merck KGaA informed us that, based on increased incidence of neutropenia and electrolyte imbalances reported in its Phase 1 trial of IMO-2055 in combination with cisplatin/5-FU and cetuximab in patients with first-line SCCHN and subsequent re-evaluation of its clinical development program, Merck KGaA had determined that it would not conduct further clinical development of IMO-2055. In November 2011, we and Merck KGaA entered into a termination agreement terminating our collaboration.

In October 2011, we submitted to FDA a new Phase 2 protocol to evaluate IMO-3100 in adult patients with moderate to severe plaque psoriasis over a four-week treatment period. In December 2011, the FDA removed the clinical hold. We expect to initiate the four-week Phase 2 clinical trial in the second quarter of 2012. The outcome of this trial or the ongoing Phase 2 clinical trial of IMO-2055 being conducted by Merck KGaA could negatively impact our ability or willingness to proceed with the further development and commercialization of IMO-3100 or IMO-2055, as the case may be, or our ability to license such compounds to a third party. Moreover, with respect to IMO-3100, we cannot be certain that the FDA will allow us to conduct further clinical trials of IMO-3100 for treatment periods of more than four weeks or at all without additional clinical or preclinical data.

Our ability to successfully develop and commercialize these drug candidates, or other potential candidates, will depend on our ability to overcome these recent challenges and on several factors, including the following:

the drug candidates demonstrating an acceptable safety profile in nonclinical toxicology studies and during clinical trials;

timely enrollment in clinical trials of IMO-3100 and other drug candidates, which may be slower than anticipated, potentially resulting in significant delays;

satisfying conditions imposed on us and/or our collaborators by the FDA or equivalent foreign regulatory authorities regarding the scope or design of clinical trials;

the ability to demonstrate to the satisfaction of the FDA, or equivalent foreign regulatory authorities, the safety and efficacy of the drug candidates through current and future clinical trials;

timely receipt of necessary marketing approvals from the FDA and equivalent foreign regulatory authorities;

the ability to combine our drug candidates and the drug candidates being developed by Merck and any other collaborators safely and successfully with other therapeutic agents;

achieving and maintaining compliance with all regulatory requirements applicable to the products;

establishment of commercial manufacturing arrangements with third-party manufacturers;

the successful commercial launch of the drug candidates, assuming FDA approval is obtained, whether alone or in combination with other products;

acceptance of the products as safe and effective by patients, the medical community, and third-party payors;

competition from other companies and their therapies;

changes in treatment regimes;

successful protection of our intellectual property rights from competing products in the United States and abroad; and

a continued acceptable safety and efficacy profile of the drug candidates following marketing approval.

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If our clinical trials are unsuccessful, or if they are delayed or terminated, we may not be able to develop and commercialize our products.

In order to obtain regulatory approvals for the commercial sale of our products, we are required to complete extensive clinical trials in humans to demonstrate the safety and efficacy of our drug candidates. Clinical trials are lengthy, complex, and expensive processes with uncertain results. We may not be able to complete any clinical trial of a potential product within any specified time period. Moreover, clinical trials may not show our potential products to be both safe and efficacious. The FDA or other equivalent foreign regulatory agencies may not allow us to complete these trials or commence and complete any other clinical trials. For example, in July 2011, the FDA placed a clinical hold on a protocol we had submitted for a proposed Phase 2 clinical trial of IMO-3100 in patients with psoriasis.

The results from preclinical testing of a drug candidate that is under development may not be predictive of results that will be obtained in human clinical trials. In addition, the results of early human clinical trials may not be predictive of results that will be obtained in larger scale, advanced stage clinical trials. Furthermore, interim results of a clinical trial do not necessarily predict final results, and failure of any of our clinical trials can occur at any stage of testing. Companies in the biotechnology and pharmaceutical industries, including companies with greater experience in preclinical testing and clinical trials than we have, have suffered significant setbacks in clinical trials, even after demonstrating promising results in earlier trials. Moreover, effects seen in nonclinical studies, even if not observed in clinical trials, may result in limitations or restrictions on clinical trials. Numerous unforeseen events may occur during, or as a result of, preclinical testing, nonclinical testing or the clinical trial process that could delay or inhibit the ability to receive regulatory approval or to commercialize drug products.

In addition to the setbacks that we have experienced with respect to the clinical development of our TLR-targeted drug candidates, other companies developing drugs targeted to TLRs have experienced setbacks in clinical trials. For example in 2007, Coley Pharmaceutical Group, which since has been acquired by Pfizer, Inc., discontinued four clinical trials for PF-3512676, its investigational TLR9 agonist compound, in combination with cytotoxic chemotherapy in cancer, and suspended its development of a TLR9 agonist, Actilon®, for HCV infection. In July 2007, Anadys Pharmaceuticals, Inc. and its partner Novartis International Pharmaceutical, Ltd. (Novartis) announced that they had decided to discontinue the development of ANA975, the investigational TLR7 agonist compound for HCV infection. Dynavax Technologies Corporation announced in May 2008 discontinuation of the clinical development program for TOLAMBA®, which comprises a TLR9 agonist covalently attached to a ragweed antigen. These setbacks with respect to TLR-targeted drug candidates may result in enhanced scrutiny by regulators or IRBs of clinical trials of TLR-targeted drug candidates, including our TLR-targeted drug candidates, which could result in regulators or IRBs prohibiting the commencement of clinical trials, requiring additional nonclinical studies as a precondition to commencing clinical trials or imposing restrictions on the design or scope of clinical trials that could slow enrollment of trials, increase the costs of trials or limit the significance of the results of trials. Such setbacks could also adversely impact the desire of investigators to enroll patients in, and the desire of patients to enroll in, clinical trials of TLR-targeted drug candidates.

Other events that could delay or inhibit conduct of our clinical trials include:

- regulators or IRBs may not authorize us to commence a clinical trial or conduct a clinical trial at a prospective trial site;
- nonclinical or clinical data may not be readily interpreted, which may lead to delays and/or misinterpretation;
- our nonclinical tests, including toxicology studies, or clinical trials may produce negative or inconclusive results, and we may decide, or regulators may require us, to conduct additional nonclinical testing or clinical trials or we may abandon projects that we expect may not be promising;
- the rate of enrollment or retention of patients in our clinical trials may be lower than we expect;

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we might have to suspend or terminate our clinical trials if the participating subjects experience serious adverse events or undesirable side effects or are exposed to unacceptable health risks;

regulators or IRBs may hold, suspend or terminate clinical research for various reasons, including noncompliance with regulatory requirements, issues identified through inspections of manufacturing or clinical trial operations or clinical trial sites, or if, in their opinion, the participating subjects are being exposed to unacceptable health risks;

regulators may hold or suspend our clinical trials while collecting supplemental information on, or clarification of, our clinical trials or other clinical trials, including trials conducted in other countries or trials conducted by other companies;

we, along with our collaborators and subcontractors, may not employ, in any capacity, persons who have been debarred under the FDA s Application Integrity Policy, or similar policy under foreign regulatory authorities. Employment of such debarred persons, even if inadvertent, may result in delays in the FDA s or foreign equivalent s review or approval of our products, or the rejection of data developed with the involvement of such person(s);

the cost of our clinical trials may be greater than we currently anticipate; and

our products may not cause the desired effects or may cause undesirable side effects or our products may have other unexpected characteristics.

The rate of completion of clinical trials is dependent in part upon the rate of enrollment of patients. For example, in our Phase 1 clinical trial of IMO-2125 in patients with chronic HCV infection who had not responded to the current standard of care therapy, completion of each cohort took longer than anticipated due to enrollment procedures. Patient accrual is a function of many factors, including:

the size of the patient population;

the proximity of patients to clinical sites;

the eligibility criteria for the study;

the nature of the study, including the pattern of patient enrollment;

the existence of competitive clinical trials; and

the availability of alternative treatments.

We do not know whether clinical trials will begin as planned, will need to be restructured or will be completed on schedule, if at all. Significant clinical trial delays also could allow our competitors to bring products to market before we do and impair our ability to commercialize our products.

Delays in commencing clinical trials of potential products could increase our costs, delay any potential revenues, and reduce the probability that a potential product will receive regulatory approval.

Our drug candidates and our collaborators drug candidates will require preclinical and other nonclinical testing and extensive clinical trials prior to submission of any regulatory application for commercial sales. In conducting clinical trials, we cannot be certain that any planned clinical trial will begin on time, if at all. Delays in commencing clinical trials of potential products could increase our product development costs, delay any potential revenues, and reduce the probability that a potential product will receive regulatory approval.

Commencing clinical trials may be delayed for a number of reasons, including delays in:

manufacturing sufficient quantities of drug candidate that satisfy the required quality standards for use in clinical trials;

demonstrating sufficient safety to obtain regulatory approval for conducting a clinical trial;

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reaching an agreement with any collaborators on all aspects of the clinical trial;

reaching agreement with contract research organizations, if any, and clinical trial sites on all aspects of the clinical trial;

resolving any objections from the FDA or any regulatory authority on an IND application or proposed clinical trial design;

obtaining IRB approval for conducting a clinical trial at a prospective site; and

enrolling patients in order to commence the clinical trial.

The technologies on which we rely are unproven and may not result in any approved and marketable products.

Our technologies or therapeutic approaches are relatively new and unproven. We have focused our efforts on the research and development of RNA- and DNA-based compounds targeted to TLRs and on GSOs. Neither we nor any other company have obtained regulatory approval to market such compounds as therapeutic drugs, and no such products currently are being marketed. It is unknown whether the results of preclinical studies with TLR-targeted compounds will be indicative of results that may be obtained in clinical trials, and results we have obtained in the initial small-scale clinical trials we have conducted to date may not be predictive of results in subsequent large-scale clinical trials. Further, the chemical and pharmacological properties of RNA- and DNA-based compounds targeted to TLRs or of GSOs may not be fully recognized in preclinical studies and small-scale clinical trials, and such compounds may interact with human biological systems in unforeseen, ineffective or harmful ways that we have not yet identified.

As a result of these factors, we may never succeed in obtaining regulatory approval to market any product. Furthermore, the commercial success of any of our products for which we may obtain marketing approval from the FDA or other regulatory authorities will depend upon their acceptance by patients, the medical community, and third-party payors as clinically useful, safe, and cost-effective. In addition, if products being developed by our competitors have negative clinical trial results or otherwise are viewed negatively, the perception of our technologies and market acceptance of our products could be impacted negatively.

Our recent setbacks with respect to our TLR-targeted compounds, together with the setbacks experienced by other companies developing TLR-targeted compounds, may result in a negative perception of our technology and our TLR-targeted compounds, impact our ability to obtain marketing approval of these drug candidates and adversely affect acceptance of our technology and our TLR-targeted compounds by patients, the medical community and third-party payors.

Our efforts to educate the medical community on our potentially unique approaches may require greater resources than would be typically required for products based on conventional technologies or therapeutic approaches. The safety, efficacy, convenience, and cost-effectiveness of our products as compared to competitive products will also affect market acceptance.

We face substantial competition, which may result in others discovering, developing or commercializing drugs before or more successfully than us.

We are developing our TLR-targeted drug candidates for use in the treatment of autoimmune and inflammatory diseases and cancer, and as vaccine adjuvants. We are also advancing our gene silencing oligonucleotide, or GSO, technology for potential application as research reagents and as therapeutic agents. For all of the disease areas in which we are developing potential therapies, there are many other companies, public and private, that are actively engaged in discovering, developing, and commercializing products and technologies that may compete with our technologies and drug candidates and technology, including TLR targeted compounds as well as non-TLR targeted therapies.

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Our principal competitors developing TLR-targeted compounds for autoimmune and inflammatory diseases include Dynavax Technologies Corporation, with its collaborator, GlaxoSmithKline plc., and for cancer treatment include Pfizer, Inc., and VentiRx Pharmaceuticals. Merck s vaccines using our TLR7, 8 or 9 agonists as adjuvants may compete with vaccines using TLR agonists as adjuvants being developed or marketed by GlaxoSmithKline plc, Novartis, Dynavax Technologies Corporation, VaxInnate, Inc., Intercell AG, Cytos Biotechnology AG, and Celldex Therapeutics, Inc.

Some of these potentially competitive products have been in development or commercialized for years, in some cases by large, well established pharmaceutical companies. Many of the marketed products have been accepted by the medical community, patients, and third-party payors. Our ability to compete may be affected by the previous adoption of such products by the medical community, patients, and third-party payors. Additionally, in some instances, insurers and other third-party payors seek to encourage the use of generic products, which makes branded products, such as our drug candidates, potentially less attractive, from a cost perspective, to buyers.

We recognize that other companies, including large pharmaceutical companies, may be developing or have plans to develop products and technologies that may compete with ours. Many of our competitors have substantially greater financial, technical, and human resources than we have. In addition, many of our competitors have significantly greater experience than we have in undertaking preclinical studies and human clinical trials of new pharmaceutical products, obtaining FDA and other regulatory approvals of products for use in health care and manufacturing, and marketing and selling approved products. Our competitors may discover, develop or commercialize products or other novel technologies that are more effective, safer or less costly than any that we are developing. Our competitors may also obtain FDA or other regulatory approval for their products more rapidly than we may obtain approval for ours.

We anticipate that the competition with our products and technologies will be based on a number of factors including product efficacy, safety, availability, and price. The timing of market introduction of our products and competitive products will also affect competition among products. We expect the relative speed with which we can develop products, complete the clinical trials, and approval processes and supply commercial quantities of the products to the market to be important competitive factors. Our competitive position will also depend upon our ability to attract and retain qualified personnel, to obtain patent protection or otherwise develop proprietary products or processes, and protect our intellectual property, and to secure sufficient capital resources for the period between technological conception and commercial sales.

Competition for technical and management personnel is intense in our industry, and we may not be able to sustain our operations or grow if we are unable to attract and retain key personnel.

Our success is highly dependent on the retention of principal members of our technical and management staff, including Dr. Sudhir Agrawal. Dr. Agrawal serves as our Chairman of the Board of Directors, President and Chief Executive Officer. Dr. Agrawal has made significant contributions to the field of oligonucleotide-based drug candidates, and has led the discovery and development of our compounds targeted to TLRs. He is named as an inventor on over 400 patents and patent applications in countries around the world. Dr. Agrawal provides us with leadership for our management team and research and development activities. The loss of Dr. Agrawal s services would be detrimental to our ongoing scientific progress and the execution of our business plan.

We are a party to an employment agreement with Dr. Agrawal that expires on October 19, 2014, but automatically extends annually for an additional year. This agreement may be terminated by us or Dr. Agrawal for any reason or no reason at any time upon notice to the other party. We do not carry key man life insurance for Dr. Agrawal.

Furthermore, our future growth will require hiring a number of qualified technical and management personnel. Accordingly, recruiting and retaining such personnel in the future will be critical to our success. There

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is intense competition from other companies and research and academic institutions for qualified personnel in the areas of our activities. If we are not able to continue to attract and retain, on acceptable terms, the qualified personnel necessary for the continued development of our business, we may not be able to sustain our operations or growth.

Regulatory Risks

We may not be able to obtain marketing approval for products resulting from our development efforts.

All of the drug candidates that we are developing, or may develop in the future, will require additional research and development, extensive preclinical studies, nonclinical testing, clinical trials, and regulatory approval prior to any commercial sales. This process is lengthy, often taking a number of years, is uncertain, and is expensive. Since our inception, we have conducted clinical trials of a number of compounds. Currently two of our compounds, IMO-3100 and IMO-2055, are in clinical development. The FDA and other regulatory authorities may not approve any of our potential products for any indication.

We may need to address a number of technological challenges in order to complete development of our products. Moreover, these products may not be effective in treating any disease or may prove to have undesirable or unintended side effects, unintended alteration of the immune system over time, toxicities or other characteristics that may preclude our obtaining regulatory approval or prevent or limit commercial use. If we do not obtain necessary regulatory approvals, our business will be adversely affected.

We are subject to comprehensive regulatory requirements, which are costly and time consuming to comply with; if we fail to comply with these requirements, we could be subject to adverse consequences and penalties.

The testing, manufacturing, labeling, advertising, promotion, export, and marketing of our products are subject to extensive regulation by governmental authorities in Europe, the United States, and elsewhere throughout the world.

In general, submission of materials requesting permission to conduct clinical trials may not result in authorization by the FDA or any equivalent foreign regulatory agency to commence clinical trials. Further, permission to continue ongoing trials may be withdrawn by the FDA or other regulatory agencies at any time after initiation, based on new information available after the initial authorization to commence clinical trials or for other reasons. In addition, submission of an application for marketing approval to the relevant regulatory agency following completion of clinical trials may not result in the regulatory agency approving the application if applicable regulatory criteria are not satisfied, and may result in the regulatory agency requiring additional testing or information.

Even if we obtain regulatory approval for any of our product candidates, we will be subject to ongoing FDA obligations and regulatory oversight. Any regulatory approval of a product may contain limitations on the approved indicated uses for which the product may be marketed or requirements for costly post-marketing testing and surveillance to monitor the safety or efficacy of the product. Any product for which we obtain marketing approval, along with the facilities at which the product is manufactured, any post-approval clinical data, and any advertising and promotional activities for the product will be subject to continual review and periodic inspections by the FDA and other regulatory agencies.

Both before and after approval is obtained, failure to comply with regulatory requirements, or discovery of previously unknown problems with a product, including adverse events of unanticipated severity or frequency, may result in:

- the regulatory agency s delay in approving, or refusal to approve, an application for marketing of a product or a supplement to an approved application;

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restrictions on our products or the marketing or manufacturing of our products;

withdrawal of our products from the market;

warning letters;

voluntary or mandatory product recalls;

fines;

suspension or withdrawal of regulatory approvals;

product seizure or detention;

refusal to permit the import or export of our products;

injunctions or the imposition of civil penalties; and

criminal penalties.

We have only limited experience in regulatory affairs and our products are based on new technologies; these factors may affect our ability or the time we require to obtain necessary regulatory approvals.

We have only limited experience in filing the applications necessary to obtain regulatory approvals. Moreover, the products that result from our research and development programs will likely be based on new technologies and new therapeutic approaches that have not been extensively tested in humans. The regulatory requirements governing these types of products may be more rigorous than for conventional drugs. As a result, we may experience a longer regulatory process in connection with obtaining regulatory approvals of any product that we develop.

Failure to obtain regulatory approval in jurisdictions outside the United States will prevent us from marketing our products abroad.

We intend to market our products, if approved, in markets outside the United States, which will require separate regulatory approvals and compliance with numerous and varying regulatory requirements. The approval procedures vary among such markets and may involve requirements for additional testing, and the time required to obtain approval may differ from that required to obtain FDA approval. Approval by the FDA does not ensure approval by regulatory authorities in other countries or jurisdictions, and approval by one foreign regulatory authority does not ensure approval by regulatory authorities in other foreign countries or by the FDA. The foreign regulatory approval process may include all of the risks associated with obtaining FDA approval. We may not obtain foreign regulatory approvals on a timely basis, if at all.

Risks Relating to Collaborators

If we are unable to establish additional collaborative alliances, our business may be materially harmed.

We seek to advance some of our products through collaborative alliances with pharmaceutical companies. Collaborators provide the necessary resources and drug development experience to advance our compounds in their programs. During the third quarter of 2011, we decided to advance our TLR-targeted programs in infectious diseases, respiratory diseases, hematologic oncology, and additional vaccine adjuvant applications only through partnerships with third parties.

Upfront payments and milestone payments received from collaborations help to provide us with the financial resources for our internal research and development programs. Our internal programs are focused on developing TLR-targeted drug candidates for the potential treatment of autoimmune and inflammatory diseases and cancer. We are also advancing our GSO technology for potential application as research reagents and as

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therapeutic agents. We believe that additional resources will be required to advance compounds in all of these areas. If we do not reach agreements with additional collaborators in the future, we may not be able to obtain the expertise and resources necessary to achieve our business objectives, our ability to advance our compounds will be jeopardized and we may fail to meet our business objectives.

We may have difficulty establishing additional collaboration alliances, particularly with respect to our TLR-targeted drug candidates and technology. Potential partners may note that our TLR collaborations with Novartis and with Merck KGaA have been terminated. Potential partners may also be reluctant to establish collaborations with respect to IMO-2125, IMO-3100, and our other TLR-targeted drug candidates, given our recent setbacks with respect to IMO-3100, IMO-2055 and IMO-2125. We also face, and expect to continue to face, significant competition in seeking appropriate collaborators.

Even if a potential partner were willing to enter into a collaborative alliance with respect to our TLR-targeted compounds or technology, the terms of such a collaborative alliance may not be on terms that are favorable to us. Moreover, collaborations are complex and time consuming to negotiate, document, and implement. We may not be successful in our efforts to establish and implement collaborations on a timely basis.

Our existing collaboration and any collaborations we enter into in the future may not be successful.

An important element of our business strategy includes entering into collaborative alliances with corporate collaborators, primarily large pharmaceutical companies, for the development, commercialization, marketing, and distribution of some of our drug candidates. In December 2007, we entered into an exclusive, worldwide license agreement with Merck KGaA to research, develop, and commercialize products containing our TLR9 agonists for treatment of cancer, excluding cancer vaccines. In December 2006, we entered into an exclusive license and research collaboration with Merck to research, develop, and commercialize vaccine products containing our TLR7, 8, and 9 agonists in the fields of cancer, infectious diseases, and Alzheimer s disease.

Any collaboration that we enter into may not be successful. For instance, in July 2011, Merck KGaA informed us that it had determined not to conduct further clinical development of IMO-2055, and in November 2011, we entered into an agreement with Merck KGaA terminating our collaboration with them. The success of our collaborative alliances, if any, will depend heavily on the efforts and activities of our collaborators. Our existing collaboration and any potential future collaborations have risks, including the following:

- our collaborators may control the development of the drug candidates being developed with our technologies and compounds including the timing of development;
- our collaborators may control the public release of information regarding the developments, and we may not be able to make announcements or data presentations on a schedule favorable to us;
- disputes may arise in the future with respect to the ownership of rights to technology developed with our collaborators;
- disagreements with our collaborators could delay or terminate the research, development or commercialization of products, or result in litigation or arbitration;
- we may have difficulty enforcing the contracts if any of our collaborators fail to perform;
- our collaborators may terminate their collaborations with us, which could make it difficult for us to attract new collaborators or adversely affect the perception of us in the business or financial communities;
- our collaboration agreements are likely to be for fixed terms and subject to termination by our collaborators in the event of a material breach or lack of scientific progress by us;

our collaborators may have the first right to maintain or defend our intellectual property rights and, although we would likely have the right to assume the maintenance and defense of our intellectual property rights if our collaborators do not, our ability to do so may be compromised by our collaborators acts or omissions;

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our collaborators may challenge our intellectual property rights or utilize our intellectual property rights in such a way as to invite litigation that could jeopardize or invalidate our intellectual property rights or expose us to potential liability;

our collaborators may not comply with all applicable regulatory requirements, or may fail to report safety data in accordance with all applicable regulatory requirements;

our collaborators may change the focus of their development and commercialization efforts. Pharmaceutical and biotechnology companies historically have re-evaluated their priorities following mergers and consolidations, which have been common in recent years in these industries. For example, we have a strategic partnership with Merck, which merged with Schering-Plough, which has been involved with certain TLR-targeted research and development programs. Although the merger has not affected our partnership with Merck to date, management of the combined company could determine to reduce the efforts and resources that the combined company will apply to its strategic partnership with us or terminate the strategic partnership. The ability of our products to reach their potential could be limited if our collaborators decrease or fail to increase spending relating to such products;

our collaborators may under fund or not commit sufficient resources to the testing, marketing, distribution or development of our products; and

our collaborators may develop alternative products either on their own or in collaboration with others, or encounter conflicts of interest or changes in business strategy or other business issues, which could adversely affect their willingness or ability to fulfill their obligations to us.

Given these risks, it is possible that any collaborative alliance into which we enter may not be successful. Collaborations with pharmaceutical companies and other third parties often are terminated or allowed to expire by the other party. For example, effective as of February 2010, Novartis terminated the research collaboration and option agreement that we entered into with it in May 2005, and in November 2011, we entered into an agreement with Merck KGaA terminating our collaboration with them. In addition, Merck may terminate its license and research collaboration agreement by giving us 90 days advance notice. The termination or expiration of our agreement with Merck or any other collaboration agreement that we enter into in the future may adversely affect us financially and could harm our business reputation.

Risks Relating to Intellectual Property

If we are unable to obtain patent protection for our discoveries, the value of our technology and products will be adversely affected.

Our patent positions, and those of other drug discovery companies, are generally uncertain and involve complex legal, scientific, and factual questions. Our ability to develop and commercialize drugs depends in significant part on our ability to:

obtain patents;

obtain licenses to the proprietary rights of others on commercially reasonable terms;

operate without infringing upon the proprietary rights of others;

prevent others from infringing on our proprietary rights; and

protect our trade secrets.

We do not know whether any of our patent applications or those patent applications that we license will result in the issuance of any patents. Our issued patents and those that may be issued in the future, or those licensed to us, may be challenged, invalidated or circumvented, and the rights granted thereunder may not

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provide us proprietary protection or competitive advantages against competitors with similar technology. Moreover, intellectual property laws may change and negatively impact our ability to obtain issued patents covering our technologies or to enforce any patents that issue. Because of the extensive time required for development, testing, and regulatory review of a potential product, it is possible that, before any of our products can be commercialized, any related patent may expire or remain in force for only a short period following commercialization, thus reducing any advantage provided by the patent.

Because patent applications in the United States and many foreign jurisdictions are typically not published until 18 months after filing, or in some cases not at all, and because publications of discoveries in the scientific literature often lag behind actual discoveries, neither we nor our licensors can be certain that we or they were the first to make the inventions claimed in issued patents or pending patent applications, or that we or they were the first to file for protection of the inventions set forth in these patent applications.

As of March 1, 2012, we owned 78 U.S. patents and U.S. patent applications and 256 corresponding patents and patent applications throughout the rest of the world for our TLR-targeted immune modulation technologies. These patents and patent applications include novel chemical compositions of matter and methods of use of our IMO compounds, including IMO-3100, IMO-2055, and IMO-8400. With respect to IMO-3100, we have patent applications that cover the chemical composition of matter of IMO-3100 and methods of its use that, if issued, would expire at the earliest in 2026. With respect to IMO-2055, we have issued patents that cover the chemical composition of matter of IMO-2055 and methods of its use, including in combination with marketed cancer products, with the earliest composition claims expiring in 2023. With respect to IMO-8400, we have patent applications that cover the chemical composition of matter of IMO-8400 and methods of its use that, if issued, would expire at the earliest in 2031.

As of March 1, 2012, we owned four U.S. patent applications and one worldwide patent application for our GSO compounds and methods of their use. Patents issuing from these patent applications, if any, would expire at the earliest in 2030.

In addition to our TLR-targeted and GSO patent portfolios, we are the owner or hold licenses of patents and patent applications related to antisense technology. As of March 1, 2012, our antisense patent portfolio included 100 U.S. patents and patent applications and 163 patents and patent applications throughout the rest of the world. These antisense patents and patent applications include novel compositions of matter, the use of these compositions for various genes, sequences and therapeutic targets, and oral and other routes of administration. Some of the patents and patent applications in our antisense portfolio were in-licensed. These in-licensed patents expire at various dates ranging from 2012 to 2022.

Third parties may own or control patents or patent applications and require us to seek licenses, which could increase our development and commercialization costs, or prevent us from developing or marketing products.

Although we have many issued patents and pending patent applications in the United States and other countries, we may not have rights under certain third party patents or patent applications related to our products. Third parties may own or control these patents and patent applications in the United States and abroad. In particular, we are aware of third party United States patents that contain broad claims related to the use of certain oligonucleotides for stimulating an immune response, although we do not believe that these claims are valid. In addition, there may be other patents and patent applications related to our products of which we are not aware. Therefore, in some cases, in order to develop, manufacture, sell or import some of our products, we or our collaborators may choose to seek, or be required to seek, licenses under third-party patents issued in the United States and abroad or under third party patents that might issue from United States and foreign patent applications. In such an event, we would be required to pay license fees or royalties or both to the licensor. If licenses are not available to us on acceptable terms, we or our collaborators may not be able to develop, manufacture, sell or import these products.

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We may lose our rights to patents, patent applications or technologies of third parties if our licenses from these third parties are terminated. In such an event, we might not be able to develop or commercialize products covered by the licenses.

Currently, we have not in-licensed any patents or patent applications related to our TLR-targeted drug candidate programs or our GSO compounds and methods of their use. However, we are party to six royalty-bearing license agreements under which we have acquired rights to patents, patent applications, and technology of third parties in the field of antisense technology, which may be applicable to our TLR antisense. Under these licenses we are obligated to pay royalties on net sales by us of products or processes covered by a valid claim of a patent or patent application licensed to us. We also are required in some cases to pay a specified percentage of any sublicense income that we may receive. These licenses impose various commercialization, sublicensing, insurance, and other obligations on us.

Our failure to comply with these requirements could result in termination of the licenses. These licenses generally will otherwise remain in effect until the expiration of all valid claims of the patents covered by such licenses or upon earlier termination by the parties. The issued patents covered by these licenses expire at various dates ranging from 2012 to 2022. If one or more of these licenses is terminated, we may be delayed in our efforts, or be unable, to develop and market the products that are covered by the applicable license or licenses.

We may become involved in expensive patent litigation or other proceedings, which could result in our incurring substantial costs and expenses or substantial liability for damages or require us to stop our development and commercialization efforts.

There has been substantial litigation and other proceedings regarding patent and other intellectual property rights in the biotechnology industry. We may become a party to various types of patent litigation or other proceedings regarding intellectual property rights from time to time even under circumstances where we are not practicing and do not intend to practice any of the intellectual property involved in the proceedings. For instance, in 2002, 2003, and 2005, we became involved in interference proceedings declared by the United States Patent and Trademark Office for some of our antisense and ribozyme patents. All of these interferences have since been resolved. We are neither practicing nor intending to practice the intellectual property that is associated with any of these interference proceedings.

The cost to us of any patent litigation or other proceeding even if resolved in our favor, could be substantial. Some of our competitors may be able to sustain the cost of such litigation or proceedings more effectively than we can because of their substantially greater financial resources. If any patent litigation or other proceeding is resolved against us, we or our collaborators may be enjoined from developing, manufacturing, selling or importing our drugs without a license from the other party and we may be held liable for significant damages. We may not be able to obtain any required license on commercially acceptable terms or at all.

Uncertainties resulting from the initiation and continuation of patent litigation or other proceedings could have a material adverse effect on our ability to compete in the marketplace. Patent litigation and other proceedings may also absorb significant management time.

Risks Relating to Product Manufacturing, Marketing and Sales, and Reliance on Third Parties

Because we have limited manufacturing experience, and no manufacturing facilities or infrastructure, we are dependent on third-party manufacturers to manufacture drug candidates for us. If we cannot rely on third-party manufacturers, we will be required to incur significant costs and devote significant efforts to establish our own manufacturing facilities and capabilities.

We have limited manufacturing experience and no manufacturing facilities, infrastructure or clinical or commercial scale manufacturing capabilities. In order to continue to develop our drug candidates, apply for regulatory approvals, and ultimately commercialize products, we need to develop, contract for or otherwise arrange for the necessary manufacturing capabilities.

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We currently rely upon third parties to produce material for nonclinical and clinical testing purposes and expect to continue to do so in the future. We also expect to rely upon third parties to produce materials that may be required for the commercial production of our products. Our current and anticipated future dependence upon others for the manufacture of our drug candidates may adversely affect our future profit margins and our ability to develop drug candidates and commercialize any drug candidates on a timely and competitive basis. We currently do not have any long term supply contracts.

There are a limited number of manufacturers that operate under the FDA s current Good Manufacturing Practices, or cGMP, regulations capable of manufacturing our drug candidates. As a result, we may have difficulty finding manufacturers for our products with adequate capacity for our needs. If we are unable to arrange for third-party manufacturing of our drug candidates on a timely basis, or to do so on commercially reasonable terms, we may not be able to complete development of our drug candidates or market them.

Reliance on third-party manufacturers entails risks to which we would not be subject if we manufactured drug candidates ourselves, including:

- reliance on the third party for regulatory compliance and quality assurance;
- the possibility of breach of the manufacturing agreement by the third party because of factors beyond our control;
- the possibility of termination or nonrenewal of the agreement by the third party, based on its own business priorities, at a time that is costly or inconvenient for us;
- the potential that third-party manufacturers will develop know-how owned by such third party in connection with the production of our drug candidates that becomes necessary for the manufacture of our drug candidates; and
- reliance upon third-party manufacturers to assist us in preventing inadvertent disclosure or theft of our proprietary knowledge.

Any contract manufacturers with which we enter into manufacturing arrangements will be subject to ongoing periodic, unannounced inspections by the FDA, or foreign equivalent, and corresponding state and foreign agencies or their designees to ensure compliance with cGMP requirements and other governmental regulations and corresponding foreign standards. For example, one of our contract manufacturers notified us that it had received a cGMP warning letter from the FDA in February 2011. Any failure by our third-party manufacturers to comply with such requirements, regulations or standards could lead to a delay in the conduct of our clinical trials, or a delay in, or failure to obtain, regulatory approval of any of our drug candidates. Such failure could also result in sanctions being imposed, including fines, injunctions, civil penalties, delays, suspension or withdrawal of approvals, product seizures or recalls, imposition of operating restrictions, total or partial suspension of production or distribution, or criminal prosecution.

Additionally, contract manufacturers may not be able to manufacture our drug candidates at a cost or in quantities necessary to make them commercially viable. To date, our third-party manufacturers have met our manufacturing requirements, but we cannot be assured that they will continue to do so. Furthermore, changes in the manufacturing process or procedure, including a change in the location where the drug substance or drug product is manufactured or a change of a third-party manufacturer, may require prior FDA review and approval in accordance with the FDA s cGMP and NDA/BLA regulations. Contract manufacturers may also be subject to comparable foreign requirements. This review may be costly and time-consuming and could delay or prevent the launch of a drug candidate. The FDA or similar foreign regulatory agencies at any time may also implement new standards, or change their interpretation and enforcement of existing standards for manufacture, packaging or testing of products. If we or our contract manufacturers are unable to comply, we or they may be subject to regulatory action, civil actions or penalties.

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We have no experience selling, marketing or distributing products and no internal capability to do so.

If we receive regulatory approval to commence commercial sales of any of our drug candidates, we will face competition with respect to commercial sales, marketing, and distribution. These are areas in which we have no experience. To market any of our drug candidates directly, we would need to develop a marketing and sales force with technical expertise and with supporting distribution capability. In particular, we would need to recruit a large number of experienced marketing and sales personnel. Alternatively, we could engage a pharmaceutical or other healthcare company with an existing distribution system and direct sales force to assist us. However, to the extent we entered into such arrangements, we would be dependent on the efforts of third parties. If we are unable to establish sales and distribution capabilities, whether internally or in reliance on third parties, our business would suffer materially.

If third parties on whom we rely for clinical trials do not perform as contractually required or as we expect, we may not be able to obtain regulatory approval for or commercialize our products and our business may suffer.

We do not have the ability to independently conduct the clinical trials required to obtain regulatory approval for our drug candidates. We depend on independent clinical investigators, contract research organizations, and other third-party service providers in the conduct of the clinical trials of our drug candidates and expect to continue to do so. We contracted with contract research organizations to manage our Phase 1 clinical trials of IMO-2125 in patients with chronic HCV infection and our Phase 1 clinical trials of IMO-3100 in healthy subjects and expect to contract with such organizations for future clinical trials. We rely heavily on these parties for successful execution of our clinical trials, but do not control many aspects of their activities. We are responsible for ensuring that each of our clinical trials is conducted in accordance with the general investigational plan and protocols for the trial. Moreover, the FDA and foreign regulatory agencies require us to comply with certain standards, commonly referred to as good clinical practices, and applicable regulatory requirements, for conducting, recording, and reporting the results of clinical trials to assure that data and reported results are credible and accurate and that the rights, integrity, and confidentiality of clinical trial participants are protected. Our reliance on third parties that we do not control does not relieve us of these responsibilities and requirements. Third parties may not complete activities on schedule, or at all, or may not conduct our clinical trials in accordance with regulatory requirements or our stated protocols. The failure of these third parties to carry out their obligations could delay or prevent the development, approval, and commercialization of our drug candidates. If we seek to conduct any of these activities ourselves in the future, we will need to recruit appropriately trained personnel and add to our infrastructure.

The commercial success of any drug candidates that we may develop will depend upon the degree of market acceptance by physicians, patients, third-party payors, and others in the medical community.

Any products that we ultimately bring to the market, if they receive marketing approval, may not gain market acceptance by physicians, patients, third-party payors or others in the medical community. If these products do not achieve an adequate level of acceptance, we may not generate significant product revenue and we may not become profitable. The degree of market acceptance of our drug candidates, if approved for commercial sale, will depend on a number of factors, including:

- the prevalence and severity of any side effects, including any limitations or warnings contained in the product s approved labeling;
- the efficacy and potential advantages over alternative treatments;
- the ability to offer our drug candidates for sale at competitive prices;
- relative convenience and ease of administration;
- the willingness of the target patient population to try new therapies and of physicians to prescribe these therapies;

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the strength of marketing and distribution support and the timing of market introduction of competitive products; and

publicity concerning our products or competing products and treatments.

Even if a potential product displays a favorable efficacy and safety profile, market acceptance of the product will not be known until after it is launched. Our efforts to educate patients, the medical community, and third-party payors on the benefits of our drug candidates may require significant resources and may never be successful. Such efforts to educate the marketplace may require more resources than are required by conventional technologies marketed by our competitors.

If we are unable to obtain adequate reimbursement from third-party payors for any products that we may develop or acceptable prices for those products, our revenues and prospects for profitability will suffer.

Most patients rely on Medicare, Medicaid, private health insurers, and other third-party payors to pay for their medical needs, including any drugs we may market. If third-party payors do not provide adequate coverage or reimbursement for any products that we may develop, our revenues and prospects for profitability will suffer. Congress enacted a limited prescription drug benefit for Medicare recipients in the Medicare Prescription Drug, Improvement, and Modernization Act of 2003. While the program established by this statute may increase demand for our products if we were to participate in this program, our prices will be negotiated with drug procurement organizations for Medicare beneficiaries and are likely to be lower than we might otherwise obtain. Non-Medicare third-party drug procurement organizations may also base the price they are willing to pay on the rate paid by drug procurement organizations for Medicare beneficiaries.

A primary trend in the United States healthcare industry is toward cost containment. In addition, in some foreign countries, particularly the countries of the European Union, the pricing of prescription pharmaceuticals is subject to governmental control. In these countries, pricing negotiations with governmental authorities can take six months or longer after the receipt of regulatory marketing approval for a product. To obtain reimbursement or pricing approval in some countries, we may be required to conduct a clinical trial that compares the cost effectiveness of our drug candidates or products to other available therapies. The conduct of such a clinical trial could be expensive and result in delays in commercialization of our products. These further clinical trials would require additional time, resources, and expenses. If reimbursement of our products is unavailable or limited in scope or amount, or if pricing is set at unsatisfactory levels, our prospects for generating revenue, if any, could be adversely affected and our business may suffer.

In March 2010, the Patient Protection and Affordable Care Act and the Health Care and Education Reconciliation Act became law. These health care reform laws are intended to broaden access to health insurance; reduce or constrain the growth of health care spending, especially Medicare spending; enhance remedies against fraud and abuse; add new transparency requirements for health care and health insurance industries; impose new taxes and fees on certain sectors of the health industry; and impose additional health policy reforms. Among the new fees is an annual assessment on makers of branded pharmaceuticals and biologics, under which a company s assessment is based primarily on its share of branded drug sales to federal health care programs. Such fees could affect our future profitability. Although it is too early to determine the effect of the new health care legislation on our future profitability and financial condition, the new law appears likely to continue the pressure on pharmaceutical pricing, especially under the Medicare program, and may also increase our regulatory burdens and operating costs.

Third-party payors are challenging the prices charged for medical products and services, and many third-party payors limit reimbursement for newly-approved health care products. These third-party payors may base their coverage and reimbursement on the coverage and reimbursement rate paid by carriers for Medicare beneficiaries. Furthermore, many such payors are investigating or implementing methods for reducing health care costs, such as the establishment of capitated or prospective payment systems. Cost containment pressures

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have led to an increased emphasis on the use of cost-effective products by health care providers. In particular, third-party payors may limit the indications for which they will reimburse patients who use any products that we may develop. Cost control initiatives could decrease the price we might establish for products that we or our current or future collaborators may develop or sell, which would result in lower product revenues or royalties payable to us.

We face a risk of product liability claims and may not be able to obtain insurance.

Our business exposes us to the risk of product liability claims that is inherent in the manufacturing, testing, and marketing of human therapeutic drugs. We face an inherent risk of product liability exposure related to the testing of our drug candidates in human clinical trials and will face an even greater risk if we commercially sell any products. Regardless of merit or eventual outcome, liability claims and product recalls may result in:

- decreased demand for our drug candidates and products;
- damage to our reputation;
- regulatory investigations that could require costly recalls or product modifications;
- withdrawal of clinical trial participants;
- costs to defend related litigation;
- substantial monetary awards to clinical trial participants or patients, including awards that substantially exceed our product liability insurance, which we would then have to pay using other sources, if available, and would damage our ability to obtain liability insurance at reasonable costs, or at all, in the future;
- loss of revenue;
- the diversion of management s attention away from managing our business; and
- the inability to commercialize any products that we may develop.

Although we have product liability and clinical trial liability insurance that we believe is adequate, this insurance is subject to deductibles and coverage limitations. We may not be able to obtain or maintain adequate protection against potential liabilities. If we are unable to obtain insurance at acceptable cost or otherwise protect against potential product liability claims, we will be exposed to significant liabilities, which may materially and adversely affect our business and financial position. These liabilities could prevent or interfere with our commercialization efforts.

Risks Relating to an Investment in Our Common Stock

Our corporate governance structure, including provisions in our certificate of incorporation and by-laws and Delaware law, may prevent a change in control or management that stockholders may consider desirable.

Section 203 of the Delaware General Corporation Law and our certificate of incorporation and by-laws contain provisions that might enable our management to resist a takeover of our company or discourage a third party from attempting to take over our company. These provisions include:

a classified board of directors;

limitations on the removal of directors;

limitations on stockholder proposals at meetings of stockholders;

the inability of stockholders to act by written consent or to call special meetings; and

the ability of our board of directors to designate the terms of and issue new series of preferred stock without stockholder approval.

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In addition, Section 203 of the Delaware General Corporation Law imposes restrictions on our ability to engage in business combinations and other specified transactions with significant stockholders. These provisions could have the effect of delaying, deferring or preventing a change in control of us or a change in our management that stockholders may consider favorable or beneficial. These provisions could also discourage proxy contests and make it more difficult for you and other stockholders to elect directors and take other corporate actions. These provisions could also limit the price that investors might be willing to pay in the future for shares of our common stock.

Our stock price has been and may in the future be extremely volatile. In addition, because an active trading market for our common stock has not developed, our investors ability to trade our common stock may be limited. As a result, investors may lose all or a significant portion of their investment.

Our stock price has been volatile. During the period from January 1, 2010 to March 1, 2012, the closing sales price of our common stock ranged from a high of $6.94 per share to a low of $0.97 per share. The stock market has also experienced significant price and volume fluctuations, particularly within the past three years, and the market prices of biotechnology companies in particular have been highly volatile, often for reasons that have been unrelated to the operating performance of particular companies. The market price for our common stock may be influenced by many factors, including:

- timing and results of nonclinical studies and clinical trials of our drug candidates or those of our competitors;
- the regulatory status of our drug candidates;
- failure of any of our drug candidates, if approved, to achieve commercial success;
- the success of competitive products or technologies;
- regulatory developments in the United States and foreign countries;
- our success in entering into collaborative agreements;
- developments or disputes concerning patents or other proprietary rights;
- the departure of key personnel;
- variations in our financial results or those of companies that are perceived to be similar to us;
- our cash resources;
- the terms of any financing conducted by us;
- changes in the structure of healthcare payment systems;

market conditions in the pharmaceutical and biotechnology sectors and issuance of new or changed securities analysts reports or recommendations; and

general economic, industry, and market conditions.

In addition, our common stock has historically been traded at low volume levels and may continue to trade at low volume levels. As a result, any large purchase or sale of our common stock could have a significant impact on the price of our common stock and it may be difficult for investors to sell our common stock in the market without depressing the market price for the common stock or at all.

As a result of the foregoing, investors may not be able to resell their shares at or above the price they paid for such shares. Investors in our common stock must be willing to bear the risk of fluctuations in the price of our common stock and the risk that the value of their investment in our stock could decline.

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We must meet the NASDAQ Global Market continued listing requirements or we risk delisting, which may decrease our stock price and make it harder for our stockholders to trade our stock.

Our common stock is currently listed on the NASDAQ Global Market and has traded as low as $0.95 per share during the fourth quarter of 2011 and has traded just under $1.20 per share during much of the fourth quarter of 2011 and the first quarter of 2012. We are required to meet specified financial requirements to maintain such listing, one of which is that we maintain a minimum closing price of at least $1.00 per share for our common stock. If we fail to maintain the $1.00 minimum closing price for 30 consecutive business days, we may be at risk of delisting. Upon receipt of a deficiency notice from NASDAQ we have 180 days to attempt to regain compliance, such as through a reverse stock split. If we do not regain compliance during this initial period, we may be eligible for an additional 180 day compliance period. To qualify, we would be required to transfer to the NASDAQ Capital Market, meet the listing requirements for that market (with the exception of the minimum closing price requirement) and present a plan to regain compliance with the $1.00 minimum closing price requirement. However, if it appears to the NASDAQ that we will not be able to cure the deficiency, or if we are otherwise not eligible, our common stock would be subject to delisting. While there is a right to appeal the NASDAQ s determination to delist our common stock, there can be no assurance they would grant our request for continued listing.

There can be no assurance that we will meet the continued listing requirements for the NASDAQ Global Market, or that our common stock will not be delisted from the NASDAQ Global Market in the future. If our common stock is delisted from NASDAQ, it may be eligible to trade on the over-the-counter market, which may be a less liquid market, or on the pink sheets. In such case, our stockholders ability to trade, or obtain quotations of the market value of, shares of our common stock would be severely limited because of lower trading volumes and transaction delays. These factors could contribute to lower prices and larger spreads in the bid and ask prices for our securities. There can be no assurance that our common stock, if delisted from the NASDAQ Global Market, will be listed on a national securities exchange, a national quotation service, the OTC Bulletin Board or the pink sheets. Delisting from NASDAQ, or even the issuance of a notice of potential delisting, would also result in negative publicity, make it more difficult for us to raise additional capital, adversely affect the market liquidity of our common stock, reduce security analysts coverage of us and diminish investor, supplier and employee confidence.

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

None.

Item 2. ***Properties.***

We lease approximately 26,000 square feet of laboratory and office space located in Cambridge, Massachusetts. The lease expires on May 31, 2014, subject to a five-year renewal option exercisable by us. We have specified rights to sublease this facility.

Item 3. ***Legal Proceedings.***

None.

Item 4. ***Mine Safety Disclosures.***

Not applicable.

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PART II.

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

Market Information

Our common stock is listed on the NASDAQ Global Market under the symbol IDRA.

The following table sets forth, for the periods indicated, the high and low sales prices per share of our common stock during each of the quarters set forth below as reported on the NASDAQ Global Market. These prices reflect inter-dealer prices without retail mark-up, mark-down or commission and may not necessarily represent actual transactions.

	High	Low
2010		
First Quarter	$ 6.33	$ 4.50
Second Quarter	7.32	3.02
Third Quarter	3.88	3.08
Fourth Quarter	3.54	2.35
2011		
First Quarter	$ 3.73	$ 2.34
Second Quarter	2.74	2.00
Third Quarter	2.24	1.02
Fourth Quarter	2.04	.95

As of January 31, 2012, we had approximately 140 common stockholders of record registered on the books of the Company, excluding shares held through banks and brokers.

Dividends

We have never declared or paid cash dividends on our common stock, and we do not expect to pay any cash dividends on our common stock in the foreseeable future.

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Comparative Stock Performance

The following performance graph and related information shall not be deemed soliciting material or to be filed with the SEC, nor shall such information be incorporated by reference into any future filing under the Securities Act of 1933 or Securities Exchange Act of 1934, each as amended, except to the extent that we specifically incorporate it by reference into such filing.

On December 10, 2007, the Company s common stock began trading on the NASDAQ Global Stock Market under the ticker symbol IDRA. Prior to December 10, 2007, the Company s common stock was quoted on the American Stock Exchange under the ticker symbol IDP.

The comparative stock performance graph shown below compares cumulative stockholder return on the Company s common stock from December 31, 2006 through December 31, 2011 with the cumulative total return of the NASDAQ Biotechnology Index and the Russell 2000 Index. This graph assumes an investment of $100 on December 31, 2006 in the Company s common stock and in each of the indices and assumes that dividends are reinvested.

	12/31/06	12/31/07	12/31/08	12/31/09	12/31/10	12/31/11
IDERA PHARMACEUTICALS, INC.	**100.00**	**243.04**	**142.49**	**95.92**	**53.62**	**19.48**
NASDAQ BIOTECHNOLOGY INDEX	**100.00**	**102.49**	**96.54**	**109.94**	**116.84**	**121.41**
RUSSELL 2000 INDEX	**100.00**	**98.43**	**65.18**	**82.89**	**105.14**	**100.75**

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

The following selected financial data are derived from our financial statements. The data should be read in conjunction with Management s Discussion and Analysis of Financial Condition and Results of Operations and the financial statements, related notes, and other financial information included herein.

	Year Ended December 31,				
	2011	2010	2009	2008	2007
	(In thousands, except per share data)				
Statement of Operations Data:					