UNITED THERAPEUTICS Corp
Form 10-K
February 26, 2013

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UNITED STATES
SECURITIES AND EXCHANGE COMMISSION

WASHINGTON, D.C. 20549

FORM 10-K

(Mark One)

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

For the fiscal year ended December 31, 2012

OR

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

For the transition period from to
Commission file number 0-26301

United Therapeutics Corporation

(Exact Name of Registrant as Specified in Its Charter)

Delaware	**52-1984749**
(State or Other Jurisdiction of Incorporation or Organization)	(I.R.S. Employer Identification No.)
1040 Spring Street, Silver Spring, MD	**20910**
(Address of Principal Executive Offices)	(Zip Code)

(301) 608-9292
Registrant's Telephone Number, Including Area Code

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

Title of each class	**Name of each exchange on which registered**
Common Stock, par value $.01 per share and associated preferred stock purchase rights	NASDAQ Global Select Market

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

None
(Title of Class)

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

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

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

Indicate by check mark whether the registrant has submitted electronically and posted on its corporate Website, 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 ý No o

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

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 definitions of "large accelerated filer," "accelerated filer," and "smaller reporting company" in Rule 12b-2 of the Exchange Act. (Check one):

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

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

The aggregate market value of the Common Stock held by non-affiliates of the registrant, based on the closing price on June 30, 2012, as reported by the NASDAQ Global Select Market was approximately $2,256,964,700.

The number of shares outstanding of the issuer's common stock, par value $0.01 per share, as of February 18, 2013, was 50,183,353.

DOCUMENTS INCORPORATED BY REFERENCE

Portions of the registrant's definitive proxy statement for the registrant's 2013 annual meeting of shareholders scheduled to be held on June 26, 2013, are incorporated by reference in Part III of this Form 10-K.

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PART I

ITEM 1. BUSINESS

United Therapeutics Corporation is a biotechnology company focused on the development and commercialization of unique products to address the unmet medical needs of patients with chronic and life-threatening conditions.

Our key therapeutic products and product candidates include:

Prostacyclin Analogues. Prostacyclin analogues are stable synthetic forms of prostacyclin, an important molecule produced by the body that has powerful effects on blood vessel health and function. Our lead product is Remodulin® (treprostinil) Injection (Remodulin), which is administered subcutaneously or intravenously for the treatment of pulmonary arterial hypertension (PAH). The United States Food and Drug Administration (FDA) initially approved Remodulin in 2002 for subcutaneous (under the skin) administration. Subsequently, the FDA broadened its approval of Remodulin for intravenous (in the vein) use and for the treatment of patients who require transition from Flolan® (epoprostenol), the first FDA-approved prostacyclin therapy for PAH. In addition to the United States, Remodulin is approved in 37 other countries, most of which have approved both routes of administration. In 2009, the FDA approved Tyvaso® (treprostinil) Inhalation Solution (Tyvaso), an inhaled prostacyclin therapy for the treatment of PAH, and we commenced commercial sales later that year. We are in the late stages of developing our oral tablet of treprostinil diolamine for the treatment of PAH, and have recently commenced pre-clinical studies of a self-injectable form of treprostinil, which we refer to as TransCon Treprostinil. Our wholly-owned subsidiary Lung LLC is separately developing beraprost, another type of prostacyclin analogue, as an oral tablet known as 314d and as an extended release injection we refer to as TransCon Beraprost, both for the treatment of PAH.

Phosphodiesterase Type 5 (PDE-5) Inhibitor. PDE-5 inhibitors act to inhibit the degradation of cyclic guanosine monophosphate (cGMP) in cells. cGMP is activated by nitric oxide (NO) to effect relaxation of vascular smooth muscle. Our PDE-5 inhibitor product is Adcirca® (tadalafil) tablets (Adcirca), a once-daily oral therapy for the treatment of PAH. We acquired exclusive U.S. commercialization rights to Adcirca from Eli Lilly and Company (Lilly) in 2008. In 2009, the FDA approved Adcirca for the treatment of PAH, and we commenced commercial sales later that year.

Monoclonal Antibodies (MAbs). MAbs act by targeting tumor-associated antigens on cancer cells to activate a patient's immune system against the cancer cells. We are developing the antibody Ch14.18 MAb for the treatment of neuroblastoma, under an agreement with the National Cancer Institute of the United States National Institutes of Health (NIH). We are also developing another antibody, 8H9 MAb, for the treatment of metastatic brain cancer, under an agreement with Memorial Sloan-Kettering Cancer Center.

Glycobiology Antiviral Agents. Glycobiology antiviral agents are a novel class of small, sugar-like molecules that have shown pre-clinical indications of efficacy against a broad range of viruses. In September 2011, we were awarded a contract from the National Institute of Allergy and Infectious Diseases of the NIH for studies directed at the development of a broad spectrum antiviral drug based on our glycobiology antiviral platform.

Cell-Based Therapy. In June 2011, we entered into a license agreement with Pluristem Ltd. (Pluristem) to develop and commercialize its cell-based product known as PLacental eXpanded (PLX) cells for the treatment of PAH using Pluristem's proprietary cell technology. We are currently conducting preclinical toxicology and pharmacology studies to support a potential investigational new drug application for the treatment of PAH, and expect to commence a phase I clinical study in Australia during the first half of 2013.

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Engineered Lungs and Lung Tissue for Transplantation. The only reported cure for PAH is a full lung transplant. Using the xenotransplantation technology we acquired through our July 2011 acquisition of Revivicor Inc. and several regenerative medicine technologies that we have licensed, we are in the early pre-clinical stage of developing engineered lungs and lung tissue which can be transplanted into patients suffering from PAH and other lung diseases.

We devote most of our research and development resources to developing these key products and product candidates.

We generate revenues primarily from the sale of Remodulin, Tyvaso and Adcirca (which we refer to as our commercial products). Our sales and marketing staff supports the availability of our commercial products in the countries in which they are approved. These efforts are supplemented by our specialty pharmaceutical distributors in the United States and our other distributors internationally.

United Therapeutics was incorporated in Delaware in June 1996. Our principal executive offices are located at 1040 Spring Street, Silver Spring, Maryland 20910. We also maintain executive offices at 55 T.W. Alexander Drive, Research Triangle Park, North Carolina 27709.

Unless the context requires otherwise or unless otherwise noted, all references in this Annual Report on Form 10-K to "United Therapeutics" and to the "company", "we", "us" or "our" are to United Therapeutics Corporation and its subsidiaries.

Our Products

Our product portfolio includes the following:

Product	Mode of Delivery	Indication/Market	Current Status	Our Territory
Remodulin	Continuous subcutaneous	Pulmonary arterial hypertension	Approved in the U.S., most of Europe*, Argentina, Australia, Canada, Chile, Israel, Mexico, Peru, Saudi Arabia, South Korea, Taiwan and Venezuela; commercial sales in most of these countries	Worldwide
Remodulin	Continuous intravenous	Pulmonary arterial hypertension	Commercial in the U.S., Canada, Israel, Switzerland, Argentina and Saudi Arabia; also approved in most of Europe*, Mexico, Peru and South Korea	Worldwide
Tyvaso	Inhaled	Pulmonary arterial hypertension	Commercial in the U.S.	Worldwide
Adcirca	Oral	Pulmonary arterial hypertension	Commercial in the U.S.	United States
Oral Treprostinil	Oral	Pulmonary arterial hypertension	NDA filed with FDA; resubmission filed in response to FDA's complete response letter	Worldwide
Oral Treprostinil Combination Therapy	Oral	Pulmonary arterial hypertension	Phase III	Worldwide
Ch14.18 MAb	Intravenous	Neuroblastoma	Phase III	Worldwide

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Product	Mode of Delivery	Indication/Market	Current Status	Our Territory
Remodulin	Continuous intravenous via implantable pump	Pulmonary arterial hypertension	Phase III	United States, United Kingdom, France, Germany, Italy and Japan
Beraprost 314d	Oral	Pulmonary arterial hypertension	Phase II	North America, Europe, Mexico, South America, Egypt, India, South Africa and Australia
8H9 MAb	Intravenous	Metastatic brain cancer	Phase I	Worldwide
TransCon Treprostinil	Self-Injection	Pulmonary arterial hypertension	Pre-Clinical	North America, Europe, Mexico, South America, Egypt, India, South Africa and Australia
TransCon Beraprost	Self-Injection	Pulmonary arterial hypertension	Pre-Clinical	North America, Europe, Mexico, South America, Egypt, India, South Africa and Australia
PLX Cells	Intravenous	Pulmonary arterial hypertension	Pre-Clinical	Worldwide
Glycobiology Antiviral Agents	Oral	Broad-spectrum agents against viral infectious diseases	Pre-Clinical	Worldwide
Engineered Lungs for Transplantation	Various	End-stage lung disease	Pre-Clinical	Worldwide

* We have obtained approval for subcutaneous Remodulin in 23 member countries of the European Economic Area (EEA), as well as other non-EEA countries in Europe, and have received pricing approval in most of these countries. We have obtained approval for intravenous Remodulin in 23 EEA countries and Switzerland, and are in the process of submitting pricing applications and our risk management plan in select countries based on market factors.

Products to Treat Cardiopulmonary Diseases

Pulmonary Arterial Hypertension

PAH is a life-threatening disease that affects the blood vessels in the lungs and is characterized by increased pressure in the pulmonary arteries, which are the blood vessels leading from the heart to the lungs. The elevated pressure in the pulmonary arteries strains the right side of the heart as it pumps blood to the lungs. This eventually leads to right heart failure and, ultimately, death. PAH is characterized by structural changes in blood vessel walls, aggregation of platelets and alteration of smooth muscle cell function. It is estimated that PAH affects between 100,000 and 200,000 individuals worldwide. The awareness of PAH continues to grow, as we have seen increases in the number of people diagnosed with the disease. However, due to the rarity of the disease and the complexity of diagnosing it, only a small fraction of patients with PAH are being treated. There is scientific interest in identifying easier, less invasive methods of diagnosing PAH. If this research is successful, more patients could be diagnosed at an earlier stage of the disease.

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Currently, treatment of PAH focuses on three distinct molecular pathways that have been implicated in the disease process: the prostacyclin pathway, the NO pathway, and the endothelin (ET) pathway. The three classes of drugs that target these three pathways are:

Prostacyclin Analogues. Patients with PAH have been shown to have reduced levels of prostacyclin, a naturally occurring substance that has the effect of relaxing the pulmonary blood vessels, preventing platelet aggregation, and inhibiting the proliferation of smooth muscle cells in the pulmonary vessels. Therefore, drugs that mimic the action of prostacyclin, known as prostacyclin analogues, are established PAH treatments.

PDE-5 Inhibitors. Patients with PAH have also been shown to have reduced levels of the enzyme responsible for producing NO, a naturally occurring substance in the body that causes relaxation of the pulmonary blood vessels. NO produces this effect by increasing intracellular levels of an intermediary known as cyclic guanosine monophosphate (cGMP). Therefore, another established therapeutic approach has been to inhibit the degradation of cGMP, using drugs that are known as PDE-5 inhibitors.

Endothelin Receptor Antagonists. PAH patients have also been shown to have elevated levels of endothelin-1, a naturally occurring substance in the body that causes constriction and structural changes of the pulmonary blood vessels. Therefore, another established therapeutic approach has been to block the action of endothelin with drugs that are known as endothelin receptor antagonists (ETRAs).

Because any or all of the three pathways may be therapeutic targets in a patient, these three classes of drugs are used alone or in combination to treat patients with PAH. We currently market drugs in two of these three classes. Remodulin and Tyvaso are prostacyclin analogues, and Adcirca is a PDE-5 inhibitor.

Remodulin

Our lead product for treating PAH is Remodulin (treprostinil) Injection, the active pharmaceutical ingredient of which is a prostacyclin analogue known as treprostinil. We sell Remodulin to specialty pharmaceutical distributors in the United States and to international pharmaceutical distributors. We recognized approximately $458.0 million, $430.1 million and $403.6 million in Remodulin revenues, representing 50 percent, 58 percent and 68 percent of our net revenues for the years ended December 31, 2012, 2011 and 2010, respectively. In 2002, Remodulin was approved by the FDA as a continuous subcutaneous infusion for the treatment of PAH in patients with New York Heart Association (NYHA) Class II-IV (moderate to severe) symptoms. In 2004, the FDA expanded its approval to permit continuous intravenous infusion of Remodulin for patients who cannot tolerate subcutaneous infusion. In 2006, the FDA expanded its approval to include transition of patients to Remodulin from Flolan® (epoprostenol), the first FDA-approved prostacyclin therapy for PAH. In 2007, the results of a prospective, open-label study demonstrated that stable patients with PAH can be safely transitioned from Flolan to intravenous Remodulin using a rapid switch protocol. Remodulin is the only prostacyclin analogue approved for patients with NYHA class II-IV symptoms.

Outside of the United States, Remodulin is approved for treatment of PAH in 37 countries by continuous subcutaneous administration. Remodulin is also approved for treatment of PAH by continuous intravenous administration in 31 countries outside the U.S., including 23 countries in Europe that granted approval in December 2011. Applications for approval of both subcutaneous and intravenous Remodulin are under review in other countries. We continue to work toward commercializing Remodulin in new territories, including China (where we filed a marketing application in September 2011) and Japan (where we expect to file a marketing application in 2013).

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We believe Remodulin offers many competitive advantages over Flolan, which is delivered continuously through a surgically implanted intravenous catheter connected to an external pump and is not approved for subcutaneous use. Flolan is approved for the treatment of patients with PAH. Generic formulations of Flolan are also available. We believe subcutaneous Remodulin provides patients with a less invasive alternative to Flolan. In contrast to Flolan, Remodulin is stable at room temperature and lasts significantly longer inside the human body. These attributes allow for potentially safer and more convenient drug delivery to patients. Unlike Flolan, Remodulin can be delivered by subcutaneous infusion with a pager-sized miniature infusion pump. Subcutaneous delivery of Remodulin also eliminates the risk of central venous catheter infection and the hospitalization required to begin intravenous infusion. Remodulin's extended presence in the body may also reduce the risk of rebound PAH, and possibly death, if treatment is abruptly interrupted. The stability of Remodulin also allows it to be packaged as an aqueous solution, so patients do not have to mix the drug, as they do with Flolan. Remodulin can be continuously infused for up to 48 hours before refilling the infusion pump, unlike Flolan, which must be mixed and refilled every 24 hours. Treprostinil, the active ingredient in Remodulin, is highly soluble in an aqueous solution, which enables us to manufacture Remodulin in highly concentrated solutions. This allows therapeutic concentrations of Remodulin to be delivered at low flow rates via miniaturized infusion pumps for both subcutaneous and intravenous infusion. Lastly, Remodulin does not require the patient to keep the drug cool during infusion. This eliminates the need for cooling packs or refrigeration to keep Remodulin stable, as is required with Flolan due to Flolan's chemical instability at room temperature.

In 2008, Teva Pharmaceuticals Industries Ltd. (Teva) announced that the FDA approved its version of generic epoprostenol (the active ingredient in Flolan) for the treatment of PAH, which has all of the attributes of Flolan discussed above. Also in 2008, the FDA approved another intravenous version of epoprostenol, which is currently marketed by Actelion Pharmaceuticals Ltd (Actelion) under the name Veletri®. Veletri is stable at room temperature but shares most of Flolan's other attributes including risk of central venous catheter infection, required hospitalization at the start of treatment, short half-life (which increases risk of rebound PAH), mixing requirements, daily pump refills and large pump size. Actelion also markets Tracleer®, an ETRA, and Ventavis®, an inhaled prostacyclin, for the treatment of PAH.

In February 2012, we received notice of an abbreviated new drug application by Sandoz Inc. requesting FDA approval to market a generic version of the 10 mg/mL strength of Remodulin. On December 7, 2012, we received notice that Sandoz had amended its previously filed abbreviated new drug application to request additional approval to market generic versions of the 1mg/mL, 2.5 mg/mL, and 5 mg/mL strengths of Remodulin. For further details, see the section below entitled *Governmental Regulation Hatch-Waxman Act* and *Item 3. Legal Proceedings.*

There are noteworthy adverse events associated with Remodulin. When infused subcutaneously, Remodulin causes varying degrees of infusion site pain and reaction (redness and swelling) in most patients. Patients who cannot tolerate the infusion site pain related to use of subcutaneous Remodulin may instead use intravenous Remodulin. Intravenous Remodulin is delivered continuously through a surgically implanted central venous catheter, similar to Flolan, Veletri and generic epoprostenol. When delivered intravenously, Remodulin bears the risk of central venous catheter infection and a serious bloodstream infection known as sepsis, as do Flolan, Veletri and generic epoprostenol. General side effects associated with Remodulin include diarrhea, jaw pain, vasodilation and edema.

International Regulatory Review of Subcutaneous and Intravenous Remodulin

Remodulin is approved in 37 countries outside the United States. In 31 of these countries, it is approved for both subcutaneous and intravenous use. In the other six countries, Remodulin is approved for subcutaneous use only.

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We used the mutual recognition process, described more fully in *Governmental Regulation Marketing Pharmaceutical Products Outside the United States*, to obtain approval of subcutaneous Remodulin in most countries in the European Union (EU). The mutual recognition process for subcutaneous Remodulin was completed in 2005, with positive decisions received from 23 member countries of the EEA. We withdrew our applications in the Republic of Ireland (Ireland), Spain and the United Kingdom (UK) following a request for additional documentation from these countries. In December 2011, we received regulatory approval by the French regulatory agency, *L'Agence Nationale de Sécurité du Médicament et des Produits de Santé* (ANSM), for the intravenous use of Remodulin to treat PAH. The ANSM approval followed a review period during which each EEA member nation which had previously approved subcutaneous Remodulin through the mutual recognition process reviewed and endorsed the final variation assessment report issued by ANSM, which will allow us to market intravenous Remodulin in those countries following pricing approval and approval of our risk management plan (RMP) in each country.

In Europe, an RMP is routinely required as part of the regulatory approval process for new medicines and also for significant variations involving a change to the route of administration, formulation or indication. For intravenous Remodulin, we will implement an RMP focused on minimizing the known risks of central venous catheter-related blood stream infections associated with intravenous administration. To date, our RMP for intravenous Remodulin has been approved in ten EEA countries.

Remodulin is available under the named-patient system in the EEA member countries where Remodulin is not approved (including the UK, Ireland and Spain). Under the named-patient system, our distributors are permitted to import Remodulin into EEA member countries based on requests for Remodulin for use in treating specific patients, but neither we nor our distributors are permitted to market the product in those countries. We are evaluating the resubmission of our applications for Remodulin in Ireland and Spain.

Intravenous Remodulin Administered via Implantable Pump

A majority of the patients who die of PAH in the United States each year have not initiated treatment with an infused prostacyclin analogue, which is a complex and burdensome form of medical therapy. In 2009, we entered into an agreement with Medtronic, Inc. (Medtronic) to develop its Synchromed® implantable pump to deliver Remodulin, which, if successful, could eliminate many of the patient burdens associated with infused prostacyclins.

Medtronic commenced a clinical trial administering Remodulin using the Synchromed in April 2011 to support FDA approval for the use of Remodulin with its implantable pump. Patient enrollment in the clinical trial was completed in late November 2012. Based on current projections of patient days and discontinuations, we expect that the clinical trial will be completed in late 2013. In certain countries in Europe, an implantable pump distributed by OMT GmbH & Co. KG is used to deliver intravenous Remodulin to some patients.

Tyvaso

We commenced commercial sales of Tyvaso in the United States in 2009. We sell Tyvaso to the same specialty pharmaceutical distributors in the United States that distribute Remodulin. For the years ended December 31, 2012, 2011 and 2010, we recognized approximately $325.6 million, $240.4 million and $151.8 million in Tyvaso revenues, representing 36 percent, 32 percent and 26 percent, respectively, of our net revenues.

Currently, the only other FDA-approved inhaled prostacyclin analogue is Ventavis. Ventavis is marketed by Actelion in the United States and by Bayer Schering Pharma AG in Europe. The active ingredient in Ventavis, iloprost, has a half-life of approximately 20 to 30 minutes and can cause a

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decrease in systemic (body-wide) blood pressure if the drug is administered at too high a dose. Patients need to inhale Ventavis six to nine times per day via a nebulizer. According to its package insert, each Ventavis inhalation consists of four to ten minutes of continuous inhalation via the nebulizer.

In contrast to iloprost, treprostinil (the active ingredient in Tyvaso) has a longer half-life and greater selectivity to the lungs. Tyvaso is administered four times a day, by inhaling up to nine breaths during each two- to three-minute treatment session. Tyvaso is required to be administered using our proprietary Tyvaso Inhalation System, which consists of an ultra-sonic nebulizer that provides a dose of Tyvaso on a breath-by-breath basis. In addition, a day's supply of Tyvaso is packaged in a single ampule emptied into the Tyvaso Inhalation System once a day. As a result, unlike the Ventavis nebulizer which requires cleaning after each use, the Tyvaso Inhalation System only needs to be cleaned once a day.

Tyvaso has been generally well tolerated in our trials, during which adverse events appeared to be similar to those previously reported for treprostinil or due to administration by inhalation. The most common adverse events were transient cough, headache, nausea, dizziness and flushing. We completed an open-label study in the United States to investigate the clinical effects of switching patients from Ventavis to Tyvaso, in which improvements in patient quality of life were observed. Patients in this study also saved an average of approximately 1.4 hours per day when administering Tyvaso compared to Ventavis.

Regulatory Approval of Tyvaso

In 2009, the FDA approved Tyvaso for the treatment of PAH using the Tyvaso Inhalation System. Tyvaso is indicated to increase walk distance in patients with NYHA Class III symptoms of PAH, which includes multiple etiologies such as idiopathic and familial PAH, as well as PAH associated with scleroderma and congenital heart disease.

In connection with the Tyvaso approval, we agreed to a post-marketing requirement (PMR) and certain post-marketing commitments (PMCs). PMRs and PMCs are studies that sponsors conduct after FDA approval to gather additional information about a product's safety, efficacy, or optimal use. PMRs are required studies, whereas a sponsor voluntarily commits to conduct PMCs.

Under the PMCs, we committed to modify particular aspects of the Tyvaso Inhalation System. As part of these modifications, we agreed to perform a usability analysis incorporating the evaluation and prioritization of user-related risk followed by a human factors study. The modifications and usability analysis have been completed, and in September 2011, the FDA notified us that we had fulfilled the requirements of the PMCs. In July 2012, we received FDA approval for a modified Tyvaso Inhalation System based on the results of the PMCs. As a result, we are currently manufacturing the modified inhalation system, which we expect to release commercially in 2013.

We are working to further improve the Tyvaso Inhalation System to make it easier for patients to use. If ultimately approved by the FDA, an improved Tyvaso Inhalation System could enhance patient convenience and potentially increase the number of patients using Tyvaso.

In accordance with our PMR, we are enrolling patients in a long-term observational study in the United States that will include 1,000 patient years of follow-up in patients treated with Tyvaso, and 1,000 patient years of follow-up in control patients receiving other PAH treatments. This study will allow us to continue assessing the safety of Tyvaso. We are required to provide the FDA with annual updates on our PMR, and to submit the results of the study by December 15, 2014. While we believe we are on schedule to complete the PMR by this deadline, any failure or delay could result in penalties, including fines or withdrawal of Tyvaso from the market, unless we are able to demonstrate good cause for the failure or delay.

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In June 2010, the FDA granted orphan drug designation for Tyvaso. Such a designation, coupled with an approval of the product for the orphan indication, confers an exclusivity period through July 2016, during which the FDA may not approve any application to market the same drug for the same indication, except in limited circumstances.

We are not seeking European Medicines Agency (EMA) approval of Tyvaso for the treatment of PAH. We expect to make Tyvaso available in certain European and Latin American countries in 2013 on an unmarketed, named-patient basis through country-specific arrangements with our distributors, to the extent physicians prescribe Tyvaso in those countries.

Adcirca

We began selling Adcirca in 2009. Adcirca is a PDE-5 inhibitor, the active pharmaceutical ingredient of which is tadalafil. Tadalafil is also the active pharmaceutical ingredient in Cialis®, which is marketed by Lilly for the treatment of erectile dysfunction. We acquired the commercial rights to Adcirca for the treatment of PAH in the U.S. from Lilly in 2008. We sell Adcirca at prices established by Lilly, which are at parity with Cialis pricing and typically set at a discount from an average wholesale price to pharmaceutical wholesalers. For the years ended December 31, 2012, 2011 and 2010, we recognized approximately $122.5 million, $70.6 million and $36.3 million in Adcirca revenues, representing 13 percent, 9 percent and 6 percent, respectively, of our net revenues.

Patients with PAH have been shown to have reduced levels of the enzyme responsible for producing NO, a naturally occurring substance in the body that has the effect of relaxing vascular smooth muscle cells. Impaired blood vessel relaxation in penile tissue is also a cause of erectile dysfunction. NO works to relax pulmonary blood vessels by increasing intracellular levels of an intermediary known as cyclic GMP. Because cyclic GMP is degraded by PDE-5, an established therapeutic approach in the treatment of PAH is to use PDE-5 inhibitors to increase levels of cGMP in blood vessels and improve cardiopulmonary function in PAH patients.

Prior to the approval of Adcirca, Revatio®, which is marketed by Pfizer Inc. (Pfizer), was the only PDE-5 inhibitor approved for the treatment of PAH. Sildenafil citrate, the active ingredient in Revatio, is also the active ingredient in Viagra®, which is marketed by Pfizer for the treatment of erectile dysfunction. Revatio is dosed three times daily. Adcirca is dosed once daily. In the fourth quarter of 2012, several companies launched generic formulations of sildenafil citrate.

FDA Approval of Adcirca

In 2009, the FDA approved Adcirca with a recommended dose of 40 mg, making it the first once-daily PDE-5 inhibitor for the treatment of PAH. Adcirca is indicated to improve exercise ability in World Health Organization Group I PAH patients, which encompasses patients with multiple forms of PAH including etiologies such as idiopathic and familial PAH as well as PAH associated with collagen vascular disease and congenital heart disease.

Commercial Rights to Adcirca

In 2008, we entered into several agreements with Lilly, namely, a license agreement, a manufacturing and supply agreement and a stock purchase agreement. Pursuant to the license agreement, Lilly granted us an exclusive license for the right to develop, market, promote and commercialize Adcirca for the treatment of pulmonary hypertension in the United States and Puerto Rico. Pursuant to the manufacturing and supply agreement, Lilly agreed to manufacture Adcirca and distribute it on our behalf via its wholesaler network, in the same manner that it distributes its own pharmaceutical products. In 2008, we made a one-time, non-refundable, non-creditable payment of $125.0 million under the manufacturing and supply agreement and a one-time payment of $25.0 million under the license agreement. Pursuant to the stock purchase agreement, Lilly purchased 6.3 million

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shares of our common stock (adjusted for our September 2009 two-for-one stock split) for an aggregate purchase price of $150.0 million. See *Strategic Licenses and Relationships* below for more details on these agreements.

UT-15C Sustained Release Tablets (Oral Treprostinil)

There are currently no approved oral prostacyclin therapies available to patients in the United States or Europe. We are developing a novel salt form of treprostinil for oral administration, treprostinil diolamine tablets. If we are successful in developing oral treprostinil, then patients and physicians may use prostacyclin earlier in the PAH disease continuum, which could increase demand for our PAH therapies.

In December 2011, we submitted to the FDA an NDA for the approval of oral treprostinil for treatment of PAH. Our NDA included the results of three phase III studies:

Combination Therapy Studies (FREEDOM-C and *FREEDOM-C^2*): Two separate 16-week studies of patients on approved background therapy using a PDE-5 inhibitor, such as Revatio, or an ETRA, such as Tracleer, or a combination of both. The FREEDOM-C and FREEDOM-C^2 trials were completed in 2008 and 2011 respectively, and neither achieved statistical significance for its primary endpoint of improvement in six-minute walk distance at week 16 (p=0.072 and p=0.089, respectively).

Monotherapy Study (FREEDOM-M): A 12-week study of PAH patients who were not on any approved background therapy. In June 2011, we announced that the FREEDOM-M trial met its primary endpoint of improvement in six-minute walk distance at week 12. Analysis of the FREEDOM-M results demonstrated that patients receiving oral treprostinil improved their six-minute walk distance by a median of approximately 23 meters (p=0.0125, Hodges-Lehmann estimate and non-parametric analysis of covariance in accordance with the trial's pre-specified statistical analysis plan) as compared to patients receiving placebo. The median change from baseline at week 12 was 25 meters for patients receiving oral treprostinil and -5 meters for patients receiving placebo.

We believe that patients in the FREEDOM-C and FREEDOM-C^2 trials needed longer-term treatment with oral treprostinil to provide a statistically significant clinical trial outcome. As such, we began enrolling patients in a new phase III clinical trial (FREEDOM-EV) in the third quarter of 2012. FREEDOM-EV is a placebo-controlled study of newly-diagnosed patients who have initiated an approved background therapy (either an ETRA or a PDE-5 inhibitor, but not both), with one co-primary endpoint being the time to clinical worsening, generally defined as (1) death; (2) an unplanned hospitalization due to PAH; (3) initiation of prostacyclin for the treatment of PAH; (4) a decrease in six-minute walk distance of at least 15 percent from baseline (or too ill to walk) as a result of the progression of PAH; or (5) unsatisfactory long-term clinical response. The other co-primary endpoint is change in six minute-walk distance at week 24. We plan to enroll up to 858 patients in order to observe 349 clinical worsening events.

On October 23, 2012, the FDA issued a complete response letter in which it declined to approve our NDA. In January 2013, we filed a resubmission of our NDA in response to the concerns raised in the FDA's complete response letter. The FDA has acknowledged our resubmission as complete and set a targeted response date of March 31, 2013. Despite the FDA's complete response letter and uncertainty as to whether our resubmission will be approved, we remain committed to further studying oral treprostinil and seeking FDA approval before the end of 2016. We currently expect to seek approval of oral treprostinil in Europe upon completion of the FREEDOM-EV study. In 2005, the EMA announced that oral treprostinil had been designated an orphan medicinal product for the treatment of PAH.

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Self-Injectable Prostacyclin Analogues

In September 2012, we announced that we signed an exclusive agreement with Ascendis Pharma A/S (Ascendis Pharma) to apply Ascendis Pharma's proprietary TransCon technology platform to our treprostinil molecule. We believe that the TransCon technology platform may enable a sustained release of a novel, carrier-linked product, which will significantly enhance the delivery of treprostinil by establishing a once-daily, self-injectable alternative for patients who currently administer Remodulin through a continuous infusion pump for the treatment of PAH. We expect that this self-injectable form of treprostinil could enable patients to avoid infusion site pain associated with subcutaneous Remodulin. Under this agreement, we also intend to pursue development of a TransCon technology-enabled sustained release formulation of beraprost, which is another prostacyclin analogue, as discussed below.

Beraprost

We have the exclusive right to develop and market a modified-release formulation of beraprost (beraprost-MR) in the United States, Canada, Mexico, South America, Europe, Egypt, India, South Africa and Australia for the treatment of cardiovascular indications, pursuant to our license agreement with Toray Industries, Inc. (Toray), which is described below under *Strategic Licenses and Relationships Toray Amended License Agreement*.

Beraprost is a chemically stable, orally bioavailable prostacyclin analogue. Like natural prostacyclin and Remodulin, beraprost is believed to dilate blood vessels, prevent platelet aggregation and prevent proliferation of smooth muscle cells surrounding blood vessels. In 2007, Toray announced that beraprost-MR received regulatory approval in Japan for use in the treatment of PAH.

In July 2011, we amended our license agreement with Toray regarding the development of beraprost-MR for the treatment of PAH. The July 2011 amendment did not materially change the terms of our license agreement, except for a reduction in royalty rates. In exchange for the reduction in royalty rates, we agreed to pay Toray $50.0 million in equal, non-refundable payments over a five-year period ending in 2015.

314d

In November 2011, we announced that a phase II trial of beraprost-MR did not provide data supporting the initiation of a phase III study using a twice-daily dosing regimen. The results of this study suggested that the efficacy of beraprost may be improved by providing more stable and consistent plasma concentrations of beraprost, thereby increasing the therapeutic exposure to the drug. Therefore, we commenced studies of a reformulated, single-isomer version of beraprost (314d), with a dosing regimen of four times per day. We completed a phase I safety trial in July 2012, and the preliminary data suggests that dosing 314d four times a day is safe. We believe that 314d and treprostinil bind selectively to different sets of prostacyclin receptors within the lung and thus could provide certain groups of patients a differing set of safety and efficacy profiles. We are developing a phase III study to evaluate the clinical benefit of 314d as an add-on therapy to Tyvaso.

TransCon Beraprost

During the third quarter of 2012, we initiated efforts to develop an extended-release injection we refer to as TransCon Beraprost, which incorporates the TransCon technology described above and is intended to be self-administered by PAH patients once daily.

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Cell-Based Therapy

In June 2011, we entered into a license agreement with Pluristem Ltd. (Pluristem) to develop and commercialize a cell-based product for the treatment of PAH using Pluristem's proprietary cell technology. The license agreement became effective in August 2011, at which time we made a one-time, non-refundable payment of $7.0 million to Pluristem, $5.0 million of which consisted of a license fee that was charged to research and development expenses during the year ended December 31, 2011. We are currently conducting preclinical toxicology and pharmacology studies to support a potential investigational new drug application for the treatment of PAH, and expect to commence a phase I clinical study in Australia in the first half of 2013.

Products to Treat Cancer

Ch14.18 Antibody

In July 2010, we entered into a Cooperative Research and Development Agreement (CRADA) with the National Cancer Institute (NCI) of the United States National Institutes of Health to collaborate on the late-stage development and regulatory agency submissions of Chimeric Monoclonal Antibody14.18 (Ch14.18) for children with high-risk neuroblastoma and patients with other forms of cancers. Ch14.18 is an antibody that has shown potential in the treatment of certain types of cancer by targeting GD2, a glycolipid on the surface of tumor cells. Neuroblastoma is a rare cancer of the sympathetic nervous system mainly affecting children. It is the most common extracranial, outside the skull, solid cancer in children and the most common cancer in infants. There are fewer than 1,000 new cases of neuroblastoma diagnosed each year. Ch14.18 is a chimera, composed of a combination of mouse and human DNA, monoclonal antibody that induces antibody-dependent cell-mediated cytotoxicity, a mechanism of cell-mediated immunity whereby the immune system actively targets a cell that has been bound by specific antibodies.

Results from NCI's phase III study were published in September 2010. In that study, immunotherapy with Ch14.18 significantly improved patient outcome compared with standard therapy in patients with high risk neuroblastoma. Specifically, the two-year estimate for event-free survival was 66%±5% in the Ch14.18 immunotherapy group and 46%±5% in the standard therapy group (p=0.01 without adjustment for interim analyses). The Ch14.18 immunotherapy group was also significantly better than the standard therapy group in the estimated rate of overall survival (86%±4% vs. 75%±5% at two years, p=0.02 without adjustment for interim analyses). This study was coordinated by the Children's Oncology Group, a national consortium of researchers supported by the NCI.

Under the terms of the CRADA, NCI has completed a second phase III clinical trial in 105 patients to define more clearly the safety and toxicity profile of Ch14.18 immunotherapy in children, and we are developing the commercial production capability for the antibody. As part of developing our commercial production capability, we will need to demonstrate comparability of our Ch14.18 to the NCI-produced Ch14.18, which typically includes a series of analytical and bioanalytical assays and human pharmacokinetics. The human pharmacokinetics study is currently open to enrollment in the United States. The NCI studies, including a previously conducted phase III clinical trial and all other necessary studies supported by NCI, will be used as the basis for a biologics license application we expect to file seeking FDA approval of Ch14.18 immunotherapy for the treatment of neuroblastoma and a marketing authorization application we expect to file with the EMA for approval in Europe. We have received orphan drug designation for Ch14.18 from the FDA and the EMA.

8H9 Antibody

Pursuant to our 2007 agreement with Memorial Sloan-Kettering Cancer Center, we obtained certain license rights to an investigational monoclonal antibody, 8H9, for the treatment of metastatic brain cancer. 8H9 is a mouse IgG1 MAb that is highly reactive with a range of human solid tumors,

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including human brain cancers. The 8H9 antibody is in early investigational development for metastases that develop in the brain from the spread of cancers from other tissues in the body. Metastatic brain cancers are ten times more common than cancers that originate in the brain, and prognosis for patients with metastatic brain cancers is very poor. In the United States, more than 100,000 cases of metastatic brain cancer are diagnosed each year.

Products to Treat Infectious Diseases Glycobiology Antiviral Agents

Pursuant to our research agreement with the University of Oxford (Oxford), we have the exclusive right to commercialize a platform of glycobiology antiviral drug candidates in various preclinical and clinical stages of testing for the treatment of a wide variety of viruses. Through our research agreement with Oxford, we are also supporting research into new glycobiology antiviral drug candidates and technologies. We are currently testing many of these compounds in preclinical studies and Oxford continues to synthesize new agents that we may elect to test.

In September 2011, we were awarded a cost plus fixed fee contract with an aggregate value of up to $45.0 million under a Broad Agency Announcement from the National Institute of Allergy and Infectious Diseases (NIAID) of the United States National Institutes of Health for studies directed at the development of a broad spectrum antiviral drug based on our glycobiology antiviral platform. Under the contract's base period of 42 months, we will receive $10.6 million in funding. In addition, there are eight milestone-based options to expand the project and funding under the contract. In August 2012, we received a contract modification exercising two of the above-mentioned milestone-based options, increasing total contract funding by $8.7 million. We recognize revenue under this contract to the extent of costs incurred, plus a proportionate amount of fee earned.

Engineered Lungs and Lung Tissue for Transplantation

In July 2011, we acquired all of the outstanding stock of Revivicor, Inc. (Revivicor), a company focused on developing genetic biotechnology platforms to provide alternative tissue sources for treatment of human degenerative disease through tissue and organ xenotransplantation. The acquisition date fair value of the consideration consisted of $4.2 million in cash and $3.4 million in contingent consideration. For further details, see Note 16 *Acquisitions Revivicor, Inc.* to our consolidated financial statements included in this Annual Report on Form 10-K.

We acquired Revivicor to pursue early-stage development of replacement lungs for transplantation. PAH has not been reported to reoccur in end-stage patients who have received a full lung transplant. Only a few hundred PAH patients receive a lung transplantation each year due to the shortage of available lungs for transplant and there is high demand for transplantable lungs by patients with end-stage pulmonary disease, such as chronic obstructive pulmonary disease and idiopathic pulmonary fibrosis.

We are also engaged in preclinical development of several regenerative medicine technologies for creating transplantable lung tissue and whole lungs for patients with end-stage lung disease.

Products to Provide Telemedicine Services for Cardiac Arrhythmias and Ischemic Heart Disease

Until March 2011, we provided telemedicine monitoring services to detect cardiac arrhythmias and ischemic heart disease through our wholly-owned subsidiary Medicomp, Inc. (Medicomp). In February 2011, we entered into an agreement and plan of merger to sell Medicomp to a group of private investors. As Medicomp did not represent a core component of our business, its sale allowed us to devote more resources to our principal operations. In March 2011, we closed the transaction and received aggregate consideration of $14.9 million, consisting of shares of United Therapeutics common stock held by the investors, with an aggregate value of $2.8 million, and a $12.1 million ten-year promissory note issued by Medicomp. Immediately after closing the sale, we purchased a 19.9 percent

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ownership interest in Medicomp in exchange for $1.0 million in cash and an approximately $2.0 million reduction in the face value of the promissory note.

Due to our agreement to sell Medicomp, we recognized an impairment charge of $6.2 million, representing the write-off of the carrying value of Medicomp's goodwill, in the fourth quarter of 2010. We recognized a gain of $860,000 on the sale of Medicomp. In addition, we have met all the criteria for reporting Medicomp as a discontinued operation. As a result, we have included the operating results of Medicomp, including the gain recognized on its disposal, within discontinued operations in our consolidated statements of operations for the years ended December 31, 2011 and 2010. For further details, see Note 17 *Sale of Medicomp, Inc.* to our consolidated financial statements included in this Annual Report on Form 10-K.

Sales and Marketing

Our marketing strategy for our commercial products is to use our sales and marketing teams to reach out to the prescriber community to: (1) increase PAH awareness; (2) increase understanding of the progressive nature of PAH; and (3) increase awareness of our commercial products and how they fit into the various stages of disease progression and treatment. Our sales and marketing teams consisted of 126 employees as of December 31, 2012. We have divided our domestic sales force into two teams. One team sells Remodulin and Tyvaso, while the other team sells Adcirca. The efforts of our sales and marketing teams are supplemented in the United States by our specialty pharmaceutical distributors for Remodulin and Tyvaso. Our U.S.-based distributors are experienced in all aspects of using and administering chronic therapies, as well as patient care, the sale and distribution of these medicines and reimbursement from insurance companies and other payers. Outside of the United States, we have entered into distribution agreements for Remodulin covering many territories worldwide. We are working with our international distributors to expand Remodulin sales into other countries in which they have distribution rights.

Domestic Distribution of Commercial Products

Remodulin and Tyvaso

We have entered into separate, non-exclusive distribution agreements with CuraScript, Inc. (CuraScript), Accredo Health Group, Inc. (Accredo), and CVS Caremark (Caremark), our specialty pharmaceutical distributors in the United States, to market, promote and distribute both Remodulin and Tyvaso. In April 2012, Express Scripts, Inc., the parent company of CuraScript, completed its acquisition of Medco Health Solutions, Inc., the parent company of Accredo. Thus far, the merger has not affected our business and we do not expect the merger to materially affect our business in the future.

Our Remodulin distribution agreements with Accredo and Caremark include automatic term renewals for additional one-year periods subject to notice of termination. Our Remodulin distribution agreement with CuraScript contains automatic term renewals for additional two-year periods subject to notice of termination. We entered into our distribution agreements for Tyvaso in 2009. Our Tyvaso distribution agreements have one-year terms and renew automatically for additional one-year periods, unless terminated earlier. We update our distribution agreements from time to time to reflect changes in the regulatory environment. Such changes have not had a significant impact on our operations or our relationships with our distributors, and tend to occur in the ordinary course of business. For specific services requested by us, we compensate our distributors on a fee-for-service basis as set forth in our distribution agreements. If any of our distribution agreements expire or terminate, we may, under certain circumstances, be required to repurchase any unsold Remodulin or Tyvaso inventory held by our distributors. None of our current agreements grants our distributors the distribution rights for oral treprostinil in the United States.

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Our specialty pharmaceutical distributors are responsible for assisting patients with obtaining reimbursement for the cost of Remodulin and Tyvaso and providing other support services. Under our distribution agreements, we sell Remodulin and Tyvaso to our distributors at a transfer price that we establish. We have also established a patient assistance program in the United States, which provides eligible uninsured or under-insured patients with Remodulin and Tyvaso at no charge for a certain period of time.

From time-to-time, we increase the price of Tyvaso. We increased the price of Tyvaso by 4.9 percent effective in April 2012, and again effective January 1, 2013.

Adcirca

We sell Adcirca to pharmaceutical wholesalers at a discount from an average wholesale price. Under our manufacturing and supply agreement with Lilly (see *Strategic Licenses and Relationships* below for more details), Lilly has agreed to manufacture Adcirca and distribute it via its wholesaler network, which includes our specialty pharmaceutical distributors, in the same manner that it distributes its own pharmaceutical products. Under the terms of this agreement, we take title to Adcirca upon completion of its manufacture by Lilly. Adcirca is shipped to customers in accordance with purchase orders received by Lilly. When customers take delivery of Adcirca, Lilly sends an invoice and collects the amount due from the customer subject to customary discounts and rebates, if any. Although Lilly provides these services on our behalf, we maintain the risk of loss as it pertains to inventory and non-payment of invoices. The manufacturing and supply agreement will continue in effect until expiration or termination of the license agreement. Lilly retains authority under the license agreement for all regulatory activities with respect to Adcirca, as well as retail pricing, which is expected to be at price parity with Cialis. Since receiving FDA approval of Adcirca, Lilly has generally increased the net wholesale price of Adcirca twice annually. During 2012, Lilly increased the price of Adcirca by 8.9 percent effective in each of January 2012 and July 2012. More recently, Lilly announced a 9.5 percent increase of the net wholesale price of Adcirca effective January 2013.

International Distribution of Remodulin

We currently sell subcutaneous and intravenous Remodulin outside the United States to five distributors, each of which has exclusive distribution rights in one or more countries within Europe, Israel and the Middle East, Asia and South and Central America. We also distribute Remodulin in Canada through a specialty pharmaceutical wholesaler. In some of the European markets where we are not licensed to market Remodulin, we sell (but do not market) Remodulin under the named-patient system in which therapies are approved for individual patients by a national medical review board on a case-by-case basis. We are working on expanding our sales of subcutaneous and intravenous Remodulin into new territories outside of the United States through our existing distributors and by creating relationships with new distributors. In 2007 and 2010, we entered into distribution agreements with Mochida Pharmaceutical Co., Ltd. (Mochida) and Lee's Pharmaceutical (HK) Limited (Lee's Pharma) to obtain approval and exclusively distribute subcutaneous and intravenous Remodulin in Japan and China, respectively. Lee's Pharma submitted an application for approval of intravenous and subcutaneous Remodulin in China in September 2011. Mochida is conducting an open-label phase III study to support a new drug application for subcutaneous and intravenous Remodulin in Japan, which we anticipate will be filed in 2013. In addition, Grupo Ferrer Internacional, S.A. (Grupo Ferrer) has been actively working toward commencing commercial sales of subcutaneous Remodulin in Taiwan and South Korea. In some countries, such as Japan, in order to commercialize Remodulin we are required to conduct new clinical trials, called bridging studies, to demonstrate the efficacy and safety of Remodulin in their local patient population prior to approval. Therefore it could take several years before we can commence commercial sales in new countries.

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Strategic Licenses and Relationships

Lilly Agreements Related to Adcirca

In 2008, we entered into several agreements with Lilly regarding Adcirca, including a license agreement, a manufacturing and supply agreement, and a stock purchase agreement.

License Agreement

Under the terms of the license agreement, which is more fully described below in *Patents and Proprietary Rights Lilly License*, Lilly granted us an exclusive license for the right to develop, market, promote and commercialize Adcirca for the treatment of pulmonary hypertension in the United States and Puerto Rico. Lilly retains authority for all regulatory activities with respect to Adcirca, as well as retail pricing, which is expected to be at price parity with Cialis.

The license agreement will continue in effect until the later of: (1) expiration, lapse, cancellation, abandonment or invalidation of the last claim to expire within a Lilly patent covering the commercialization of Adcirca for the treatment of pulmonary hypertension in the United States and Puerto Rico; or (2) expiration of any government-conferred exclusivity rights to use Adcirca for the treatment of pulmonary hypertension in the United States and Puerto Rico. We have the right to terminate the license agreement upon six months written notice to Lilly. Either party may terminate the license agreement upon a material breach by the other party of it or the manufacturing and supply agreement, described below. Lilly has the right to terminate the license agreement in connection with certain changes of control of our company.

Manufacturing and Supply Agreement

Under the terms of the manufacturing and supply agreement, Lilly agreed to manufacture Adcirca and distribute it on our behalf via its pharmaceutical wholesaler network, in the same manner that it distributes its own pharmaceutical products. Under the terms of this agreement, we take title to Adcirca upon its manufacture by Lilly. Adcirca is shipped to customers, generally pharmaceutical wholesalers, in accordance with customers' purchase orders received by Lilly. Lilly invoices and collects amounts due from the customer subject to customary discounts and rebates, if any, and remits the collections to us. Although Lilly is providing these services on our behalf, we maintain the risk of loss as it pertains to inventory and nonpayment of sales invoices. The manufacturing and supply agreement will continue in effect until expiration or termination of the license agreement.

As consideration for Lilly's agreement to manufacture and supply Adcirca, we made a non-refundable payment to Lilly of $125.0 million in 2008, which was expensed. We also agreed to purchase Adcirca at a fixed manufacturing cost. The agreement provides a mechanism, generally related to the increase in the national cost of pharmaceutical manufacturing, pursuant to which Lilly may raise the manufacturing cost of Adcirca.

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Stock Purchase Agreement

Under the terms of the stock purchase agreement, in 2008, we issued 6.3 million shares of our common stock to Lilly from treasury for an aggregate purchase price of $150.0 million, representing approximately 13.6% of the then-current outstanding shares of our common stock. In September 2010, Lilly filed with the SEC a Form 4 (Statement of Changes in Beneficial Ownership) disclosing that it had entered into forward contracts to sell up to an aggregate of approximately 3.1 million shares of our common stock held. According to the Schedule 13G/A filed by Lilly on February 16, 2012, Lilly currently beneficially owns approximately 3.2 million shares of our common stock.

Toray Amended License Agreement

In 2000, we licensed from Toray the exclusive right to develop and market beraprost-SR for cardiovascular indications. Beraprost-SR is a chemically stable oral prostacyclin analogue in a sustained release formulation, which produces $300 million of sales annually in Japan primarily for peripheral vascular disease, for the treatment of cardiovascular indications. In 2007, Lung LLC entered into an amended agreement with Toray to assume and amend the rights and obligations of our 2000 agreement concerning the commercialization of beraprost-MR, a modified release formulation of beraprost. The amended agreement granted us additional exclusive rights to commercialize beraprost-MR in Europe and broadened the indication to vascular disease (excluding renal disease), among other revisions. In 2010, we entered into a supplement to our license agreement under which we agreed on the timing of two of the milestone payments under our existing agreement. In July 2011, we amended and replaced our existing 2007 license agreement regarding beraprost-MR. The terms of the July 2011 license agreement did not materially change from the previous license agreement and license agreement supplements except for a reduction in royalty rates. Our exclusive rights to develop beraprost-MR extend to North America, Europe, Mexico, South America, Egypt, India, South Africa and Australia.

Significant Agreement Terms

In 2007, we issued 400,000 shares of our common stock to Toray in exchange for the cancellation of Toray's existing right under the 2000 agreement to receive an option grant to purchase 1,000,000 shares of our common stock. Toray has the right to request that we repurchase the 400,000 shares of our common stock upon 30 days prior written notice at the price of $27.21 per share. The 2007 amendment also provided for certain milestone payments during the development period and upon receipt of regulatory approval in the United States or the European Union.

In 2011, we amended our license agreement with Toray. The amendment did not materially change the terms of our license agreement, except for a reduction in royalty rates. In exchange for the reduction in royalty rates, we agreed to pay Toray $50.0 million in equal, non-refundable payments over the five-year period ending in 2015. Since these payments are non-refundable and have no contingencies attached to them, we recognized an obligation and a corresponding charge to research and development expense of $46.3 million, which represented the present value of the related payments discounted by our estimated current cost of debt. Toray has the right to terminate the license agreement in the event of a change of control of our company under certain circumstances.

NEBU-TEC Agreement of Sale and Transfer

In 2008, we entered into an agreement with NEBU-TEC International Med Products Eike Kern GmbH (NEBU-TEC), to purchase its line of business relating to the manufacture of the Tyvaso Inhalation System for €5.0 million plus future milestone payments of up to €10.0 million (of which we have already paid €2.5 million). The transaction closed in 2009 after we received FDA approval for Tyvaso. Under the terms of our agreement, we manage all aspects of the manufacturing process for the

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Tyvaso Inhalation System and NEBU-TEC supplies the labor to assemble the devices. NEBU-TEC also granted us an option to acquire its next generation inhalation device, the SIM-Neb.

In December 2011, we closed on an agreement with NEBU-TEC to purchase all rights to its SIM-Neb device, which is currently under development. Under the terms of the agreement, we assumed all funding responsibilities for the development and production of the SIM-Neb and NEBU-TEC will receive milestone payments for FDA and EMA approvals and additional milestone payments based on the number of commercial patients using the SIM-Neb.

Pluristem License Agreement

In June 2011, we entered into a license agreement with Pluristem Ltd. (Pluristem) for exclusive worldwide rights to develop and commercialize a cell-based product for the treatment of PAH using Pluristem's proprietary PLX cell technology. The license agreement became effective in August 2011, at which time we made a one-time, non-refundable payment of $7.0 million to Pluristem, $5.0 million of which consisted of a license fee that was charged to research and development expenses. The agreement provides for additional milestone payments to Pluristem at various stages, as well as royalties on commercial sales.

Patents and Proprietary Rights

Our success depends in part on our ability to obtain and maintain patent protection for our products, preserve trade secrets, prevent third parties from infringing upon our proprietary rights and operate without infringing upon the proprietary rights of others in the United States and worldwide.

Glaxo Assignment

In January 1997, GlaxoSmithKline PLC (formerly Glaxo Wellcome, Inc.) (Glaxo) assigned to us all rights to the use of the stable prostacyclin analogue now known as treprostinil, the active ingredient in Remodulin, Tyvaso and our oral treprostinil tablet. The patent covering the use of treprostinil for PAH expires in the United States in October 2014 (as extended see *Patent Term Extensions* below) and on various dates from May 2011 to June 2014 in three other countries. Under the agreement, Glaxo is entitled to receive royalties on sales exceeding a specified threshold for a minimum period of ten years (or until expiration of the licensed patents) following the date of the first commercial sale of any product containing treprostinil. Glaxo retains an exclusive option and right of first refusal to negotiate an agreement with us if we decide to license any commercialization rights with respect to treprostinil-based products anywhere in the world.

Pfizer License

In December 1996, Pharmacia & Upjohn Company (now Pfizer) exclusively licensed to us certain patents, a patent application and know-how for the composition and production of treprostinil. We filed our own patent application for a new synthesis and production method for treprostinil in October 1997 in the United States, Europe and various other countries. We believe that our method of synthesis is a substantial improvement over the Pharmacia method and we are using our unique synthesis method rather than the licensed Pharmacia method for the production of treprostinil. Our obligation to pay royalties under this license agreement expired in May 2012. However, this has not resulted in any immediate impact on our aggregate royalty rate for Remodulin because the royalty offset provisions under the Glaxo assignment agreement (which does not expire until the Glaxo patent expires) caused a corresponding increase in our royalty rate to Glaxo. Our 1997 synthesis application resulted in the grant of three patents in the United States, all of which expire in October 2017, as well as granted patents in a number of other countries, expiring in October 2018. Our synthesis application remains pending in Canada. We continue to conduct research into new methods to synthesize treprostinil and

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have filed a number of additional patent applications relating to production of treprostinil, several of which have already been granted in the United States. We have also been granted a U.S. patent covering an improved diluent for Remodulin, which will expire in March 2029.

Patent Term Extension

In February 2005, we were granted a five-year patent term extension by the United States Patent and Trademark Office for a patent covering the method of treating PAH using Remodulin and Tyvaso. U.S. Patent Number 5,153,222, entitled "Method of Treating Pulmonary Hypertension with Benzidine Prostaglandins", was originally scheduled to expire on October 6, 2009. It will now expire on October 6, 2014. The five-year Hatch-Waxman Act extension is the maximum extension allowed under 35 U.S.C. §156. Additional patents covering other products to which we have rights may also be eligible for extensions of up to five years based upon patent term restoration procedures under the Hatch-Waxman Act in the United States. Similar procedures exist in Europe and other countries for obtaining patent extensions on new products that are approved after a regulatory review period. See *Governmental Regulation Hatch-Waxman Act* below for further details.

Lilly License

In 2008, we entered into a license agreement with Lilly pursuant to which Lilly granted us the exclusive right to develop, market, promote and commercialize Adcirca for the treatment of pulmonary hypertension in the United States and Puerto Rico.

In exchange for the license, we paid Lilly a non-refundable fee of $25.0 million in 2008, which was expensed since Adcirca had not yet received regulatory approval for commercial sales. We also agreed to pay Lilly royalties equal to 5 percent of our net sales of Adcirca in the United States and Puerto Rico, as a pass through of Lilly's third-party royalty obligations, for so long as Lilly is required to make such payments.

Lilly retained the exclusive rights to develop, manufacture and commercialize pharmaceutical products containing tadalafil, the active pharmaceutical ingredient in Adcirca, for the treatment of pulmonary hypertension outside of the United States and Puerto Rico and for the treatment of other diseases worldwide. Lilly retained authority for all regulatory activities with respect to Adcirca, including retail pricing, which is expected to be at price parity with Cialis.

The license agreement will continue in effect until the later of: (1) expiration, lapse, cancellation, abandonment or invalidation of the last claim to expire within a Lilly patent covering the commercialization of Adcirca for the treatment of pulmonary hypertension in the United States and Puerto Rico; or (2) expiration of any government-conferred exclusivity rights to use Adcirca for the treatment of pulmonary hypertension in the United States and Puerto Rico.

We have the right to terminate the license agreement upon six months written notice to Lilly. Lilly has the right to terminate in the event of a change of control of our company. Either party may terminate upon a material breach by the other party of the license agreement or the manufacturing and supply agreement, described above.

Supernus Pharmaceutical License

In 2006, we entered into an exclusive license agreement with Supernus to use certain of its technologies in our sustained release oral treprostinil tablet. Under the agreement, we will pay Supernus certain amounts upon the achievement of specified milestones based on the development of oral treprostinil and a $2.0 million payment upon its commercial launch. In addition, the agreement provides that we will pay a royalty to Supernus based on net worldwide sales. Any such royalty will be paid for approximately twelve years commencing with the first product sale and is subject to

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adjustments as specified in the agreement. Additional milestone payments and royalty payments may be due for the development and commercialization of other products developed using the technology granted under this license.

National Cancer Institute

In July 2010, we entered into a CRADA with NCI to collaborate on the late-stage development and regulatory agency submissions of Chimeric Monoclonal Antibody 14.18 (Ch14.18) for children with high-risk neuroblastoma and patients with other cancers. Neuroblastoma is a rare cancer of the sympathetic nervous system mainly affecting children. Under the terms of the CRADA, NCI has completed a second phase III clinical trial in 105 patients to define more clearly the safety and toxicity profile of Ch14.18 immunotherapy in children and we are developing the commercial manufacturing capability for the antibody. As part of developing our commercial manufacturing capability, we will need to demonstrate comparability of our Ch14.18 to the NCI-produced Ch14.18, which typically includes a series of analytical and bioanalytical assays and human pharmacokinetics. The human pharmacokinetics study is currently open to enrollment in the United States. The NCI studies, including a previously-conducted phase III study and all other studies supported by NCI will be used in support of a biologics license application we plan to file seeking FDA approval of Ch14.18 immunotherapy for the treatment of neuroblastoma.

Memorial Sloan Kettering License

Pursuant to a 2007 agreement with Memorial Sloan-Kettering Cancer Center, we obtained certain license rights to an investigational monoclonal antibody, 8H9, for the treatment of metastatic brain cancer. 8H9 is a mouse IgG1 MAb that is highly reactive with a range of human solid tumors, including human brain cancers. The 8H9 antibody is in early investigational development for metastases that develop in the brain from the spread of cancers from other tissues in the body. Metastatic brain cancers are ten times more common than cancers that originate in the brain, and prognosis for patients with metastatic brain cancers is very poor. In the United States, more than 100,000 cases of metastatic brain cancer are diagnosed each year.

Ascendis Pharma A/S

In September 2012, we signed an exclusive agreement with Ascendis Pharma to apply Ascendis Pharma's proprietary TransCon technology platform to our treprostinil molecule. We believe that the TransCon technology platform may enable a sustained release of a novel, carrier-linked product, which will significantly enhance the delivery of treprostinil by establishing a once-daily, self-injectable alternative for patients who currently administer Remodulin through a continuous infusion pump for the treatment of PAH. We expect that this self-injectable form of treprostinil could enable patients to avoid the infusion site pain associated with subcutaneous Remodulin. Under this agreement, we also intend to pursue development of a TransCon technology-enabled sustained release formulation of beraprost, which is another prostacyclin analogue. Under the agreement, we may be required to make future development-related milestone payments and royalty payments based on commercial sales.

Research & Development Expenditures

We are engaged in research and development and have incurred substantial expenses for these activities. These expenses generally include the cost of acquiring or inventing new technologies and products, as well as new product development. Research and development expenses during the years ended December 31, 2012, 2011 and 2010 totaled approximately $173.4 million, $180.0 million and $165.3 million, respectively. See *Item 7 Management's Discussion and Analysis of Financial Condition and Results of Operations Major Research and Development Projects* for additional information regarding expenditures related to major research and development projects.

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Production and Supply

We synthesize treprostinil, the active ingredient in Remodulin and Tyvaso, and treprostinil diolamine, the active ingredient for oral treprostinil, at our facility in Silver Spring, Maryland. In March 2011 and August 2011, we received FDA approval to produce Tyvaso and Remodulin, respectively, at our Silver Spring facility. In June 2012, we received a Good Manufacturing Practice certificate from the U.K. Medicines and Health Products Regulatory Agency to produce Remodulin and Tyvaso in our Silver Spring facility.

Baxter Pharmaceutical Solutions, LLC (Baxter) currently produces Remodulin for commercial use for us. In 2009, we amended our contract with Baxter to extend the contract term through the end of 2013. During the fourth quarter of 2012, we notified Baxter that we will not renew our current contract when it expires at the end of 2013. However, we expect to negotiate and enter into a new contract with Baxter prior to the expiration of the current contract. In 2009, we also agreed with Baxter, that Remodulin will be produced using a different set of equipment and in larger quantities than the currently approved process. Since Baxter will produce Remodulin on different equipment and in a larger batch than the current process, we are required to have the new equipment and process approved by the FDA. We are currently conducting the validation and stability testing for the new equipment and process. If the validation and stability testing are successful and we are successful in negotiating a new contract with Baxter, we anticipate filing for regulatory approval of the new equipment and process shortly after entering into the new contract with Baxter. Baxter continues to produce Remodulin for us according to the currently-approved process. In 2011, the FDA and European regulatory authorities approved Jubilant Hollister-Stier Contract Manufacturing and Services as an additional Remodulin producer, in the larger quantities described above.

We rely on Catalent Pharma Solutions, Inc. (Catalent) to do the following: (1) conduct stability studies on Remodulin, (2) serve as an additional producer of Tyvaso and oral treprostinil tablets, and (3) analyze other products we develop. We are also manufacturing oral treprostinil tablets, which are being used in our clinical trials, in our facility in Research Triangle Park, North Carolina (RTP Facility).

We intend to use our own facilities to produce our primary supply of Remodulin, Tyvaso and oral treprostinil tablets, and we will continue to contract with third parties to supplement our production capacity. Also, although we maintain a two-year inventory of Remodulin and Tyvaso based on expected demand, we believe that having third parties approved to produce these products will mitigate some of our risks, including the risk that we might not be able to produce sufficient quantities to meet patient demand.

Under our manufacturing and supply agreement with Lilly, Lilly manufactures and distributes Adcirca through its wholesaler network in the same manner that it distributes its own pharmaceutical products. Under the terms of this agreement, we take title to Adcirca upon completion of its manufacture by Lilly. Adcirca is shipped to customers, generally pharmaceutical wholesalers, in accordance with purchase orders received by Lilly. Although Lilly provides these services on our behalf, we maintain the risk of loss as it pertains to inventory and non-payment of invoices.

We manufacture the nebulizer used in our Tyvaso Inhalation System. While we manage the manufacturing process, NEBU-TEC supplies all the labor to manufacture the nebulizers. In December 2010, Minnetronix, Inc. (Minnetronix) was approved by the FDA as a second manufacturer of the Tyvaso Inhalation System.

In July 2012, we received FDA approval for a modified Tyvaso Inhalation System based on the results of the completion of certain post marketing commitments relating to the inhalation device. As a result, we are currently manufacturing the modified inhalation system (TD-100), which we expect to release commercially during 2013. Consequently, as of December 31, 2012, we increased our reserves

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for inventory obsolescence by $8.9 million based on the estimated cost of inhalation device inventory we do not expect to be salable as a result of the commercial release of TD-100.

Although we believe that other third parties could provide similar products, services and materials, there are few companies that could replace our existing producers and suppliers. A change in supplier or manufacturer could cause a delay in the manufacture, distribution and research efforts associated with our respective products or result in increased costs. See also *Item 1A Risk Factors* included in this Annual Report on Form 10-K.

Competition

Many drug companies engage in research and development to commercialize products to treat cardiovascular and infectious diseases and cancer. For the treatment of PAH, we compete with many approved products in the United States and the rest of the world, including the following:

Flolan. The first product approved by the FDA for treating PAH, Flolan (epoprostenol) is a prostacyclin that is delivered by intravenous infusion. Glaxo began marketing Flolan in the United States in 1996. In 2006, Myogen, Inc. (Myogen) acquired the marketing rights from Glaxo for Flolan in the United States. In 2006, Myogen was acquired by Gilead Sciences, Inc. (Gilead). In 2009, Gilead returned the rights to Flolan to Glaxo. The generic exclusivity period for Flolan expired in April 2007;

Generic epoprostenol and Veletri. In 2008, Teva announced that the FDA approved its version of generic epoprostenol for the treatment of PAH. In 2008, GeneraMedix Inc. (GeneraMedix) received FDA approval for its version of epoprostenol, which is stable at room temperature. In 2009, Actelion announced that it had entered into an agreement with GeneraMedix to acquire its epoprostenol product, marketed as Veletri, and began commercial sales in 2010;

Ventavis and Ilomedin®. Approved in 2004 in the United States and in 2003 in Europe, Ventavis (iloprost) is an inhaled prostacyclin analogue. Ventavis was initially marketed by CoTherix, Inc. (CoTherix) in the United States and is marketed by Bayer Schering Pharma AG (Bayer) in Europe as Iloprost. In 2007, CoTherix was acquired by Actelion, the manufacturer and distributor of Tracleer and distributor of Veletri. Iloprost is also marketed by Bayer in certain countries outside the United States in an intravenous form known as Ilomedin;

Tracleer. The first oral drug to be approved for PAH, Tracleer (bosentan) is also the first drug in its class, which consists of drugs known as ETRAs. Tracleer was approved in 2001 in the United States and in 2002 in Europe. Tracleer is marketed worldwide by Actelion;

Letairis®. Approved in 2007 in the United States, Letairis (ambrisentan) is an oral therapy marketed by Gilead for the treatment of PAH. Like Tracleer, Letairis is an ETRA. In 2008, Glaxo received marketing authorization from the EMA for Letairis in Europe, where it is known as Volibris®;

Revatio. Approved in 2005 in the United States, Revatio (sildenafil citrate) is also an oral therapy and is marketed by Pfizer. Revatio contains sildenafil citrate, the same active ingredient as Viagra, and is the first PDE-5 inhibitor to be approved for PAH; and

Generic sildenafil citrate. In the fourth quarter of 2012, several companies began marketing generic formulations of sildenafil citrate.

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There are also a variety of investigational PAH therapies in the later stages of development, including the following:

Macitentan, an oral ETRA being developed by Actelion. In November 2012, Actelion submitted an MAA for macitentan to the EMA. In December 2012, the FDA accepted Actelion's NDA for macitentan;

Riociguat, an oral agent targeting a similar vasodilatory pathway as PDE-5 inhibitors. In February 2013, Bayer announced that it had filed an NDA and a Marketing Authorization Application (MAA) for the approval of Riociguat for the treatment of PAH in the United States and Europe;

Selexipag, an oral prostacyclin receptor agonist being developed jointly by Actelion and Nippon Shinyaku Co., Ltd. in Japan, and by Actelion outside Japan, is currently undergoing a phase III trial; and

Gleevec® (imatinib), a small molecule kinase inhibitor in oral tablet form approved for treating various cancers, is being studied for the treatment of PAH. Novartis Pharmaceuticals Corporation (Novartis) completed a phase III trial of Gleevec for the treatment of PAH in September 2011. During the third quarter of 2012, Novartis withdrew its NDA in order to submit additional data to the FDA and during the first quarter of 2013 withdrew the MAA it had filed with the EMA.

Oral therapies (Adcirca, Revatio, generic sildenafil citrate, Tracleer and Letairis) are commonly prescribed as first-line treatments for the least severely ill patients (NYHA Class II patients). As patients progress in their disease severity (NYHA Class III and IV), inhaled therapies (Tyvaso and Ventavis) or infusion therapies (Remodulin and Flolan) are commonly added. The use of the available oral therapies and Tyvaso, either alone or in combination, could delay the need for infusion therapy for many patients. As a result, the success of other therapies in preventing disease progression affects our commercial products. Furthermore, the commercialization of generic forms of other approved PAH therapies and the development of new PAH therapies may exert downward pressure on the pricing of our products. For further discussion on this risk, see *Item 1A Risk Factors We may not compete successfully with established and newly developed drugs or products, or the companies that develop and market them.*

We could also face competition from generic pharmaceutical companies in the future. In February 2012, we received notice of an abbreviated new drug application by Sandoz Inc. requesting FDA approval to market a generic version of the 10 mg/mL strength of Remodulin. On December 7, 2012, we received notice that Sandoz had amended its previously filed abbreviated new drug application to request additional approval to market generic versions of the 1 mg/mL, 2.5 mg/mL, and 5 mg/mL strengths of Remodulin. For further details, see the section below entitled *Governmental Regulation Hatch-Waxman Act* and *Item 3. Legal Proceedings.*

In addition, certain Revatio patents expired in 2012, leading several manufacturers to launch generic formulations of sildenafil citrate, which physicians could prescribe for the treatment of PAH. Generic sildenafil citrate's lower price, relative to Adcirca, could lead to an erosion of Adcirca's market share and limit its growth potential. Although we believe Adcirca's once-daily dosing regimen provides a significant competitive advantage over generic sildenafil citrate's dosing regimen of three times per day, we expect government payers and private insurance companies to favor the use of the less expensive generic sildenafil citrate instead of Adcirca.

We compete with the developers, manufacturers and distributors of all of these products for customers, funding, access to licenses, personnel, third-party collaborators, product development and commercialization. Almost all of these companies have substantially greater financial, marketing, sales,

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distribution and technical resources, and more experience in research and development, product development and marketing, clinical trials and regulatory matters, than we have.

Governmental Regulation

Pharmaceutical Product Approval Process

The research, development, testing, manufacture, promotion, marketing, distribution, sampling, storage, approval, labeling, record keeping, post-approval monitoring and reporting, and import and export of pharmaceutical products (drugs or biological products, hereinafter collectively drugs) are extensively regulated by governmental agencies in the United States and in other countries. In the United States, failure to comply with requirements under the Federal Food, Drug, and Cosmetic Act (FDC Act), the Public Health Service Act, and other federal statutes and regulations, may subject a company to a variety of administrative or judicial sanctions, such as FDA refusal to approve pending NDAs or biologics license applications (BLAs), warning letters, product recalls, product seizures, total or partial suspension of production or distribution, injunctions, fines, civil penalties, and criminal prosecution.

Satisfaction of FDA pre-market approval requirements typically takes many years, and the actual time required may vary substantially based upon the type, complexity and novelty of the product or disease. Drugs are subject to rigorous regulation by the FDA in the United States, the EMA in the EU and similar regulatory authorities in other countries. The steps ordinarily required before a new drug may be marketed in the United States, which are similar to steps required in most other countries, include:

Preclinical laboratory tests, preclinical studies in animals, formulation studies and the submission to the FDA of an investigational new drug application (IND) for a new drug, which must become effective before clinical testing may commence;

Clinical studies in healthy volunteers;

Clinical studies in patients to explore safety, efficacy and dose-response characteristics;

Adequate and well-controlled clinical trials to establish the safety and efficacy of the drug for each indication;

The submission of an NDA or BLA to the FDA; and

FDA review and approval of the NDA or BLA prior to any commercial sale or shipment of the drug.

Preclinical tests include laboratory evaluation of product chemistry and formulation, as well as animal studies to explore toxicity and for proof-of-concept. The conduct of the preclinical tests must comply with federal regulations and requirements including good laboratory practices. In the United States, the results of preclinical testing are submitted to the FDA as part of an IND, along with other information including information about product chemistry, manufacturing and controls and a proposed clinical trial protocol. Long-term preclinical tests, such as animal tests of reproductive toxicity and carcinogenicity, may continue after the IND is submitted. Absent FDA objection within 30 days after submission of an IND, the IND becomes effective and the clinical trial proposed in the IND may begin. At any time during this 30-day period or at any time thereafter, the FDA may halt proposed or ongoing clinical trials. The IND process may be extremely costly and may substantially delay development of our products. Moreover, positive results of preclinical tests will not necessarily indicate positive results in clinical trials.

Clinical trials involve the administration of the investigational new drug or biologic to healthy volunteers or patients under the supervision of a qualified investigator. Clinical trials must be

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conducted: (i) in compliance with federal regulations; (ii) in compliance with good clinical practices (GCP), an international standard meant to protect the rights and health of patients and to define the roles of clinical trial sponsors, administrators, and monitors; and (iii) under protocols detailing the objectives of the trial, the parameters to be used in monitoring safety and the criteria to be evaluated. Each protocol involving testing on U.S. patients and subsequent protocol amendments must be submitted to the FDA as part of the IND.

The FDA may order the temporary or permanent discontinuation of a clinical trial at any time or impose other sanctions if it believes that the clinical trial is not being conducted in accordance with FDA requirements or presents an unacceptable risk to the clinical trial patients. The study protocol and informed consent information for patients in clinical trials must also be submitted to an institutional review board (IRB) for approval. An IRB may also require the clinical trial at a site to be halted temporarily or permanently for failure to comply with the IRB's requirements, or may impose other conditions.

Clinical trials in support of an NDA or a BLA are typically conducted in three sequential phases, but the phases may overlap. During phase I, the initial introduction of the drug into healthy human subjects or patients, the drug is tested to assess metabolism, pharmacokinetics, pharmacological actions, side effects associated with increasing doses, and, if possible, early evidence on effectiveness. Phase II usually involves studies in a limited patient population to: assess the efficacy of the drug in specific, targeted indications; assess tolerance and optimal dosage; and identify possible adverse effects and safety risks. If a compound is found to be potentially effective and to have an acceptable safety profile in phase II evaluations, then phase III trials, also called pivotal studies, major studies or advanced clinical trials, are undertaken to demonstrate clinical efficacy and safety in a larger number of patients, typically at geographically diverse clinical study sites, to permit the FDA to evaluate the overall benefit-risk relationship of the drug and to provide adequate information for the labeling of the drug.

After successful completion of the required clinical testing, an NDA or a BLA is typically submitted to the FDA in the United States, and an MAA is typically submitted to the EMA in the EU. FDA approval of the NDA or BLA is required before marketing of the product may begin in the U.S. The NDA or BLA must include the results of all preclinical, clinical and other testing and a compilation of data relating to the product's pharmacology, chemistry, manufacture, and controls. The cost of preparing and submitting an NDA or BLA is substantial. Under federal law, the submission of most NDAs and BLAs is additionally subject to a substantial application fee, currently exceeding $1.95 million, and the manufacturer and/or sponsor of an approved new drug application are also subject to annual product and establishment fees, currently exceeding $98,000 per product and $526,000 per establishment. These fees are typically increased annually. However, the application fees may be waived for orphan drugs if certain requirements are met.

The FDA has 60 days from its receipt of an NDA or a BLA to determine whether the application will be accepted for filing based on the agency's threshold determination that it is sufficiently complete to permit substantive review. Once the submission is accepted for filing, the FDA begins an in-depth review. The FDA has agreed to certain performance goals in the review of new drug applications. Most such applications for non-priority drug products are reviewed within ten to twelve months, while most applications for priority review drugs are reviewed in six to eight months. Priority review can be applied to drugs that the FDA determines offer major advances in treatment, or provide a treatment where no adequate therapy exists. For biologics, priority review is further limited to drugs intended to treat a serious or life-threatening disease. The review process may be extended by the FDA for three additional months to consider certain information submitted during FDA review, including information intended to clarify information already provided in the submission. The FDA may also refer applications for novel pharmaceutical products or pharmaceutical 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

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approved. The FDA is not bound by the recommendation of an advisory committee, but it generally follows such recommendations. Before approving an NDA or a BLA, the FDA will typically inspect one or more clinical sites to assure compliance with GCP. Additionally, the FDA will inspect the facility or the facilities at which the drug is manufactured. The FDA will not approve the product unless compliance with current good manufacturing practices is satisfactory and the NDA or BLA contains data that provide substantial evidence that the pharmaceutical product is safe and effective for the indication studied.

In the United States, after the FDA evaluates the NDA and the manufacturing facilities, the FDA may issue either an approval letter or a complete response letter. 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 conditions have been addressed to the FDA's satisfaction in a resubmission of the NDA or BLA, the FDA will issue an approval letter. The FDA has committed to reviewing such resubmissions in two or six months depending on the type of information included. A Class 1 resubmission may contain only limited information such as labeling, safety updates, stability updates, or minor analysis updates or clarifying information and is subject to a two-month review period. All other resubmissions are categorized as Class 2 and are subject to a six-month review period.

An approval letter authorizes commercial marketing of the drug with specific prescribing information for specific indications. As a condition of NDA approval, the FDA may require a risk evaluation and mitigation strategy (REMS) to help ensure that the benefits of the drug outweigh the potential risks. A REMS can include medication guides, communication plans for healthcare professionals, and elements to assure safe use (ETASU). ETASU can include, but are not limited to, special training or recertification for prescribing or dispensing, dispensing only under certain circumstances, special monitoring, and the use of patient registries. The requirement for a REMS can materially affect the potential market and profitability of the drug. To continue marketing our products after approval, applicable regulations require us to maintain a positive risk-benefit profile, maintain regulatory applications through periodic reports to regulatory authorities, fulfill pharmacovigilance requirements, maintain manufacturing facilities according to the FDA's current Good Manufacturing Practices requirements, and successfully complete regulatory agency inspections, among other requirements. Our manufacturing facilities are subject to continual review and periodic inspections. Once granted, product approvals may be withdrawn if compliance with regulatory standards is not maintained or problems are identified following initial marketing.

Disclosure of Clinical Trial Information

Sponsors of clinical trials of FDA-regulated drugs and other products are required to register and disclose certain clinical trial information related to the product, patient population, phase of investigation, study sites and investigators, and other aspects of the clinical trial. This clinical trial information is then made public as part of the sponsor's registration. Sponsors are also obligated to disclose the results of their clinical trials after completion. Competitors may use this publicly-available information to gain knowledge regarding the progress of development programs.

Orphan Drugs

Under the Orphan Drug Act, an applicant can request the FDA to designate a product as an "orphan drug" in the United States if the drug is intended to treat an orphan, or rare, disease or condition. A disease or condition is considered orphan if it affects fewer than 200,000 people in the United States. Orphan drug designation must be requested before submitting an NDA or BLA. 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

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orphan drug designation and FDA approval for a particular active ingredient to treat a particular disease is entitled to a seven-year exclusive marketing period in the U.S. for that product, for that indication. During the seven-year period, the FDA may not approve any other application to market the same drug for the same disease, except in limited circumstances, such as a showing of clinical superiority to the product with orphan drug exclusivity. 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.

The FDA granted orphan drug designation for the active ingredient treprostinil for the treatment of PAH as a continuous infusion. However, this designation does not preclude us from seeking orphan drug designation for other formulations or routes of administration, such as oral or inhaled, of treprostinil to treat PAH, or for treprostinil used to treat other orphan diseases. In order for the FDA to grant orphan drug designation for other formulations or routes of administration of treprostinil to treat PAH, we must demonstrate that such new formulation or route of administration is clinically superior to the formulation or route of administration previously granted orphan drug designation. The FDA has granted orphan drug designation for Tyvaso.

Pediatric Information

Under the Pediatric Research Equity Act of 2007 (PREA), NDAs, BLAs and supplements to NDAs and BLAs must contain data to assess the safety and effectiveness of the drug for the claimed indication(s) in all relevant pediatric subpopulations and to support dosing and administration for each such pediatric subpopulation for which the drug is safe and effective. The FDA may grant deferrals for submission of data or full or partial waivers. Unless otherwise required by regulation, the PREA does not apply to any drug for an indication for which orphan drug designation has been granted.

The Best Pharmaceuticals For Children Act (BPCA) provides NDA holders a six-month extension of any exclusivity, patent or non-patent, for a drug if certain conditions are met. Conditions for exclusivity include the FDA's determination that information relating to the use of a new drug in the pediatric population may produce health benefits in that population, the FDA making a written request for pediatric studies, and the applicant agreeing to perform, and reporting on, the requested studies within the statutory timeframe. Applications under the BPCA are treated as priority applications, with all of the benefits that designation confers.

Hatch-Waxman Act

The Hatch-Waxman Act (also known as the Drug Price Competition and Patent Term Restoration Act) was enacted in 1984 to encourage research and development of new drugs and competition between brand and generic pharmaceutical companies. It created a faster approval process for generic drugs, called the abbreviated new drug application (ANDA), while it provided protection to brand pharmaceuticals by extending their patent protection to compensate for patent time lost during the FDA review and approval process and periods of market exclusivity to encourage continuing research on, for example, new uses, strengths or dosage forms for existing drugs. In seeking approval of a drug through an NDA, applicants are required to submit to the FDA each patent that covers the applicant's product or FDA approved method of using this product. Upon approval of a drug, each of the patents listed in the application 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 ANDA. Generally, an ANDA provides for marketing of a drug product that has the same active ingredients in the same strength(s), route of administration, and dosage form as the listed drug and has been shown through bioequivalence testing to be therapeutically equivalent to the listed drug. ANDA applicants are not required to conduct or submit results of pre-clinical 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.

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The ANDA applicant is required to certify to the FDA concerning any patents listed for the approved product in the FDA's Orange Book. Specifically, the applicant must certify that: (i) the required patent information has not been filed; (ii) the listed patent has expired; (iii) the listed patent has not expired, but will expire on a particular date and approval is sought after patent expiration; or (iv) the listed patent is invalid or will not be infringed by the new product. A certification that the new product will not infringe the already approved product's listed patents or that such patents are invalid is called a Paragraph IV certification. If the applicant does not challenge the listed patents, the ANDA application will not be approved until all the listed patents claiming the referenced product have expired. Alternatively, for a patent covering an approved method of use, an ANDA applicant may submit a statement to the FDA that the company is not seeking approval for the covered use.

If the ANDA applicant has submitted 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 of 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 application also will not be approved 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. 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. Following approval of a listed drug that contains previously approved active ingredients but is approved in a new dosage form, route of administration or combination, or for a new condition of use that was required to be supported by new clinical trials conducted by or for the sponsor, federal law provides for an exclusivity period of three years, during which the FDA cannot grant effective approval of an ANDA for such new condition of use, dosage form or strength that meets certain statutory requirements. Both of the five-year and three-year exclusivity periods, as well as any unexpired patents listed in the Orange Book for the listed drug, can be extended by six months if the FDA grants the NDA sponsor a period of pediatric exclusivity based on studies submitted by the sponsor in response to a written request.

The Hatch-Waxman Act provides that patent terms may be extended to compensate for some of the patent life that is lost during the FDA regulatory review period for a product. This extension period would generally be one-half the time between the effective date of an IND and the submission date of an NDA, plus all of the time between the submission date of an NDA and its approval, subject to a maximum extension of five years. Similar patent term extensions are available under European laws. Following FDA approval, we filed a patent term extension application with the United States Patent and Trademark Office for our patent covering the method of treating PAH using Remodulin. The application was approved in February 2005 with the maximum patent term extension of five years, and the patent will expire on October 6, 2014.

In February 2012, we received notice of an abbreviated new drug application by Sandoz Inc. requesting FDA approval to market a generic version of the 10 mg/mL strength of Remodulin. On December 7, 2012, we received notice that Sandoz had amended its previously filed abbreviated new drug application, and was requesting additional approval to market generic versions of the 1mg/mL, 2.5 mg/mL, and 5 mg/mL strengths of Remodulin. For further details, see *Item 3. Legal Proceedings.*

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Section 505(b)(2) New Drug Applications

Most drug products (other than biological 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 finding of safety and efficacy data for an existing product, or published literature, in support of its application.

Section 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. The applicant may rely upon certain preclinical or clinical studies conducted for an approved 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 labeled indications for which the referenced product has been approved, as well as for any new indication for which the Section 505(b)(2) NDA applicant has submitted data.

To the extent that the Section 505(b)(2) applicant is relying on prior FDA findings of safety and efficacy, 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. Thus, approval of a Section 505(b)(2) NDA can be delayed 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) NDA applicant.

Other Regulatory Requirements

Once an NDA or a BLA is approved, a product will be subject to certain post-approval requirements. For instance, the FDA closely regulates the post-approval marketing and promotion of drugs, including standards and regulations for direct-to-consumer advertising, off-label promotion, industry-sponsored scientific and educational activities and promotional activities involving the internet.

Pharmaceutical products may be marketed only for the approved indications and in accordance with the provisions of the approved labeling. Changes to some of the conditions established in an approved application, including changes in indications, labeling, or manufacturing processes or facilities, require submission and FDA approval of a new or supplemental NDA/BLA before the change can be implemented. An NDA/BLA supplement for a new indication typically requires clinical data similar to that in the original application, and the FDA uses the same procedures and actions in reviewing supplements as it does in reviewing NDAs or BLAs.

Adverse event reporting and submission of periodic reports continue to be required following FDA approval of an NDA or a BLA. The FDA also may require post-marketing testing, known as phase IV testing, risk minimization action plans, and surveillance to monitor the effects of an approved product or place conditions on an approval that could restrict the distribution or use of the product. In addition, quality control as well as drug manufacture, packaging, and labeling procedures must continue to conform to current good manufacturing practices (cGMPs) after approval. Manufacturers and certain of their subcontractors are required to register their establishments with the FDA and certain state agencies, and are subject to periodic unannounced inspections by the FDA during which the agency inspects manufacturing facilities to assess compliance with cGMPs. Accordingly, manufacturers must continue to expend time, money and effort in the areas of production and quality control to maintain compliance with cGMPs. Regulatory authorities may withdraw product approvals or request

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product recalls if a company fails to comply with regulatory standards or if previously unrecognized problems are subsequently discovered.

Marketing Pharmaceutical Products Outside the United States

Outside of the United States, our ability to market our products is also contingent upon receiving marketing authorizations from regulatory authorities. The foreign regulatory approval process may include some or all of the risks associated with FDA approval set forth above. The requirements governing the conduct of clinical trials and marketing authorization vary widely from country to country.

In the EU, marketing authorizations may be submitted through a centralized body or through a decentralized/mutual recognition or a national level process. The centralized procedure is mandatory for the approval of biotechnology products, high technology products and orphan products and may be available at the applicant's option for other products. The centralized procedure provides for the grant of a single marketing authorization that is valid in all EU member countries. The decentralized/mutual recognition procedure is available for all medicinal products that are not subject to the centralized procedure. The decentralized/mutual recognition procedure provides for mutual recognition of national approval decisions, changes existing procedures for national approvals and establishes procedures for coordinated EU actions on products, suspensions and withdrawals. Under this procedure, the holder of a national marketing authorization for which mutual recognition is sought may submit an application to one or more EU member countries, certify that the dossier is identical to that on which the first approval was based, or explain any differences and certify that identical dossiers are being submitted to all EU member countries for which recognition is sought. Within 90 days of receiving the application and assessment report, each EU member country is required to decide whether to recognize approval. The procedure encourages member states to work with applicants and other regulatory authorities to resolve disputes concerning mutual recognition. Lack of objection of a given country within 90 days automatically results in approval in that country. Following receipt of marketing authorization in an EU member country, the applicant is then usually (depending on the country) required to engage in pricing discussions and negotiations with a separate prescription pricing authority in that country. Commercial sales typically only commence in a country once pricing approval has been obtained.

To secure European regulatory approvals for subcutaneous Remodulin for PAH, we used the mutual recognition process. Under the rules then applicable, centralized filing was not required and we perceived the decentralized/mutual recognition procedure to be the most effective means for approval. We filed our first MAA in France in February 2001. Review of our application was completed in 2005. As a result, Remodulin was approved in 23 member countries of the EEA under the mutual recognition process described above. We withdrew applications in Spain, the United Kingdom and Ireland and are currently evaluating resubmitting applications in Spain and Ireland. In December 2011, we received approval for intravenous Remodulin in all of the 23 member nations where subcutaneous Remodulin is approved.

To secure European regulatory approval for Tyvaso, we submitted an MAA to the EMA via the centralized process in 2008. Regulations in Europe have changed since we made our initial filing for Remodulin and all therapies for orphan diseases must now use the centralized process. In February 2010, we withdrew our MAA from consideration by the EMA due to the EMA's major objection related to findings of non-compliance with good clinical practice at two clinical sites. The EMA stated that these findings would preclude a recommendation for approval of Tyvaso in the EU. The EMA had no major objections at the time of withdrawal related to the safety or efficacy of Tyvaso.

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Biologics

Biological products used for the prevention, treatment, or cure of a disease, or condition, of a human being are subject to regulation under the FDC Act, except the section of the FDC Act which governs NDA applications. Instead, biological products are approved for marketing under provisions of the Public Health Service Act (PHSA) via a BLA. However, the application process and requirements for approval of BLAs are very similar to those for NDAs. To help reduce the increased risk of the introduction of adventitious agents, the PHSA emphasizes the importance of manufacturing control for products whose attributes cannot be precisely defined. The PHSA also provides authority to the FDA to immediately suspend licenses in situations where there exists a danger to public health, to prepare or procure products in the event of shortages and critical public health needs, and to authorize the creation and enforcement of regulations to prevent the introduction, or spread, of communicable diseases in the United States and between states.

After a BLA is approved, the product may also be subject to official lot release. As part of the manufacturing process, the manufacturer is required to perform certain tests on each lot of the product before it is released for distribution. If the product is subject to official lot release by the FDA, the manufacturer submits samples of each lot of product to the FDA together with a release protocol showing a summary of the history of manufacture of the lot and the results of all of the manufacturer's tests performed on the lot. The FDA may also perform certain confirmatory tests on lots of some products, such as viral vaccines, before releasing the lots for distribution by the manufacturer. In addition, the FDA conducts laboratory research related to the regulatory standards on the safety, purity, potency, and effectiveness of biological products. As with drugs, after approval of biologics, manufacturers must address any safety issues that arise, are subject to recalls or a halt in manufacturing, and are subject to periodic inspection after approval.

The PPACA included a subtitle called the Biologics Price Competition and Innovation Act of 2009, or BPCI Act, which created an abbreviated approval pathway for biological products shown to be similar to, or interchangeable with, an FDA-licensed reference biological product. This is conceptually similar to the Hatch-Waxman Act in that it attempts to minimize duplicative testing. Biosimilarity, which requires that there be no clinically meaningful differences between the biological product and the reference product in terms of safety, purity, and potency must be shown through analytical studies, animal studies, and at least one clinical study absent a waiver. Interchangeability requires that a product must demonstrate that it can be expected to produce the same clinical results as the reference product and, for products administered multiple times, the biologic and the reference biologic may be switched after one has been previously administered without increasing safety risks or risks of diminished efficacy relative to exclusive use of the reference biologic. However, complexities associated with the larger, and often more complex, structures of biological products, as well as the processes by which such products are manufactured, pose significant hurdles to implementation which are still being addressed by the FDA.

A reference biologic is granted twelve years of exclusivity from the time of first licensure of the reference product. The first biologic product submitted under the abbreviated approval pathway that is determined to be interchangeable with the reference product has exclusivity against other biologics submitted under the abbreviated approval pathway for the lesser of (i) one year after first commercial marketing; (ii) eighteen months after the initial application if there is no legal challenge; (iii) eighteen months after the resolution in the applicant's favor of a lawsuit challenging the biologics' patents if an application has been submitted; or (iv) 42 months after the application has been approved if a lawsuit is ongoing within the 42 month period.

Because biologically sourced raw materials are subject to unique contamination risks, their use may be restricted in some countries.

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Cell and Tissue Based Biologics

Manufacturers of cell and tissue based products must comply with the FDA's current good tissue practices (cGTP), which are FDA regulations that govern the methods used in, and the facilities and controls used for, the manufacture of such products. The primary intent of the cGTP requirements is to ensure that cell and tissue based products are manufactured in a manner designed to prevent the introduction, transmission and spread of communicable diseases. Cell and tissue based products may also be subject to the same approval standards, including demonstration of safety and efficacy, as other biologic and drug products, if they meet certain criteria such as if the cells or tissues are more than minimally manipulated or if they are intended for a non-homologous use (a use different from the cell's origin).

U.S. Regulation of Medical Devices

New medical devices are also subject to FDA approval and extensive regulation under the FDCA. Under the FDCA, medical devices are classified into one of three classes: Class I, Class II, or Class III. The classification of a device into one of these three classes generally depends on the degree of risk associated with the medical device and the extent of control needed to ensure safety and effectiveness.

Class I devices are those for which safety and effectiveness can be assured by adherence to a set of general controls. These general controls include compliance with the applicable portions of the FDA's Quality System Regulation (QSR), which sets forth good manufacturing practice requirements; facility registration and product reporting of adverse medical events listing; truthful and non-misleading labeling; and promotion of the device only for its cleared or approved intended uses. Class II devices are also subject to these general controls and to any other special controls as deemed necessary by the FDA to ensure the safety and effectiveness of the device. Review and clearance by the FDA for these devices is typically accomplished through the so-called 510(k) pre-market notification procedure. A Class III device requires approval of a premarket application (PMA), an expensive, lengthy and uncertain process requiring many years to complete.

When 510(k) clearance is sought, a sponsor must submit a pre-market notification demonstrating that the proposed device is substantially equivalent to a previously approved device. If the FDA agrees that the proposed device is substantially equivalent to the predicate device, then 510(k) clearance to market will be granted. After a device receives 510(k) clearance, any modification that could significantly affect its safety or effectiveness, or that would constitute a major change in its intended use, requires a new 510(k) clearance or could require pre-market approval.

Clinical trials are almost always required to support a PMA and are sometimes required for a 510(k) pre-market notification. These trials generally require submission of an application for an investigational device exemption, or IDE. An IDE must be supported by pre-clinical data, such as animal and laboratory testing results, which show that the device is safe to test in humans and that the study protocols are scientifically sound. The IDE must be approved in advance by the FDA for a specified number of patients, unless the product is deemed a non-significant risk device and is eligible for more abbreviated investigational device exemption requirements.

Both before and after a medical device is commercially distributed, manufacturers and marketers of the device have ongoing responsibilities under FDA regulations. The FDA reviews design and manufacturing practices, labeling and record keeping, and manufacturers' required reports of adverse experiences and other information to identify potential problems with marketed medical devices. Device manufacturers are subject to periodic and unannounced inspection by the FDA for compliance with the QSR, current good manufacturing practice requirements that govern the methods used in, and the facilities and controls used for, the design, manufacture, packaging, servicing, labeling, storage, installation, and distribution of all finished medical devices intended for human use.

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If the FDA finds that a manufacturer has failed to comply or that a medical device is ineffective or poses an unreasonable health risk, it can institute or seek a wide variety of enforcement actions and remedies, ranging from a public warning letter to more severe actions such as:

- fines, injunctions, and civil penalties;
- recall or seizure of products;
- operating restrictions, partial suspension or total shutdown of production;
- refusing requests for 510(k) clearance or PMA approval of new products;
- withdrawing 510(k) clearance or PMA approvals already granted; and
- criminal prosecution.

The FDA also has the authority to require repair, replacement or refund of the cost of any medical device.

The FDA also administers certain controls over the export of medical devices from the United States, as international sales of medical devices that have not received FDA approval are subject to FDA export requirements. Additionally, each foreign country subjects such medical devices to its own regulatory requirements. In the EU, a single regulatory approval process has been created, and approval is represented by the CE Mark.

The nebulizer used with our Tyvaso Inhalation System was included in our NDA for Tyvaso, and was cleared by the FDA subject to compliance with the QSR as it applies to combination products. In July 2012, we received FDA approval for a modified Tyvaso Inhalation System using an updated nebulizer (TD-100) based on the results of the completion of the QSR compliance commitments.

Government Reimbursement of Pharmaceutical Products

In the United States, many independent third-party payers, as well as the Medicare and State Medicaid programs, reimburse buyers of our commercial products. Medicare is the federal program that provides health care benefits to senior citizens and certain disabled and chronically ill persons. Medicaid is the federal program administered by the states to provide health care benefits to certain indigent persons. The Medicare contractors who administer the program provide reimbursement for Remodulin at a rate equal to 95% of the published average wholesale price as of October 1, 2003 (the Medicare Part B payment formula, under the Durable Medical Equipment Regional Carrier Guidelines, for drugs infused through durable medical equipment) and for Tyvaso at a rate of 106% of the average sales price (the Medicare Part B payment formula for drugs inhaled through durable medical equipment and also under the Durable Medical Equipment Regional Carrier Guidelines). Adcirca, an oral drug, is reimbursed under the Medicare Part D program. The State Medicaid programs also generally provide reimbursement for our commercial products, at reimbursement rates that are below the published average wholesale price and that vary from state to state. In return for including our pharmaceutical commercial products in the Medicare Part B and Medicaid programs, we have agreed to pay a rebate to State Medicaid agencies that provide reimbursement for those products. We have also agreed to sell our commercial products under contracts with the Department of Veterans Affairs, Department of Defense, Public Health Service and numerous other federal agencies as well as certain hospitals that are designated as 340B covered entities (entities designated by federal programs to receive drugs at discounted prices) at prices that are significantly below the price we charge to our specialty pharmaceutical distributors. These programs and contracts are highly regulated and impose restrictions on our business. Failure to comply with these regulations and restrictions could result in a loss of our ability to continue receiving reimbursement for our drugs. We estimate that between 35-50% of Remodulin, Tyvaso and Adcirca sales in the United States are reimbursed under the Medicare and Medicaid programs.

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Anti-Kickback, False Claims Laws and The Prescription Drug Marketing Act

In addition to FDA restrictions on marketing 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. Many 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 payer. Sanctions under these federal and state laws may include civil monetary penalties, exclusion of a manufacturer's products from reimbursement under government programs, criminal fines, and imprisonment.

As part of the sales and marketing process, pharmaceutical companies frequently provide samples of approved drugs to physicians. The Prescription Drug Marketing Act (PDMA) imposes requirements and limitations upon the provision of drug samples to physicians, and 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.

Patient Protection and Affordable Care Act of 2010

The Patient Protection and Affordable Care Act of 2010, as amended by the Health Care and Education Reconciliation Act of 2010 (PPACA) is intended to expand healthcare coverage within the U.S.

Several provisions of the new law, which have varying effective dates, may affect us and will likely increase certain of our costs. For example, an increase in the minimum Medicaid rebate rate from 15.1 percent to 23.1 percent of average manufacturer price became effective as of January 2010, and the volume of rebated drugs has been expanded to include beneficiaries in Medicaid managed care organizations, effective as of March 2010. The PPACA also imposes an annual fee on pharmaceutical manufacturers, based on the manufacturer's sale of branded pharmaceuticals and biologics (excluding orphan drugs) to certain U.S. government programs during the preceding year; expands the 340B drug discount program (excluding orphan drugs) including the creation of new penalties for non-compliance;

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and includes a 50% discount on brand name drugs for Medicare Part D participants in the coverage gap, or "donut hole". The law also revised the definition of "average manufacturer price" for reporting purposes effective October 2010, which could increase the amount of the Medicaid drug rebates paid to states.

The PPACA also created a regulatory pathway for the abbreviated approval of biological products that are demonstrated to be "biosimilar" or "interchangeable" with an FDA-approved biological product. In order to meet the standard of interchangeability, a sponsor must demonstrate that the biosimilar product can be expected to produce the same clinical result as the reference product, and for a product that is administered more than once, that the risk of switching between the reference product and biosimilar product is not greater than the risk of maintaining the patient on the reference product. Such biosimilars would reference biological products approved in the U.S. The law establishes a period of 12 years of data exclusivity for reference products, which protects the data in the original BLA by prohibiting sponsors of biosimilars from gaining FDA approval based in part on reference to data in the original BLA.

In addition, the PPACA imposes new reporting requirements for pharmaceutical and device manufacturers with regard to payments or other transfers of value made to physicians and teaching hospitals, with the first report due on March 31, 2013. In addition, pharmaceutical and device manufacturers will be required to report investment interests held by physicians and their immediate family members during the preceding calendar year. Such information is to be made publicly available by the Secretary of Health and Human Services in a searchable format beginning September 30, 2013. Failure to submit required information may result in civil monetary penalties of up to $150,000 per year (and up to $1 million per year for "knowing failures") for all payments, transfers of value or ownership or investment interests not reported in an annual submission. Further, the PPACA amends the intent requirement of the federal anti-kickback and criminal health care fraud statute. A person or entity no longer needs to have actual knowledge of this statute or specific intent to violate it. In addition, the government may assert that a claim including items or services resulting from a violation of the federal anti-kickback statute constitutes a false or fraudulent claim for purposes of the false claims laws.

State Pharmaceutical and Medical Device Marketing Laws

If not preempted by the PPACA, several jurisdictions, including the District of Columbia, Maine, Massachusetts, Minnesota, Vermont and West Virginia, require pharmaceutical companies to report expenses relating to the marketing and promotion of pharmaceutical products and to report gifts and payments to healthcare practitioners in those jurisdictions. Some of these jurisdictions also prohibit various marketing related activities. Still other states require the posting of information relating to clinical studies and their outcomes. In addition, certain states, such as California, Connecticut, Nevada, and Massachusetts, require pharmaceutical companies to implement compliance programs or marketing codes and several other states are considering similar proposals. Compliance with these laws is difficult and time consuming, and companies that do not comply with these state laws face civil penalties.

Employees

We had 623 employees as of February 8, 2013. The success of our business is highly dependent on attracting and retaining highly talented and qualified personnel.

Industry Segments and Geographic Areas

Prior to the sale of Medicomp in March 2011, we operated in two business segments: pharmaceuticals and telemedicine. Our core business is pharmaceuticals in which we closely monitor the revenues and gross margins generated by our commercial products. We sell our products in the United States and throughout the rest of the world. The information required by Item 101(b) and 101(d) of Regulation S-K relating to financial information about industry segments and geographical areas, respectively, is contained in Note 18 *Segment Information* to our consolidated financial statements included in this Annual Report on Form 10-K.

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Corporate Website

Our Internet website address is *http://www.unither.com*. Our filings on Form 10-K, Form 10-Q, Form 3, Form 4, Form 5, Form 8-K and any and all amendments thereto are available free of charge through this internet website as soon as reasonably practicable after they are filed or furnished to the Securities and Exchange Commission (SEC). They are also available through the SEC at *http://www.sec.gov/edgar/searchedgar/companysearch.html*.

EXECUTIVE OFFICERS OF THE REGISTRANT

The following is a list, as of February 26, 2013, setting forth certain information regarding our executive officers. Each executive officer holds office until the first meeting of the Board of Directors after the annual meeting of shareholders, and until his or her successor is elected and qualified or until his or her earlier resignation or removal. Each executive officer's employment will end pursuant to the terms of his or her employment contract. Each of the employment contracts generally provides for an initial term of service of five years, which five-year term may be renewed after each year for additional one-year periods.

Name	Age	Position
Martine A. Rothblatt, Ph.D., J.D., M.B.A.	58	Chairman, Chief Executive Officer and Director
Roger Jeffs, Ph.D.	51	President, Chief Operating Officer and Director
John M. Ferrari	58	Chief Financial Officer and Treasurer
Paul A. Mahon, J.D.	49	Executive Vice President, General Counsel and Corporate Secretary

Martine A. Rothblatt, Ph.D., J.D., M.B.A., founded United Therapeutics in 1996 and has served as Chairman and Chief Executive Officer since its inception. Prior to United Therapeutics, she founded and served as Chairman and Chief Executive Officer of Sirius XM Satellite Radio. She also represented the radio astronomy interests of the National Academy of Sciences' Committee on Radio Frequencies before the Federal Communications Commission and led the International Bar Association's efforts to present the United Nations with a draft Human Genome Treaty. Her book, *YOUR LIFE OR MINE: HOW GEOETHICS CAN RESOLVE THE CONFLICT BETWEEN PUBLIC AND PRIVATE INTERESTS IN XENOTRANSPLANTATION*, was published by Ashgate in 2004. She is a co-inventor on three of our patents pertaining to treprostinil.

Roger Jeffs, Ph.D., received his undergraduate degree in chemistry from Duke University and his Ph.D. in pharmacology from the University of North Carolina. Dr. Jeffs joined United Therapeutics in September 1998 as Director of Research, Development and Medical. He was promoted to Vice President of Research, Development and Medical in 2000 and to President and Chief Operating Officer in 2001. From 1993 to 1995, Dr. Jeffs worked at Burroughs Wellcome & Company where he was a member of the clinical research team that developed Flolan, the first FDA-approved therapy for patients with pulmonary arterial hypertension. From 1995 to 1998, Dr. Jeffs worked at Amgen, Inc. where he served as the worldwide clinical leader of the Infectious Disease Program. Dr. Jeffs currently leads our global clinical, commercial, manufacturing and business development efforts.

John M. Ferrari joined United Therapeutics in May 2001 as Controller. Mr. Ferrari was promoted to Vice President of Finance in December 2003 and to Vice President of Finance and Treasurer in June 2004. In August 2006, Mr. Ferrari was promoted to Chief Financial Officer and Treasurer. Prior to joining United Therapeutics, Mr. Ferrari served as Controller for Blackboard, Inc., from 1998 to 2001. Prior to his employment with Blackboard, Inc., Mr. Ferrari served in various senior financial management positions since beginning his accounting career in 1984.

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Paul A. Mahon, J.D., has served as General Counsel and Corporate Secretary of United Therapeutics since its inception in 1996. In June 2001, Mr. Mahon joined United Therapeutics full-time as Senior Vice President, General Counsel and Corporate Secretary. In November 2003, Mr. Mahon was promoted to Executive Vice President, General Counsel and Corporate Secretary. Prior to June 2001, he served United Therapeutics, beginning with its formation in 1996, in his capacity as principal and managing partner of a law firm specializing in technology and media law.

ITEM 1A. RISK FACTORS

Forward-Looking Statements

This Annual Report on Form 10-K contains forward-looking statements made pursuant to the safe harbor provisions of Section 21E of the Securities Exchange Act of 1934 (the Exchange Act) and the Private Securities Litigation Reform Act of 1995 which are based on our beliefs and expectations as to future outcomes. These statements include, among others, statements relating to the following:

Expectations of revenues, expenses, profitability, and cash flows;

The sufficiency of current and future working capital to support operations;

Our ability to obtain future financing;

The value of our common stock and our ability and plans to complete future common stock repurchases;

The maintenance of domestic and international regulatory approvals;

The expected volume and timing of sales of Remodulin® (treprostinil) Injection (Remodulin), Tyvaso® (treprostinil) Inhalation Solution (Tyvaso), and Adcirca® (tadalafil) tablets (Adcirca);

Our expectations to commercially launch in 2013 a modified Tyvaso Inhalation System approved by United States Food and Drug Administration (FDA) in 2012 (TD-100) and regarding the potential to increase the number of patients using Tyvaso through the further improvement of the Tyvaso Inhalation System;

Our expectation to make Tyvaso available in certain European and Latin American countries in 2013 on an unmarketed, named-patient basis based on physicians' prescriptions in those countries;

The timing and outcome of clinical studies and related regulatory filings, including: (1) our further studies of oral treprostinil and our aim to obtain FDA approval for oral treprostinil before the end of 2016; (2) our plan to file for approval for oral treprostinil in Europe upon the completion of the FREEDOM-EV study; and (3) the expectation that Medtronic Inc. (Medtronic) will complete its phase III study of Remodulin administered with the Synchromed implantable pump;

The timing and outcome of required pricing approvals and risk management plan approvals in individual European countries, in order to begin marketing intravenous Remodulin in those countries;

The expected likelihood and timing of regulatory submissions and approvals for drug candidates under development and the timing of related sales, including our anticipated application for approval of Remodulin in Japan, our pending application for approval of Remodulin in China, and our expected filing of a biologics license application with the FDA and a marketing authorization application with the European Medicines Agency (EMA) for Ch14.18;

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Our expectation that we will enter into a new contract with Baxter Pharmaceutical Solutions, LLC (Baxter), relating to the production of Remodulin, by the end of 2013 when the current contract term expires;

The outcome of potential future regulatory actions, including audits and inspections, from the FDA and international regulatory agencies;

The impact of competing therapies, including generic products and newly-developed therapies, on sales of our commercial products;

The expectation that we will be able to produce sufficient quantities and maintain adequate inventories of our commercial products, through both our in-house production capabilities and third-party production sites for our products, and our ability to obtain and maintain related approvals by the FDA and other regulatory agencies;

The adequacy of our intellectual property protections and the expiration dates of the patents we own and our licensed patents and products;

Our expectations regarding our ability to defend our intellectual property relating to Remodulin against generic challenges, including the abbreviated new drug application filed by Sandoz Inc. (Sandoz);

The potential impact of the Patient Protection and Affordable Care Act and the Health Care and Education Reconciliation Act of 2010 on our business;

The impact of the business combination between Express Scripts, Inc. (the parent company of CuraScript, Inc.) and Medco Health Solutions, Inc. (the parent company of Accredo Health Group, Inc.) on our business;

Any statements that include the words "believe," "seek," "expect," "anticipate," "forecast," "project," "intend," "estimate," "should," "could," "may," "will," "plan," or similar expressions; and

Other statements contained or incorporated by reference in this Annual Report on Form 10-K that are not historical facts.

The statements identified as forward-looking statements may appear in *Item 7 Management's Discussion and Analysis of Financial Condition and Results of Operations* or elsewhere in this Annual Report on Form 10-K. These statements are subject to risks and uncertainties and our actual results may differ materially from anticipated results. Factors that may cause such differences include, but are not limited to, those discussed below. We undertake no obligation to publicly update forward-looking statements, whether as a result of new information, future events or otherwise.

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Risks Related to Our Business

We rely heavily on sales of Remodulin, Tyvaso and Adcirca to generate revenues and support our operations.

Sales of Remodulin, Tyvaso and Adcirca comprise virtually all of our revenues. A wide variety of events, many of which are described in other risk factors below, could cause sales of these products to decline. For instance, if regulatory approvals for any of these products were withdrawn, we would be unable to sell the product and our business could be jeopardized. Any substantial change in the prescribing practices or dosing patterns of patients using Remodulin, Tyvaso or Adcirca due to combination therapies, side effects, adverse events, deaths or any other reasons, could decrease related revenues. For example, during the fourth quarter of 2012, generic sildenafil citrate became commercially available, which could result in a decrease in Adcirca's market share, or limit its growth potential. In addition, we rely on third parties to produce, market, distribute and sell Remodulin, Tyvaso and Adcirca. The inability of any one of these third parties to perform these functions satisfactorily could negatively affect our revenues. We are also increasingly internalizing elements of our production process for Remodulin and Tyvaso, and any failure to manage our internal production processes could result in an inability to meet demand. Because we are highly dependent on sales of Remodulin, Tyvaso and Adcirca, a reduction in sales of any one of these products could have a negative and material adverse impact on our operations.

We have had periods in which we incurred losses and may not maintain profitability.

We have experienced financial reporting periods in which we incurred net losses. While we believe we develop our annual cash-based operating budgets using reasonable assumptions and targets, unanticipated factors, including those outside of our control, could affect our profitability and cause uneven quarterly and/or annual operating results.

If our products fail in clinical trials, we will be unable to obtain or maintain FDA and international regulatory approvals and will be unable to sell those products.

To obtain regulatory approvals from the FDA and international regulatory agencies such as the EMA, we must conduct clinical trials demonstrating that our products are safe and effective. In the past, several of our product candidates failed or were discontinued at various stages in the development process. Moreover, we may need to amend ongoing trials or the FDA and international regulatory agencies may require us to perform additional trials beyond those we planned. Such occurrences could result in significant delays and additional costs, and related clinical trials may be unsuccessful. Approval of an NDA could be subject to delays if the FDA determines that it cannot review or approve the NDA as submitted. In such a case, the FDA would issue a refuse-to-file letter or a complete response letter outlining deficiencies in the submission, and the FDA may require substantial additional studies, testing or information in order to complete its review of the application. We may fail to address any of these deficiencies adequately and consequently would be unable to obtain FDA approval to market the product candidate.

In addition, we have commenced a new phase III clinical trial, FREEDOM-EV, which is a study of oral treprostinil in combination with other approved PAH therapies. One co-primary end point of the study is time to clinical worsening. Based on a complete response letter we received from the FDA regarding our NDA for oral treprostinil, it appears that the clinical worsening endpoint has become increasingly important to demonstrate efficacy in PAH patients to the FDA's standards. We have not previously conducted a study with a time to clinical worsening primary endpoint. Our inexperience with this type of trial design may impact our ability to achieve positive results. Failure to prove the efficacy of oral treprostinil in combination with other PAH therapies could hinder our ability to obtain FDA approval of oral treprostinil. In light of the complete response letter from the FDA, we may need to

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amend or replace the FREEDOM-EV study, or supplement it with additional studies which could further delay the approval of oral treprostinil.

The length of time that it takes for us to complete clinical trials and obtain regulatory approval for marketing varies by product, product use and country. Furthermore, we cannot predict with certainty the length of time it will take to complete necessary clinical trials or obtain regulatory approval of our future products.

Our clinical trials may be discontinued, delayed or disqualified for various reasons. These reasons include:

- The drug is ineffective, or physicians believe that the drug is ineffective;
- Patients do not enroll in our studies at the rate we expect;
- Ongoing or new clinical trials conducted by drug companies in addition to our own clinical trials reduce the availability of patients for our trials;
- Patients experience severe side effects during treatment;
- Other investigational or approved therapies are viewed as more effective or convenient by physicians or patients;
- Our clinical trial sites, contracted clinical trial administrators or clinical studies conducted entirely by third parties do not adhere to trial protocols and required quality controls under good clinical practice (GCP) under FDA regulations and similar regulations outside the United States;
- Our trials do not comply with applicable regulations or guidelines;
- We do not pass inspections by regulatory agencies;
- Patients die during our trials because of an adverse event related to the trial drug, their disease is too advanced, or they experience other medical complications;
- Drug supplies are unavailable or unsuitable for use in our studies;
- The results of preclinical testing raise concerns regarding product safety or efficacy; and
- The results of our clinical trials conducted in countries outside of the United States are not acceptable to the United States or other countries, and the results of our clinical trials conducted in the United States are not acceptable to regulators in other countries.

In addition, the FDA and its international counterparts have substantial discretion over the approval process for pharmaceutical products. As such, these regulatory agencies may not agree that we have demonstrated the requisite level of product safety and efficacy to grant approval.

Our future growth depends, in part, on our plans to develop oral treprostinil. If we fail to secure FDA approval for oral treprostinil, our revenue growth prospects could be materially adversely affected.

In 2008, we reported that our FREEDOM-C phase III clinical trial of oral treprostinil in patients with pulmonary arterial hypertension (PAH) did not achieve statistical significance for its primary endpoint (p=0.072). These results prompted us to amend the protocol for our FREEDOM-M phase III clinical trial of oral treprostinil and initiate an additional phase III clinical trial of oral treprostinil, FREEDOM-C^2. In June 2011, we announced the completion of the FREEDOM-M trial, which achieved statistical significance for its primary endpoint (p=0.0125). However, our FREEDOM-C^2 trial did not achieve statistical significance for its primary endpoint (p=0.089), as we announced in August 2011. In October 2012, the FDA issued a complete response letter, declining to approve our NDA for oral treprostinil. Although we have resubmitted our NDA in response to the complete response letter,

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and the FDA has set a targeted response date of March 31, 2013, there can be no guarantee that the FDA will complete its review of our resubmission in a timely manner. Although we aim to obtain regulatory approval of oral treprostinil before the end of 2016, the FDA may not approve oral treprostinil on this timetable, or at all. For example, approval may be further delayed if the results of our FREEDOM-EV phase III clinical trial or other clinical studies are required for approval. Future studies of oral treprostinil may ultimately fail to support FDA approval for oral treprostinil, for the reasons described above under the risk factor entitled "*If our products fail in clinical trials, we will be unable to obtain or maintain FDA and international regulatory approvals and will be unable to sell those products",* among others, which would have a significant impact on our future revenue growth.

We may not compete successfully with established and newly developed drugs or products, or the companies that develop and market them.

We compete with well-established drug companies for, among other things, funding, licenses, expertise, personnel, clinical trial patients and investigators, consultants and third-party collaborators. We also compete with these companies for market share. Most of these competitors have substantially greater financial, marketing, manufacturing, sales, distribution and technical resources than we do. These competitors also possess more experience in areas such as research and development, clinical trials, sales and marketing and regulatory matters. There are several treatments that compete with our commercial therapies, as well as several other therapies under development, including various late-stage investigational products that have recently completed or are undergoing phase III pivotal trials. For the treatment of PAH, we compete with a number of approved products in the United States and worldwide, including the following: Flolan®, Ventavis®, Ilomedin®, Tracleer®, Revatio®, Letairis®, Veletri®, generic epoprostenol and generic sildenafil citrate. Patients and doctors may perceive these competing products, or products developed in the future, as safer, more effective, more convenient and/or less expensive than our therapies. Alternatively, doctors may reduce the prescribed doses of our products if they prescribe them in combination with our competitors' products. In addition, certain competing products are less invasive than Remodulin and the use of these products may delay or prevent initiation of Remodulin therapy. Any of these circumstances may suppress our sales growth or cause our revenues to decline.

Certain of our competitors, such as Actelion Ltd. and Gilead Sciences, Inc., have achieved considerable market penetration and dominance in the PAH therapeutic area. Furthermore, the future commercialization and introduction of new PAH therapies and generic versions of our competitors' products may saturate the market which could exert downward pressure on the pricing of our products and/or reduce our market share.

Discoveries or development of new products or technologies by others may make our products obsolete or seemingly inferior.

Other companies may discover or introduce new products that render all or some of our technologies and products obsolete or noncompetitive. Our commercial therapies may have to compete with numerous investigational products currently in development, including several investigational PAH therapies for which phase III pivotal trials are underway or have been recently completed. In addition, alternative approaches to treating chronic diseases, such as gene therapy or cell therapy, may make our products obsolete or noncompetitive. If introduced into the market, investigational therapies for PAH could be used in combination with, or as a substitute for, our therapies. If this occurs, doctors may reduce or discontinue the use of our products for their patients.

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Sales of our products are subject to reimbursement from government agencies and other third parties. Pharmaceutical pricing and reimbursement pressures may negatively impact our sales.

The commercial success of our products depends, in part, on the availability of reimbursements by governmental payers such as Medicare and Medicaid, and private insurance companies. Accordingly, our commercial success is tied to such third-party payers. In the United States, the European Union and other significant or potentially significant markets for our products, government payers and/or third-party payers are increasingly attempting to limit or regulate the price of medicinal products and are frequently challenging the pricing of new and expensive drugs. Our prostacyclin analogue products (Remodulin and Tyvaso) are expensive therapies. Consequently, it may be difficult for our specialty pharmaceutical distributors or wholesalers to obtain adequate reimbursement for our products from third-party payers to yield sufficient profit to motivate such distributors or wholesalers to support our products. Alternatively, third-party payers may reduce the amount of reimbursement for our products based on changes in pricing of other therapies for PAH. If third-party payers do not approve our products for reimbursement, or limit reimbursements, patients could choose competing products that are approved for reimbursement or provide lower out-of-pocket costs. Presently, most third-party payers, including Medicare and Medicaid, provide reimbursement for our commercial products. Future reimbursements under Medicare and Medicaid could be subject to reduction. Furthermore, to the extent that private insurers or managed care programs follow any reduced Medicaid and Medicare coverage and payment developments, the negative impact on our business would be compounded. We continue to assess the potential effect of the Patient Protection and Affordable Care Act and the related Health Care and Education Reconciliation Act of 2010 (the Acts) on our business. While our business has not been impacted materially thus far as a result of the Acts, we continue to monitor the developments of this legislation as many of its provisions are not yet effective and still subject to finalization.

In the United States, there is an increased focus from the federal government and others on analyzing the impact of various regulatory programs on the federal deficit, which could result in increased pressure on federal programs to reduce costs. In addition, financial pressures may cause government or other third-party payers to seek cost containment more aggressively through mandatory discounts or rebates on our products, policies requiring the automatic substitution of generic products, higher hurdles for initial reimbursement approvals for new products or other similar measures. For example, there have been recent proposals to reduce reimbursement rates and/or adopt mandatory rebates under Medicare Part B, which covers Remodulin and Tyvaso. A reduction in the availability or extent of reimbursement from government health care programs could have a material adverse effect on sales of our products, our business and results of our operations.

In Europe, the success of our commercial products and future products depends largely on obtaining and maintaining government reimbursement. In many European countries, patients are unlikely to use prescription drugs that are not reimbursed by their governments. Countries in Europe are under increasing pressure to reduce the cost of health care. Changes to current reimbursement policies may adversely affect our ability to sell our products or sell our products on a profitable basis. In many markets outside the United States, governments control the prices of prescription pharmaceuticals through the implementation of reference pricing, price cuts, rebates, revenue-related taxes and profit control. Furthermore, international governments expect prices of prescription pharmaceuticals to decline over the life of the product or as prescription volumes increase. In addition, in December 2011, we received marketing approval for the intravenous use of Remodulin in most of the countries that are members of the European Economic Area (EEA); however, we are in the process of obtaining approval of our risk management plan on a country-by-country basis, and we must obtain pricing approval in each of these member countries before we can market Remodulin for intravenous use. Delays in obtaining these approvals could have a significant impact on our future revenue growth. Additionally, in granting pricing approval for the intravenous use of Remodulin, a

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member country may approve a lower reimbursement price for intravenous Remodulin than for subcutaneous Remodulin, or reduce the reimbursement price for both methods of administering Remodulin. Any regulatory action requiring additional information or a reduction in the reimbursement rates for intravenous and subcutaneous Remodulin could have a material adverse effect on our revenues, results of operations and our business.

Finally, the ultimate pricing and reimbursement of our investigational products, upon their approval, is inherently uncertain and subject to the risks discussed above.

Our production strategy exposes us to significant risks.

We must be able to produce sufficient quantities of our commercial products to satisfy increases in demand for our products. The process of producing our products is difficult and complex, and currently involves a number of third parties. We synthesize treprostinil, the active ingredient in Remodulin and Tyvaso, and treprostinil diolamine, the active ingredient in oral treprostinil, in our Silver Spring, Maryland facility using raw materials and advanced intermediate compounds supplied by vendors. Although we formulate Remodulin and Tyvaso at our own facilities, we also outsource the formulation of Remodulin to Baxter and Jubilant Hollister-Stier Contract Manufacturing and Services (Jubilant Hollister-Stier) and we outsource the formulation of Tyvaso to Catalent Pharma Solutions, Inc. (Catalent). We manufacture the Tyvaso Inhalation System at our facility in Germany and also through Minnetronix, Inc.

As long as we utilize third-party vendors for significant portions of our production process, we will remain exposed to the risks described below under the risk factor entitled "*We rely in part on third parties to perform activities that are critical to our business. Our ability to generate commercial sales or conduct clinical trials could suffer if our third-party suppliers and service providers fail to perform*." In addition, while we are in the process of internalizing additional processes to increase our control of production, this approach will also subject us to risks as we engage in increasingly complex production processes. For example, Remodulin and Tyvaso must be formulated in a sterile environment and we have limited experience with sterile manufacturing on a commercial scale. Some of the products we are developing will involve even more complicated production processes than our current products. For example, we are developing Ch14.18 MAb, a monoclonal antibody. As with all biologic products, monoclonal antibodies are inherently more difficult to produce than our current products and involve increased risk of viral and other contaminants.

In 2011, the FDA issued an advisory to manufacturers regarding the potential formation of glass fragments in injectable drugs filled in small-volume glass vials. We conducted a review of our manufacturing processes and those of our third-party suppliers and have no conclusive evidence at this time to suggest that the glass vials we use for Remodulin form glass fragments. We continue to assess our products, but cannot guarantee that our production process will not result in hazards such as these.

Additional risks presented by our production strategy include:

- We and our third-party producers are subject to the FDA's current Good Manufacturing Practices in the United States and similar regulatory standards internationally. While we have significant control over regulatory compliance with respect to our internal production processes, we do not exercise the same level of control over regulatory compliance by our third-party producers;

- As we expand our production operations to include new elements of the production process or new products, we may experience difficulty designing and implementing processes and procedures to ensure compliance with applicable regulations;

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Even if we and our third-party producers are in compliance with domestic and international drug production regulations, the sterility and quality of the products being produced could be substandard and, therefore, such products would be unavailable for sale or use;

If we had to replace our own production operations or a third-party producer, the FDA and its international counterparts would require new testing and compliance inspections. Furthermore, a new producer would have to be familiarized with the processes necessary to produce and commercially validate our products, as producing our treprostinil-based products is complex. Any new third-party producer and any new production process at our own facilities would be subject to approval by the FDA and its international counterparts before being used to produce commercial supply of our products;

We may be unable to contract with needed producers on satisfactory terms or at all; and

The supply of materials and components necessary to produce and package our products may become scarce or interrupted. Disruptions to the supply of these materials could delay the production and subsequent sale of such products. Any products produced with substituted materials or components would be subject to approval from the FDA and international regulatory agencies before they could be sold. The timing of any such regulatory approval is difficult to predict.

Any of these factors could disrupt sales of our commercial products, delay clinical trials or commercialization of new products, result in product liability claims and product recalls, and entail higher costs.

We rely in part on third parties to perform activities that are critical to our business. Our ability to generate commercial sales or conduct clinical trials could suffer if our third-party suppliers and service providers fail to perform.

We involve third parties extensively to assist us in: (1) conducting clinical trials, (2) obtaining regulatory approvals, (3) conducting pharmacovigilance-related activities, including drug safety and reporting of adverse events, and (4) marketing and distributing our products. The involvement of third parties is necessary because we do not possess the internal capacity, and in certain cases the expertise, to perform all of these functions. Accordingly, the success of these third parties in performing their contractual obligations is critical to our operations.

We synthesize treprostinil using raw materials and advanced intermediate compounds supplied by vendors. The inability of our vendors to supply these raw materials and advanced intermediate compounds in the quantities we require could delay the production of treprostinil for commercial use and for use in our clinical trials.

We rely on Baxter and Jubilant Hollister-Stier to formulate Remodulin for us. As part of an existing contract with Baxter, we agreed that Baxter will formulate Remodulin in greater quantities using larger production equipment than under its current process. This new formulation process and related equipment will require FDA and international approvals. During the fourth quarter of 2012, we notified Baxter that we will not renew our current contract when it expires at the end of 2013. We believe that we will be able to negotiate a new contract with Baxter prior to the expiration of the current contract. There can be no assurance, however, that these negotiations will be successful. Although we have received FDA and international approvals to produce Remodulin using our Silver Spring, Maryland facility, we remain reliant on third parties such as Baxter and Jubilant Hollister-Stier for additional capacity and production for international sales.

We received FDA approval to formulate Tyvaso in our Silver Spring, Maryland facility; however, we remain reliant on Catalent to supplement our production capacity and serve as a backup producer.

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We also rely substantially on NEBU-TEC and Minnetronix, Inc. to manufacture the nebulizer used in the Tyvaso Inhalation System.

We substantially rely on these third parties to adhere to and maintain production processes in accordance with all applicable regulatory requirements. If any of these critical third-party production and supply arrangements are interrupted for compliance issues or other reasons, we may not have sufficient inventory to meet future demand.

We rely on Accredo Health Group, Inc. (Accredo), CuraScript, Inc. (CuraScript) and CVS Caremark (Caremark) to distribute and sell Remodulin and Tyvaso in the United States. These distributors are also partially responsible for negotiating reimbursements from third-party payers for the cost of our therapies. From time-to-time, we increase the price of products sold to our U.S.-based and international distributors. Our price increases may not be fully reimbursed by third-party payers. If our distributors do not achieve acceptable profit margins on our products, they may reduce or discontinue the sale of our products. Furthermore, if our international distributors devote fewer resources to selling our products or are unsuccessful in their sales efforts, our revenues may decline materially.

In April 2012, Express Scripts, Inc. (the parent company of CuraScript) acquired Medco Health Solutions, Inc. (the parent company of Accredo). As a result of the merger, our products may be less significant to the overall operations of the combined company and the merged company may devote fewer resources toward the sale and support of our products, which could adversely impact our revenues. In addition, the combined company's pharmacy benefit management business may have increased leverage in negotiating the terms of rebates and discounts on behalf of third-party payers, which could impact reimbursement levels for our products.

We rely on Eli Lilly and Company (Lilly) to manufacture and supply Adcirca for us, and we use Lilly's pharmaceutical wholesaler network to distribute Adcirca in the United States and Puerto Rico. If Lilly is unable to manufacture or supply Adcirca or its distribution network is disrupted, it could delay, disrupt or prevent us from selling Adcirca, which could slow the growth of our business. In addition, Lilly has the right to determine the wholesale price of Adcirca, which generally moves in parity with the wholesale price Lilly sets for Cialis® (both of these products contain the same active ingredient). Since FDA approval of Adcirca, Lilly has generally announced price increases on both Cialis and Adcirca twice per year. Changes in Lilly's wholesale prices could adversely impact demand or reimbursement for Adcirca, particularly in light of the commercial availability of generic sildenafil citrate, the active ingredient in Revatio.

Although most of our current suppliers and service providers could eventually be replaced, a change in suppliers and/or service providers could interrupt the manufacture and distribution of our commercial products and our other products and services, and impede the progress of our clinical trials, commercial launch plans and related revenues. Interruptions in our production process could be significant given the length of time and complexity involved in obtaining necessary regulatory approvals for alternative arrangements, through either third parties or internal manufacturing processes.

We rely heavily on third-parties to conduct our clinical trials. In addition, the success of certain products we are developing will depend on clinical trials sponsored by third parties. Examples of such clinical trials include a phase III study of Ch14.18 conducted by the National Cancer Institute, and an ongoing study conducted by Medtronic using its implantable pump to deliver intravenous Remodulin. Failure by any of these parties to conduct or assist us in conducting clinical trials in accordance with study protocols, quality controls and GCP could limit our ability to rely on results of those trials in seeking regulatory approvals.

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Our operations must comply with extensive laws and regulations in the United States and other countries, including FDA regulations. Failure to obtain approvals on a timely basis or to achieve continued compliance could delay, disrupt or prevent the commercialization of our products.

The products we develop must be approved for marketing and sale by regulatory agencies and, once approved, are subject to extensive regulation. Our research and development efforts must comply with extensive regulations, including those promulgated by the FDA and the United States Department of Agriculture. The process of obtaining and maintaining regulatory approvals for new drugs is lengthy, expensive and uncertain. The manufacture, distribution, advertising and marketing of these products are also subject to extensive regulation, including strict pharmacovigilance and adverse event reporting requirements. Any future product approvals we receive could be accompanied by significant restrictions on the use or marketing of a given product. Furthermore, our product candidates may fail to receive marketing approval on a timely basis, or at all. If granted, product approvals can be withdrawn for failure to comply with regulatory requirements, such as post-marketing requirements and post-marketing commitments, or upon the occurrence of adverse events subsequent to commercial introduction.

Discovery of previously unknown problems with our marketed products or problems with our manufacturing, regulatory, compliance, research and development, pharmacovigilance and adverse event reporting, marketing or sales activities could result in regulatory restrictions on our products up to and including withdrawal of our products from the market. If we fail to comply with applicable regulatory requirements, we could be subject to penalties that may consist of fines, suspension of regulatory approvals, product recalls, seizure of our products and/or criminal prosecution. In addition, our reputation could be harmed as a result of any such regulatory restrictions or actions, and patients and physicians may avoid the use of our products even after we have resolved the issues that led to such regulatory action.

We are subject to ongoing regulatory review of our currently marketed products.

After our products receive regulatory approval, they remain subject to ongoing regulation, which can impact, among other things, product labeling, manufacturing practices, pharmacovigilance and adverse event reporting, storage, distribution, advertising and promotion, and record keeping. If we do not comply with applicable regulations, the range of possible sanctions may include: (1) adverse publicity, (2) product recalls or seizures, (3) fines, (4) total or partial suspensions of production and/or distribution, (5) suspension of marketing applications, and (6) enforcement actions, including injunctions and civil or criminal prosecution. Further, the FDA often requires post-marketing testing and surveillance to monitor the effects of approved products. The FDA and comparable international regulatory agencies may condition approval of our product candidates on the completion of such post-marketing clinical studies. These post-marketing studies may suggest that a product causes undesirable side effects or may present a risk to the patient. If data we collect from post-marketing studies suggest that one of our approved products may present an unacceptable safety risk, regulatory authorities could withdraw the product's approval, suspend production or place other marketing restrictions on that product. If regulatory sanctions are applied or if regulatory approval is delayed or withdrawn, our operating results and the value of our company may be adversely affected.

Regulatory approval for our currently marketed products is limited by the FDA to those specific indications and conditions for which clinical safety and efficacy have been demonstrated.

Any regulatory approval of our products is limited to specific diseases and indications for which our products have been deemed safe and effective by the FDA. In addition to the FDA approval required for new formulations, any new indication for an approved product also requires FDA approval. If we are not able to obtain FDA approval for any desired future indications for our products, our ability to effectively market and sell our products may be reduced.

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While physicians may choose to prescribe drugs for uses that are not described in the product's labeling and for uses that differ from those approved by regulatory authorities (called "off-label" uses), our ability to promote the products is limited to those indications that are specifically approved by the FDA. Although U.S. regulatory authorities generally do not regulate the behavior of physicians, they do restrict communications by companies on the subject of off-label use. If our promotional activities fail to comply with these regulations or guidelines, we may be subject to warnings from, or enforcement action by, these authorities. In addition, failure to follow FDA rules and guidelines relating to promotion and advertising can result in the FDA's refusal to approve a product, suspension or withdrawal of an approved product from the market, product recalls, fines, disgorgement of money, operating restrictions, injunctions or criminal prosecution.

We must comply with various laws in jurisdictions around the world that restrict certain marketing practices in the pharmaceutical and medical device industries. Failure to comply with such laws could result in penalties and have a material adverse effect on our business, financial condition and results of operations.

Various laws in jurisdictions around the world, including anti-kickback and false claims statutes, the Foreign Corrupt Practices Act and the UK Bribery Act, restrict particular marketing practices in the pharmaceutical and medical device industries. Our business activities may be subject to challenge under these laws, and any penalties imposed upon us could have a material adverse effect on our business, financial condition and results of operations. Furthermore, we have significantly expanded our sales and marketing staff. Any expansion of sales and marketing efforts can increase the risks of noncompliance with these laws.

In the United States, the federal health care program anti-kickback statute prohibits, among other things, knowingly and willfully offering, paying, soliciting, or receiving remuneration to induce (or in return for) the purchase, lease, order or arranging the purchase, lease or order of any health care product or service reimbursable under Medicare, Medicaid or any other federally financed health care program. This statute has been interpreted to apply to arrangements between pharmaceutical manufacturers and prescribers, purchasers, and formulary managers. Although a number of statutory exemptions and regulatory safe harbors exist to protect certain common activities from prosecution, the exemptions and safe harbors are narrow, and practices that involve remuneration intended to induce prescriptions, purchases, or recommendations may be subject to scrutiny if they do not qualify for an exemption or safe harbor. Our practices may not always meet all of the criteria for safe harbor protection.

Federal false claims laws prohibit any person from knowingly presenting (or causing the presenting of) a false claim for payment by the federal government, or knowingly making, or causing a false statement to be made in order to receive payment of a false claim. Several pharmaceutical and health care companies have been prosecuted under these laws for allegedly providing free product to customers with the expectation that the customers would bill federal programs for the product. Other companies have been prosecuted for causing false claims to be submitted because of the company's marketing of the product for unapproved, and thus non-reimbursable, uses. 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 payer. Sanctions under these federal and state laws may include civil monetary penalties, exclusion of a manufacturer's product from reimbursement under government programs, criminal fines, and imprisonment.

The Patient Protection and Affordable Care Act (PPACA) imposes new reporting requirements for pharmaceutical and device manufacturers with regard to payments or other transfers of value made to physicians and teaching hospitals, effective March 31, 2013. In addition, pharmaceutical and device manufacturers will be required to report and disclose investment interests held by physicians and their

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immediate family members during the preceding calendar year. Such information is to be made publicly available by the Secretary of Health and Human Services in a searchable format beginning September 30, 2013.

Failure to submit required information may result in civil monetary penalties of up to $150,000 per year (and up to $1.0 million per year for "knowing failures") for all payments, transfers of value or ownership or investment interests not reported in an annual submission. Further, the PPACA amends the intent requirement of the federal anti-kickback and criminal health care fraud statutes. A person or entity no longer needs to have actual knowledge of this statute or specific intent to be in violation of it. In addition, the government may assert that a claim including items or services resulting from a violation of the federal anti-kickback statute constitutes a false or fraudulent claim for purposes of the false claims laws.

If not preempted by this federal law, several states currently require pharmaceutical companies to report expenses relating to the marketing and promotion of pharmaceutical products and to report gifts and payments to individual physicians in those states. Depending on the state, legislation may prohibit various other marketing related activities, or require the posting of information relating to clinical studies and their outcomes. In addition, certain states, such as California, Nevada, and Massachusetts, require pharmaceutical companies to implement compliance programs or marketing codes and several other states are considering similar proposals. Compliance with these laws is difficult and time consuming, and companies that do not comply with these state laws will face civil penalties.

Government health care reform could increase our costs, which would adversely affect our revenue and results of operations.

Our industry is highly regulated and changes in law may adversely impact our business, operations or financial results. The PPACA is a sweeping measure intended to expand health care coverage within the United States, primarily through the imposition of health insurance mandates on employers and individuals and expansion of the Medicaid program. The reforms imposed by the new law will significantly impact the pharmaceutical industry; however, the full effects of the PPACA will be unknown until these provisions are implemented and the Centers for Medicare and Medicaid Services and other federal and state agencies issue applicable regulations or guidance. Moreover, in the coming years, additional changes could be made to governmental health care programs that could significantly impact the success of our products or product candidates.

Reports of actual or perceived side effects and adverse events associated with our products, such as sepsis, could cause physicians and patients to avoid or discontinue use of our products in favor of alternative treatments.

Reports of side effects and adverse events associated with our products could have a significant adverse impact on the sale of our products. An example of a known risk associated with intravenous Remodulin is sepsis, which is a serious and potentially life-threatening infection of the bloodstream caused by a wide variety of bacteria. Intravenous prostacyclins, such as intravenous Remodulin and Flolan, are infused continuously through a catheter placed in a large vein in the patient's chest, and sepsis is a known risk associated with this type of delivery. As a result, sepsis is included as a risk in both the Remodulin and Flolan package inserts. Although a discussion of the risk of sepsis is currently included on the Remodulin label, and the occurrence of sepsis is familiar to physicians who prescribe intravenously administered therapies, concerns about bloodstream infections may adversely affect a physician's decision to prescribe Remodulin.

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Our corporate compliance program cannot guarantee that we comply with all potentially applicable federal, state and international regulations.

The development, manufacture, distribution, pricing, sales, marketing, and reimbursement of our products, together with our general operations, are subject to extensive federal, state, local and international regulations, which are constantly evolving. These regulations are subject to frequent revisions that often introduce more stringent requirements. If we fail to comply with any of these regulations, we could be subject to a range of penalties including, but not limited to: (1) the termination of clinical trials, (2) the failure to receive approval of a product candidate, (3) restrictions on our products or manufacturing processes, (4) withdrawal of our products from the market, (5) significant fines, (6) exclusion from government health care programs and (7) other sanctions or litigation.

Negative attention from special interest groups may impair our business.

As is common with pharmaceutical and biotechnology companies, our early-stage research and development involves animal testing, which we conduct both directly and through contracts with third parties. Notwithstanding the vital role of animal research in the drug discovery and development process, certain special interest groups categorically object to the use of animals for research purposes. Historically, our research and development activities have not been the subject of significant animal rights media attention. However, research activities with animals have been the subject of adverse attention, generally including demonstrations near facilities operated by other companies in our industry. Any negative attention, threats or acts of vandalism directed against our animal research activities in the future could impair our ability to operate our business effectively.

If any of the license or other agreements under which intellectual property rights are licensed to, or were acquired by us are breached or terminated, our right to continue to develop, produce and sell the products covered by such agreement could be impaired or lost.

Our business depends upon our continuing ability to exploit our intellectual property rights in the drugs and other products that have been discovered and initially developed by others and those for which we are developing further and commercializing. These intellectual property rights have either been contractually licensed to us or have been acquired by us. Under each of our product license agreements, we are granted a license to exploit certain intellectual property owned by others that covers a drug or other product. Under each of our purchase agreements, we have purchased certain intellectual property that covers a drug or other product. We may be required to obtain a license of other intellectual property owned by third parties to continue to develop and commercialize our products.

This dependence on intellectual property developed by others involves the following risks:

We may be unable to obtain rights to intellectual property that we determine we need for our business at a reasonable cost or at all;

If any of our product licenses or purchase agreements are terminated, we may lose our rights to develop, make and sell the products to which such licenses or agreements relate;

Our license and purchase agreements generally provide the licensor or seller with the right to terminate the agreement in the event we breach such agreement *e.g.*, if we fail to pay royalties and other fees timely and do not cure the failure within a stated time period; and

If a licensor of intellectual property that is exclusively licensed to us breaches its obligation or otherwise fails to maintain the intellectual property licensed to us, we may lose any ability to prevent others from developing or marketing similar products that are covered by such intellectual property. In addition, we may be forced to incur substantial costs to maintain the intellectual property ourselves or take legal action seeking to force the licensor to do so.

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Certain agreements under which we acquired or licensed intellectual property rights may restrict our ability to develop related products in certain countries or for particular diseases and may impose other restrictions that affect our ability to develop and market related products in the most effective manner.

When we acquire or license intellectual property rights to drugs and other products that have been discovered and initially developed by others, these rights are frequently limited. For instance, our rights to market Adcirca are geographically limited to the United States and Puerto Rico. Furthermore, we cannot undertake any additional investigational work with respect to Adcirca in other indications of pulmonary hypertension without Lilly's prior approval. Lilly also has authority over all regulatory activities and has the right to determine the net wholesale price for Adcirca. Provisions in our license and purchase agreements may impose other restrictions that affect our ability to develop and market products to which the intellectual property relates. For example, GlaxoSmithKline PLC retained an exclusive option and right of first refusal to negotiate an agreement with us if we decide to license any commercialization rights with respect to Remodulin and Tyvaso anywhere in the world.

Our intellectual property rights may not effectively deter competitors from developing competing products that, if successful, could materially adversely affect our revenues and profits.

The period under which our commercial and developmental therapies are protected by our patent rights is limited. Our U.S. patent for the method of treating PAH with Remodulin will expire in October 2014. Three of our U.S. patents covering our current methods of synthesizing and producing treprostinil, the active ingredient in both Remodulin and Tyvaso, expire in October 2017. Other patents and patent applications in the U.S. and other countries relating to our treprostinil products remain in force or are pending, respectively. We also have been granted one patent in the European Union and one patent in Japan, each of which covers our treprostinil synthesis and production methods that will expire in October 2018. Our U.S. patent covering an improved diluent for Remodulin will expire in March 2029. The patent for Adcirca for the treatment of pulmonary hypertension will expire in 2017 and our patents for Tyvaso will expire in the United States and in various countries throughout the European Union in 2018 and 2020, respectively.

We continue to conduct research into new methods to synthesize treprostinil and have pending U.S. and international patent applications and granted patents relating to such methods. However, we cannot be sure that these additional patents will successfully deter competitors, or that additional patent applications will result in grants of patents. Upon the expiration of any of our patents, competitors may develop generic versions of our products that were covered by the expired patents and may market those generic versions to compete with our products. Competitors may also seek to design around our patents prior to their expiration in an effort to develop competing products that do not infringe our patents.

The scope of any patent we hold may not deter competitors from developing a product that competes with the product we sell that is covered by the patent. Patent laws of foreign jurisdictions may not protect our patent rights to the same extent as the patent laws of the United States. Furthermore, our suppliers who have granted us exclusive rights may have inadequate intellectual property protections. Competitors also may attempt to invalidate our existing patents before they expire.

In addition to patent protection, we also rely on trade secrets to protect our proprietary know-how and other technological advances that we do not disclose to the public. We enter into confidentiality agreements with our employees and others to whom we disclose trade secrets and other confidential information. These agreements do not necessarily prevent our trade secrets from being used or disclosed without our authorization and confidentiality agreements may be difficult to enforce or may not provide an adequate remedy in the event of unauthorized disclosure.

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The validity, enforceability and scope of certain of our patents covering Remodulin are currently being challenged as a result of a recent abbreviated new drug application (ANDA) filing from a generic drug company. The outcome of current or any future challenges to the validity, enforceability or scope of our patent portfolio could significantly reduce revenues from Remodulin.

In February 2012, we received a Paragraph IV Certification Notice Letter (Original Notice Letter) from Sandoz advising that Sandoz has submitted an ANDA to the FDA requesting approval to market a generic version of the 10 mg/mL strength of Remodulin. In December 2012, we received notice (Second Notice Letter) that Sandoz had amended its previously filed ANDA to request approval to market generic versions of the 1 mg/mL, 2.5 mg/mL, and 5 mg/mL strengths of Remodulin. In the Notice Letters, Sandoz states that it intends to market a generic version of Remodulin before the expiration of U.S. Patent No. 5,153,222, which expires in October 2014; U.S. Patent No. 6,765,117, which expires in October 2017; and U.S. Patent No. 7,999,007, which expires in March 2029.

We responded to the Original Notice Letter by filing a lawsuit in March 2012 against Sandoz in the U.S. District Court for the District of New Jersey alleging patent infringement. We responded to the Second Notice Letter by filing an additional lawsuit in January 2013 for patent infringement in the U.S. District Court for the District of New Jersey. The current status of our litigation with Sandoz is further described in *Item 3. Legal Proceedings*, elsewhere in this Annual Report on Form 10-K.

There can be no assurance that we will prevail in our defense of our patent rights. Our existing patents could be invalidated, found unenforceable or found not to cover a generic form of Remodulin. If Sandoz or another ANDA filer were to receive approval to sell a generic version of Remodulin and/or prevail in any patent litigation, Remodulin would become subject to increased competition and our revenue would be adversely affected. In addition, regardless of the outcome, any patent litigation could be costly, distracting to our management and time-consuming.

Third parties may allege that our products or services infringe their patents and other intellectual property rights, which could result in the payment of royalties. Payment of royalties would negatively affect our profits; furthermore, if we chose to contest these allegations, we could be subject to costly and time-consuming litigation or could lose the ability to continue to sell the related products.

Third parties may seek to invalidate or otherwise challenge our patents. We may initiate litigation to enforce or defend our patents or intellectual property rights; however, litigation can be time consuming, distracting to our operations, costly and may not conclude favorably. In addition, the outcome of patent infringement litigation often is difficult to predict. If we are unsuccessful with respect to any future legal action in the defense of our patents and our patents are invalidated or determined to be unenforceable, our business could be negatively impacted. Even if our patents are not determined to be invalid or unenforceable, it is possible that a competitor could circumvent our patents by effectively designing around the claims of our patents. Accordingly, our patents may not provide us with any competitive advantage.

To the extent third-party patents for which we currently do not hold licenses cover our products or services, licenses to these patents would be necessary to manufacture, use, sell or provide these products and services without infringing these patents. In the case of products or services that utilize intellectual property of strategic collaborators or other suppliers, such suppliers may have an obligation to secure the needed license to these patents at their cost. Otherwise, we would be responsible for the cost of these licenses. Payments of royalties and other amounts under these licenses would reduce our profits from the sale of related products and services. Moreover, we may be unable to obtain these licenses on acceptable terms or at all. If we fail to obtain a required license or are unable to alter the design of the product alleged to be infringed to avoid infringing a third-party patent, we would be unable to continue to manufacture or sell the related products.

If a third party commences legal action against us for infringement, we could be compelled to incur significant costs to defend the action and our management's attention could be diverted, whether

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or not the action were to have any merit. We cannot be certain that we could prevail in the action, and an adverse judgment or settlement resulting from the action could require us to pay substantial amounts in damages for infringement or substantial amounts to obtain a license to continue to use the intellectual property that is the subject of the infringement claim.

We may not maintain adequate insurance coverage to protect us against significant product liability claims.

The testing, manufacturing, marketing, and sale of drugs and diagnostics involve product liability risks. We may not be able to maintain our current product liability insurance at an acceptable cost, if at all. In addition, our insurance coverage may not be adequate for all potential claims. If claims or losses significantly exceed our liability insurance coverage, we may experience financial hardship or be forced out of business.

If we fail to attract and retain key management and qualified scientific and technical personnel, we may not be able to achieve our business objectives.

Members of our management team, including our founder, Chairman and Chief Executive Officer, Dr. Martine Rothblatt, and our President and Chief Operating Officer, Dr. Roger Jeffs, play a critical role in defining our business strategy and maintaining our corporate culture. The loss of the services and leadership of Dr. Rothblatt, Dr. Jeffs or any other members of our senior management team could have an adverse effect on our business. We do not maintain key person life insurance on our senior management team members. In addition, effective succession planning is important to our long-term success. Failure to identify and retain adequate replacements for members of our senior management team and ensure effective transfer of knowledge could hinder the achievement of our business objectives. Our future success also depends on our ability to attract and retain qualified scientific and technical personnel. Competition for skilled scientific and technical personnel in the biotechnology and pharmaceutical industries is intense. Our compensation arrangements may not be sufficient to attract new qualified scientific and technical employees or retain existing scientific and technical employees. If we fail to attract and retain such employees, we may not be successful in developing and commercializing new therapies for PAH and other diseases and conditions.

Improper handling of hazardous materials used in our activities could expose us to significant remediation liabilities.

Our research and development and manufacturing activities involve the controlled use of chemicals and hazardous substances and we are expanding these activities in both scale and location. In addition, patients may dispose of our products using means we do not control. Such activities subject us to numerous federal, state, and local environmental and safety laws and regulations that govern the management, storage and disposal of hazardous materials. Compliance with current and future environmental laws and regulations can require significant costs; furthermore, we can be subject to substantial fines and penalties in the event of noncompliance. The risk of accidental contamination or injury from these materials cannot be completely eliminated. Furthermore, once chemical and hazardous materials leave our facilities, we cannot control what our hazardous waste removal contractors choose to do with these materials. In the event of an accident, we could be liable for substantial civil damages or costs associated with the cleanup of the release of hazardous materials. Any related liability could exceed our resources and could have a material adverse effect on our business.

We may encounter substantial difficulties managing our growth relative to product demand.

We have spent considerable resources building and expanding our offices, laboratories and production facilities, and we are currently seeking regulatory approvals for some of our facilities. However, our facilities may be insufficient to meet future demand for our products. Alternatively, we

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may have excess capacity at our facilities if future demand falls short of our expectations, or if we do not receive regulatory approvals for the products we intend to produce at our facilities. Constructing our facilities is expensive and our ability to satisfactorily recover our investment will depend on sales of the products manufactured at these facilities in sufficient volume. If we do experience substantial sales growth, we may have difficulty managing inventory levels as marketing new therapies is complicated and gauging future demand can be difficult and uncertain.

If we need additional financing and cannot obtain it, our product development and sales efforts may be limited.

We may be required to seek additional sources of financing to meet unplanned or planned expenditures. Unplanned expenditures could be significant and may result from necessary modifications to product development plans or product offerings in response to difficulties encountered with clinical trials. We may also face unexpected costs in preparing products for commercial sale, or in maintaining sales levels of our currently marketed therapeutic products. If we are unable to obtain additional funding on commercially reasonable terms or at all, we may be compelled to delay clinical studies, curtail operations or obtain funds through collaborative arrangements that may require us to relinquish rights to certain products or potential markets.

We may require additional financing to meet significant future obligations. For example, upon maturity or conversion of our 1.0 percent Convertible Senior Notes due September 15, 2016 (2016 Convertible Notes), subject to certain provisions, we must repay our investors in cash up to the principal balance of $250.0 million. Further, in certain circumstances constituting a fundamental change under the 2016 Convertible Notes, we may be required to repurchase the 2016 Convertible Notes for cash. In addition, awards granted under our Share Tracking Awards Plans (which we collectively refer to as the STAP) entitle participants to receive in cash an amount equal to the appreciation in the price of our common stock, which is calculated as the positive difference between the closing price of our common stock on the date of exercise and the date of grant. Consequently, our STAP will likely require significant future cash payments to participants to the extent the price of our common stock appreciates and the number of vested STAP awards increases over time. If we do not have sufficient funds to meet such contractual obligations or the ability to secure alternative sources of financing, we could be in default, face litigation and/or lose key employees, which could have a material adverse effect on our business or financial condition.

Security breaches and other disruptions could compromise our information and expose us to liability, which would cause our business and reputation to suffer.

In the ordinary course of our business, we collect and store sensitive data, including intellectual property, our proprietary business information and that of our suppliers, customers and business partners, and personally identifiable information. The secure maintenance of this information is critical to our operations and business strategy. Despite our security measures, our information technology and infrastructure may be vulnerable to attacks by hackers or breached due to employee error, malfeasance or other disruptions. Any such breach could compromise our networks and the information stored there could be accessed, publicly disclosed, lost or stolen. Any such access, disclosure or other loss of information could result in legal claims or proceedings, liability under laws that protect the privacy of personal information, disrupt our operations, and damage our reputation which could adversely affect our business.

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Risks Related to Our Common Stock

The price of our common stock can be highly volatile and may decline.

The price of common stock can be highly volatile within the pharmaceutical and biotechnology sector. Consequently, there can be significant price and volume fluctuations in the market that may not relate to operating performance. The following table sets forth the high and low closing prices of our common stock for the periods indicated:

		High	Low
January 1, 2012	December 31, 2012	$ 58.91	$ 40.42
January 1, 2011	December 31, 2011	$ 70.70	$ 37.21
January 1, 2010	December 31, 2010	$ 64.24	$ 46.22

The price of our common stock could decline sharply due to the following factors, among others:

Failure to meet estimates or expectations of securities analysts or our own revenue guidance;

Quarterly and annual financial results;

Timing of enrollment and results of our clinical trials;

Physician, patient, investor or public concerns regarding the efficacy and/or safety of products marketed or being developed by us or by others;

Changes in, or new legislation and regulations affecting reimbursement of, our therapeutic products by Medicare, Medicaid or other government payers, and changes in reimbursement policies of private health insurance companies;

Announcements by us or others of technological innovations or new products or announcements regarding our existing products, including in particular the development of new, competing PAH therapies;

Announcements by us or others regarding generic challenges to the intellectual property relating to our products, including the recent abbreviated new drug applications filed by Sandoz relating to certain of our Remodulin patents and to our pending lawsuit defending our patents rights;

Substantial sales of our common stock by us or our existing shareholders;

Future issuances of common stock by us or any other activity which could be viewed as being dilutive to our shareholders;

Rumors among, or incorrect statements by, investors and/or analysts concerning our company, our products, or operations;

Failure to obtain or maintain regulatory approvals from the FDA or international regulatory agencies;

Discovery of previously unknown problems with our marketed products, or problems with our production, regulatory, compliance, promotional, marketing or sales activities that result in regulatory restrictions on our products, including withdrawal of our products from the market;

Accumulation of significant short positions in our common stock by hedge funds or other investors or the significant accumulation of our common stock by hedge funds or other institutional investors with investment strategies that may lead to short-term holdings; and

General market conditions.

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We may fail to meet our own projected revenues, as well as third-party projections for our revenues or profits.

Many securities analysts publish quarterly and annual projections of our revenues and profits. In addition, we provide forward-looking guidance for revenues associated with our commercial products. Such estimates are inherently subject to uncertainty. As a result, actual revenues and profits may differ from these projections, and even small variations in reported revenues and profits compared to securities analysts' expectations or our own projected revenues could have a significant impact on the price of our common stock.

Sales or issuances of our common stock may depress our stock price.

The price of our common stock could decline if: (1) we issue common stock to raise capital or to acquire a license or business; (2) our shareholders transfer ownership of our common stock, or sell substantial amounts in the public market (for example, in 2011, Lilly sold a significant portion of our common stock); (3) our investors become concerned that substantial sales of our common stock may occur; or (4) we issue shares upon the settlement of warrants relating to the hedging transaction for our 2016 Convertible Notes. A decrease in the price of our common stock could make it difficult for us to raise capital or fund acquisitions through the issuance of our stock.

Any sales of common stock issued to holders of our 2016 Convertible Notes could adversely affect the prevailing market price of our common stock or result in short selling by market participants in expectation of a decline in the price of our common stock.

Our share repurchases may affect the value of our common stock.

Recently, our Board of Directors authorized several programs to repurchase our common stock. The effect of any of these repurchase programs on the market price of our common stock will depend in part on market conditions.

We are subject to counterparty risk with respect to the convertible note hedge transaction.

The counterparty to the convertible note hedge transaction we entered into in connection with the issuance of our 2016 Convertible Notes (call options) will subject us to counterparty risk in that the counterparty may default on fulfilling potential obligations under the call options. Our exposure to the credit risk of the counterparty will not be secured by any collateral. Recent global economic conditions have resulted in the actual or perceived failure or financial difficulties of many financial institutions. If such counterparty becomes subject to insolvency proceedings, we will become an unsecured creditor in those proceedings with a claim based on our exposure at that time under the call options. Our exposure will depend on many factors but, generally, the increase in our exposure will be correlated to the increase in the market price and in the volatility of our common stock. In addition, upon a default by the counterparty, we may suffer adverse tax consequences and dilution with respect to our common stock due to our obligation to deliver shares upon conversion of the notes. We cannot provide any assurance as to the financial stability or viability of the counterparty to our convertible note hedge transaction.

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Provisions of Delaware law and our amended and restated certificate of incorporation, second amended and restated by-laws, shareholder rights plan, 2016 Convertible Notes, convertible note hedge transaction and employment and license agreements, among other things, could prevent or delay a change of control or change in management that may be beneficial to our public shareholders.

Certain provisions of Delaware law and our amended and restated certificate of incorporation, second amended and restated by-laws and shareholder rights plan may prevent, delay or discourage:

A merger, tender offer or proxy contest;

The assumption of control by a holder of a large block of our securities; and/or

The replacement or removal of current management by our shareholders.

For example, our amended and restated certificate of incorporation divides our Board of Directors into three classes. Members of each class are elected for staggered three-year terms. This provision may make it more difficult for shareholders to replace the majority of directors. It may also deter the accumulation of large blocks of our common stock by limiting the voting power of such blocks.

Non-competition and all other restrictive covenants in most of our employment agreements will terminate upon a change of control that is not approved by our Board.

We may be required to repurchase the 2016 Convertible Notes from their holders in the event of a fundamental change and increase the conversion rate in connection with a make whole adjustment event in certain circumstances, including a change of control of our company. This may delay or prevent a change in control of our company that would otherwise be beneficial to our shareholders.

Terminating or unwinding the convertible note hedge transaction could require us to make substantial payments to the counterparty or may increase the price of our common stock. The costs or any increase in stock price that may arise from terminating or unwinding the transaction could make an acquisition of our company significantly more expensive to the purchaser.

Similarly, a change of control, under certain circumstances, could also result in an acceleration of the vesting of outstanding STAP awards. This, together with any increase in our stock price resulting from the announcement of a change of control, could make an acquisition of our company significantly more expensive to the purchaser. We also have a broad-based change of control severance program, under which employees may be entitled to severance benefits in the event they are terminated without cause (or they terminate their employment for good reason) following a change of control. This program could also increase the cost of acquiring our company.

We enter into certain license agreements that generally prohibit our counterparties or their affiliates from taking necessary steps to acquire or merge with us, directly or indirectly throughout the term of these agreements, plus a specified period thereafter. We are also party to certain license agreements that restrict our ability to assign or transfer the rights licensed to us to third parties, including parties with whom we wish to merge, or those attempting to acquire us. These agreements often require that we obtain the prior consent of the counterparties to these agreements if we are contemplating a change of control. If these counterparties withhold their consent, related agreements could be terminated and we would lose related license rights. For example, both Lilly and Toray have the right to terminate our license agreements relating to Adcirca and beraprost, respectively, in the event of certain change of control transactions. These restrictive change of control provisions could impede or prevent mergers that could benefit our shareholders.

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Because we do not intend to pay cash dividends, our shareholders must rely on stock appreciation for any return on their investment in us.

We have never declared or paid cash dividends on our common stock. Furthermore, we do not intend to pay cash dividends in the future. As a result, the return on an investment in our common stock will depend entirely upon the future appreciation in the price of our common stock. There can be no assurances that our common stock will provide a return to investors.

ITEM 1B. UNRESOLVED STAFF COMMENTS

None.

ITEM 2. PROPERTIES

Maryland We own a 232,000 square foot combination laboratory and office building complex in Silver Spring, Maryland that serves as our corporate headquarters and is used for the synthesis of treprostinil-based compounds and monoclonal antibodies. We use this facility to produce Remodulin and Tyvaso for commercial use. We also own several other buildings in Silver Spring used principally for office space, and we lease and own warehouse space near Silver Spring.

North Carolina We own a 380,000 square foot combination manufacturing facility and office building in Research Triangle Park, North Carolina (RTP facility), which is occupied by our clinical research and development and commercialization personnel. We warehouse and distribute Remodulin and Tyvaso and manufacture oral treprostinil at this location. In June 2012, we acquired an 132 acre property containing approximately 703,000 square feet of building space adjacent to our RTP facility, which we intend to use for future expansion. We expect to begin preparing a portion of the property for development during the first half of 2013, which will house research, development and production facilities relating to our regenerative medicine and organ transplantation programs.

Europe We own an office building near London, England which serves as our European headquarters. We also own a building in Oxford, England. In Germany, we lease office and production space from NEBU-TEC for production of the Tyvaso Inhalation System.

District of Columbia We own two adjacent buildings in Washington, D.C., which serve as office space.

Florida We own an office building in Satellite Beach, Florida. In addition, we lease office space in Melbourne, Florida.

Certain of our Maryland and North Carolina properties serve as collateral under our $70.0 million Credit Agreement with Wells Fargo Bank, National Association and Bank of America, N.A. For further details, see *Item 7. Management's Discussion and Analysis of Financial Condition and Results of Operations Liquidity and Capital Resources Mortgage Financing*.

We believe that these facilities, along with various other owned and leased office facilities, are adequate for our current operations and that additional land and facilities for future expansion are reasonably available.

ITEM 3. LEGAL PROCEEDINGS

Sandoz Inc.

In February 2012, we received a Paragraph IV Certification Notice Letter (the Original Notice Letter) from Sandoz Inc. (Sandoz) advising that Sandoz had submitted an abbreviated new drug application (ANDA) to the FDA requesting approval to market a generic version of the 10 mg/mL strength of Remodulin. In December 2012, we received notice (the Second Notice Letter) that Sandoz

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had amended its previously filed ANDA to request additional approval to market generic versions of the 1 mg/mL, 2.5 mg/mL, and 5 mg/mL strengths of Remodulin. In the Original Notice Letter and the Second Notice Letter, Sandoz stated that it intends to market a generic version of Remodulin before the expiration of the following patents relating to Remodulin: U.S. Patent No. 5,153,222, which expires in October 2014; U.S. Patent No. 6,765,117, which expires in October 2017; and U.S. Patent No. 7,999,007, which expires in March 2029. Each of these patents is listed in the Orange Book.

We responded to the Original Notice Letter by filing a lawsuit in March 2012 against Sandoz in the U.S. District Court for the District of New Jersey alleging patent infringement (the First Lawsuit). We responded to the Second Notice Letter by filing an additional lawsuit in January 2013 for patent infringement in the U.S. District Court for the District of New Jersey (the Second Lawsuit). Sandoz has filed its answer to our complaint in the First Lawsuit, and has also filed counterclaims alleging that the patents at issue in the litigation are invalid or will not be infringed by the commercial manufacture, use or sale of the proposed product described in Sandoz's ANDA submission. On February 21, 2013 Sandoz filed its answer to our complaint in the Second Lawsuit, and filed counter claims against us.

Under the Hatch-Waxman Act, the FDA is automatically precluded from approving Sandoz's ANDA with respect to each concentration of Remodulin for up to 30 months from receipt of the Notice Letter corresponding to such concentration or until the issuance of a district court decision that is adverse to us, whichever occurs first. We intend to vigorously enforce our intellectual property rights relating to Remodulin.

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 (and associated preferred stock purchase rights) trades on the NASDAQ Global Select Market under the symbol "UTHR". The table below sets forth the high and low closing prices for our common stock for the periods indicated:

	2012		2011	
	High	Low	High	Low
January 1 March 31	$ 50.99	$ 45.54	$ 69.54	$ 64.28
April 1 June 30	$ 49.38	$ 40.42	$ 70.70	$ 53.49
July 1 September 30	$ 58.30	$ 49.87	$ 57.38	$ 37.47
October 1 December 31	$ 58.91	$ 44.99	$ 47.54	$ 37.21

Number of Holders

As of February 18, 2013, there were 38 holders of record of our common stock.

Dividend Policy

We have never paid and have no present intention to pay cash dividends on our common stock in the foreseeable future. We intend to retain any earnings for use in our business operations.

Issuer Purchases of Equity Securities

Period	Total Number of Shares (or Units) Purchased	Average Price Paid Per Share (or Unit)(1)	Total Number of Shares (or Units) Purchased as Part of Publicly Announced Plans or Programs	Maximum Number (or Approximate Dollar Value) of Shares (or Units) That May Yet Be Purchased Under the Plans or Programs(2)(3)
Beginning repurchase authority				$ 57,075,344
October 1, 2012 October 31, 2012	554,215	$ 48.03	554,215	$ 30,454,749
November 1, 2012 November 30, 2012	631,941	$ 48.19	631,941	$
December 1, 2012 December 31, 2012				$
Total	1,186,156	$ 48.12	1,186,156	$

(1) Average price paid per share calculated at settlement, including commission.

(2) As previously disclosed in our Form 10-Q for the quarter ende