Raptor Pharmaceutical Corp
Form 10-K
February 26, 2016

UNITED STATES

SECURITIES AND EXCHANGE COMMISSION

Washington, D.C. 20549

FORM 10-K

x ANNUAL REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934
For the fiscal year ended December 31, 2015

o TRANSITION REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934
For the transition period from to

Commission File Number: 000-25571

RAPTOR PHARMACEUTICAL CORP.

(Exact name of registrant as specified in its charter)

Delaware	86-0883978
(State or other jurisdiction of incorporation or organization)	(I.R.S. Employer Identification No.)

7 Hamilton Landing, Suite 100, Novato, CA 94949

(Address of Principal Executive Offices)

(415) 408-6200

(Registrant's telephone number)

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

Title of Each Class	Name of Each Exchange on Which Registered

Common Stock, $0.001 par value The NASDAQ Global Select Market
Securities registered under Section 12(g) of the Act: None

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

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 x

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 x 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 x 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. o

Indicate by check mark whether the registrant is a large accelerated filer, an accelerated filer, a non-accelerated filer, or a smaller reporting company.

Large accelerated filer x Accelerated filer o Non-accelerated filer o 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 x

The aggregate market value of the voting and non-voting common equity held by non-affiliates of the registrant as of June 30, 2015 (the last business day of the registrant's most recently completed second quarter) was $1,267 million.

The number of shares of the registrant's common stock outstanding, par value $0.001, on February 22, 2016 was 85,243,864.

The documents incorporated by reference are as follows: Portions of the registrant's definitive Proxy Statement to be filed with the Securities and Exchange Commission under Regulation 14A within 120 days after the end of registrant's fiscal year covered by this Annual Report are incorporated by reference into Part III.

RAPTOR PHARMACEUTICAL CORP.

2015 Form 10-K Annual Report

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FORWARD-LOOKING STATEMENTS

Forward-Looking Statements

In this Annual Report on Form 10-K, in our other filings with the Securities and Exchange Commission, or the SEC, and in press releases and other public statements by our officers throughout the year, we make or will make statements that plan for or anticipate the future. These "forward-looking statements," within the meaning of the Private Securities Litigation Reform Act of 1995, include statements about our future business plans and strategies, as well as other statements that are not historical in nature. These forward-looking statements are based on our current expectations.

In some cases, these statements can be identified by the use of terminology such as "believes," "expects," "anticipates," "plans," "may," "might," "will," "could," "should," "would," "projects," "anticipates," "predicts," "intends," "continues," "esti "opportunity" or the negative of these terms or other comparable terminology. All such statements, other than statements of historical facts, including, but not limited to:

- statements regarding our financial condition and future results of operations;
- projected revenues from sales of PROCYSBI, QUINSAIR or future product candidates;
- business strategies and operating efficiencies or synergies;
- our products' competitive positions;
- potential clinical efficacy of our product candidates;
- growth opportunities for existing intellectual properties and technologies;
- patient market size for our products and product candidates, and market adoption of our products by patients and physicians;
- timing of or costs of our clinical trials;
- plans and objectives of management,
- markets for our securities;
- the impact of changes in laws and accounting standards;
- our ability to repay our notes or raise capital in the public markets; and
- our estimates of the timing of our need to raise capital.

These and other prospective matters, involve substantial risks and uncertainties and constitute forward-looking statements for the purpose of the safe harbor provided by Section 27A of the Securities Act of 1933, as amended, or the Securities Act, and Section 21E of the Securities Exchange Act of 1934, as amended, or the Exchange Act. You should not place undue reliance on these statements, which only reflect information available as of the date that they were made. Our business' actual operations, performance, developments and results might differ materially from any forward-looking statement due to various known and unknown risks, uncertainties, assumptions and contingencies, including those described in the section titled "Risk Factors" in Part I, Item 1A of this Annual Report on Form 10-K as well as other documents we file with the SEC. In light of the significant uncertainties inherent in such forward-looking statements, you should not regard the inclusion of this information as a representation by us or any other person that the results or conditions described in those statements or our objectives and plans will be achieved.

All subsequent forward-looking statements attributable to us or any person acting on our behalf are expressly qualified in their entirety by the cautionary statements contained or referred to herein. Unless required by U.S. federal securities laws and the rules and regulations of the SEC, we do not undertake any obligation and disclaim any intention to update or release publicly any revisions to these forward-looking statements after the filing of this Annual Report on Form 10-K to reflect later events or circumstances or to reflect the occurrence of unanticipated events or for any other reason.

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PART I

1. BUSINESS

You should read the following discussion in conjunction with our consolidated financial statements as of December 31, 2015, and the notes to such consolidated financial statements included elsewhere in this Annual Report on Form 10-K.

Unless otherwise stated or the context requires otherwise, for the period from and after the effective time of the 2009 Merger (as described below under "Corporate Information"), all references in this Annual Report on Form 10-K to the "Company," "we," "our," "us," "Raptor" and similar references refer to the company formerly known as TorreyPines Therapeutics, Inc. and now known as Raptor Pharmaceutical Corp. and its direct and indirect wholly-owned subsidiaries Raptor Pharmaceuticals Inc., Raptor European Products, LLC, RPTP European Holdings C.V., Raptor Pharmaceuticals Europe B.V., Raptor Pharmaceuticals France SAS and Raptor Pharmaceuticals Germany GmbH.

Corporate History

In September 2009, our subsidiary merged with and into Raptor Pharmaceutical Corp., a Delaware corporation, or RPC, pursuant to which the stockholders of RPC received shares of our common stock in exchange for their shares of stock and RPC survived as our wholly-owned subsidiary. This merger is referred to herein as the 2009 Merger. Immediately prior to the 2009 Merger, we changed our corporate name from "TorreyPines Therapeutics, Inc." to "Raptor Pharmaceutical Corp." At the time of the 2009 Merger, RPC had two principal subsidiaries, Raptor Discoveries, a development-stage research and development company, and Raptor Therapeutics, which focused on developing clinical-stage drug product candidates through to commercialization and, in connection with the 2009 Merger, these two subsidiaries became our subsidiaries. In December 2012, the two principal subsidiaries were merged and currently operate under the name Raptor Pharmaceuticals Inc. Due to the amount of our stock issued to the stockholders of RPC in the 2009 Merger, RPC was treated as the "accounting acquirer" in the merger, and its board of directors and officers managed and operated the combined company. In December 2011, we merged RPC with and into us and it ceased to exist as a separate company. TorreyPines Therapeutics was incorporated in July 1997 under the name "Axonyx, Inc." and RPC was incorporated in May 2006 under the name "Highland Clan Creations Corp."

Overview

We are a biopharmaceutical company focused on developing and commercializing transformative treatments for people affected by rare and debilitating diseases.

Our first commercial product, PROCYSBI® (cysteamine bitartrate) delayed-release capsules ("PROCYSBI"), received marketing approval from the U.S. Food and Drug Administration ("FDA") on April 30, 2013 for the management of nephropathic cystinosis in adults and children six years and older. On August 14, 2015, we received FDA approval for the expanded use of PROCYSBI to treat children two to six years of age with nephropathic cystinosis. In Europe, PROCYSBI® gastro-resistant hard capsules of cysteamine (as mercaptamine bitartrate), received marketing authorization on September 6, 2013 from the European Commission ("EC"), for marketing in the European Union ("EU") as an orphan medicinal product for the management of proven nephropathic cystinosis. The EU marketing authorization allows us to commercialize PROCYSBI in the 28 Member States of the EU plus Norway, Liechtenstein and Iceland (which are not EU Member States but are part of the European Economic Area or EEA). PROCYSBI received seven years of market exclusivity, through 2020 for patients six years and older as an orphan drug in the United States and ten years of market exclusivity, through 2023, as an orphan drug in Europe. Recently, PROCYSBI received orphan drug designation for the treatment of patients ages two years to six years, through 2022. We commenced commercial sales of PROCYSBI in the United States in June 2013 and in Europe in April 2014. For at

least the near term, our ability to generate revenue is dependent upon sales of PROCYSBI in the United States for the management of nephropathic cystinosis in adults and children two years and older and in the EU for the management of proven nephropathic cystinosis.

As of December 31, 2015, insurers of U.S. commercial patients reimburse Raptor for PROCYSBI therapy at a Wholesale Acquisition Cost, or WAC, price for PROCYSBI of $17,812.50 per bottle of 250 75-mg capsules and $4,275.00 per bottle of 60 25-mg capsules. Prices for PROCYSBI therapy vary among patients because doses are individually based on a patient's weight. In September 2013, we executed an agreement to participate in the U.S. State Medicare/Medicaid rebate program, which is reflected in our net revenues in mandatory rebates on reimbursements for patients receiving state Medicare and Medicaid insurance coverage. As of December 31, 2015, our price to German, Swiss and Austrian pharmacies was €5,850.23 per bottle of 250 75-mg capsules and €468.02 per bottle of 60 25-mg capsules.

In October 2015, we acquired various assets and rights related to levofloxacin solution for inhalation, a pharmaceutical product also known as "MP-376" and commercially as "QUINSAIR," from Tripex Pharmaceuticals, LLC ("Tripex"). QUINSAIR received marketing authorization by the EC for treating chronic lung infection caused by the bacteria Pseudomonas aeruginosa in adults who

have cystic fibrosis in March 2015 and Health Canada in June 2015 for the management of cystic fibrosis in patients aged 18 years or older with chronic pulmonary Pseudomonas aeruginosa infections. QUINSAIR is the first inhaled fluoroquinolone approved for the management of chronic pulmonary infections due to Pseudomonas aeruginosa in patients with cystic fibrosis 18 years old and older. We plan to launch QUINSAIR in Europe in the first half of 2016 and Canada later in 2016. We plan to discuss the path to potential approval in the same indication in the United States with the FDA in 2016. We will also pursue a clinical program for the development of MP-376 in non-cystic fibrosis related bronchiectasis in 2016 and are planning to do work in preparation to support further clinical development of MP-376 in nontuberculous mycobacteria. QUINSAIR is not approved in the United States, and we may not market or commercialize QUINSAIR in the United States for any indication unless we receive FDA approval, which we may not be able to obtain.

Cysteamine Mechanism of Action

Cysteamine, or 2-aminoethanethiol, the active pharmaceutical ingredient in PROCYSBI, is a molecule generated naturally in human cells during the metabolism of cysteine. Cysteamine is used to construct the key enzymatic cofactor involved in energy produced from sugars and lipids. Cysteamine's uniquely reactive properties result in a number of physiological effects when given in pharmaceutical doses.

- Antioxidation – Cysteamine is known to increase levels of a key cellular antioxidant, glutathione. Glutathione is composed of the amino acids gamma-glutamate, cysteine and glycine. The availability of cysteine is the major rate-limiting factor in glutathione production. Cysteamine may release cysteine in the circulation, or from within the cell. Cysteamine has been shown to activate the NRF2 pathway, which leads to the increased expression of a wide variety of proteins involved in antioxidation which may help to reduce oxidative stress in CNS, hepatic and mitochondrial disorders.
- Proteostasis – Heat shock proteins, or HSPs, are chaperones that play an important role in protein-protein interactions such as folding and assist in the establishment of proper protein conformation. Proper protein folding may also prevent unwanted protein aggregation. By helping to stabilize partially unfolded proteins, HSPs aid in transporting proteins across membranes within the cell. HSPs are typically produced by cells in response to stress or injury, or other metabolic imbalance. HSPs are part of a cell's mechanism for protein maintenance. The presence of cysteamine within a cell has been shown to increase transcription of certain HSPs that are key components to the cell's ability to maintain the integrity of proteins.
- Anti-fibrosis – Cysteamine blocks TGF- signaling and thereby inhibits the production and proliferation of myofibroblasts. It also inhibits formation of three cross-links in collagen protein, each of which exacerbate formation of fibrotic tissue: gamma-glutamyl peptide bonds, formed by transglutaminase; oxidized lysyl-lysine conjugates, formed by lysyl oxidase; and inter-chain disulfide bonds.
- Transcription inhibition-Cysteamine inhibits transcription of a variety of collagens and basement membrane-related proteins:
- Metal chelation – In vitro studies have shown that cysteamine chelates metals, including copper, zinc and iron. High doses of cysteamine can lead to copper depletion, implying that chelation effects also occur in vivo.
- Induction of DNA repair mechanisms – Cysteamine has been known for over sixty years to mitigate the effects of radiation by upregulating cell cycle checkpoints and repair mechanisms.

MARKETED PRODUCT

PROCYSBI®

PROCYSBI is an approved therapy for the management of nephropathic cystinosis, a rare, life-threatening metabolic lysosomal storage disorder that causes the rapid, toxic accumulation of cystine in all cells, tissues and organs in the body. PROCYSBI capsules contain cysteamine bitartrate in the form of innovative microspheronized beads that are individually coated to create delayed and extended-release properties, allowing patients to maintain consistent

therapeutic systemic drug levels over a 12-hour dosing period. The enteric-coated beads are pH sensitive and bypass the stomach for dissolution and absorption in the more alkaline environment of the proximal small intestine. Randomized controlled clinical trials and extended treatment with PROCYSBI therapy demonstrated consistent cystine depletion as monitored by levels of the biomarker (and surrogate marker), white blood cell cystine.

About Nephropathic Cystinosis

We estimate that there are approximately 500 patients diagnosed with cystinosis living in the United States and an estimated 2,000 worldwide. Nephropathic cystinosis comprises 95% of known cases of cystinosis. In these patients, elevated cystine leads to cellular dysfunction and death; without treatment, the disease is usually fatal by the end of the first decade of life. Cystinosis is progressive, eventually causing irreversible tissue damage and multi-organ failure, including kidney failure, blindness, muscle wasting

and premature death. Nephropathic cystinosis is usually diagnosed in infancy after children present with symptoms including markedly increased urination, thirst, dehydration, gastrointestinal distress, failure to thrive, rickets, photophobia and kidney symptoms specific to Fanconi syndrome. Management of cystinosis requires lifelong therapy.

Cystine depletion is the only approved treatment strategy for nephropathic cystinosis. Committed adherence and persistence to cystine depletion therapy is critical to achieve optimal clinical outcomes. Failure to adhere to prescribed dosing of cystine depletion therapy results in disease progression, including kidney failure leading to dialysis and kidney transplantation, muscle wasting and in most cases, premature death. Even brief interruptions in daily therapy can permit toxic accumulation of cystine, exposing tissues to renewed, progressive deterioration.

In addition to the population of patients who have already been identified, we believe that a number of patients with atypical phenotypic presentation and end-stage renal disease have their condition as a result of undiagnosed late-onset nephropathic cystinosis, and would benefit from treatment with PROCYSBI. We currently are collaborating with the Marshfield Clinic to develop an algorithm to identify late onset cystinosis patients.

APPROVED PRODUCT IN CANADA AND EUROPE

QUINSAIR®

QUINSAIR is a formulation of the antibiotic drug levofloxacin, suitable for inhalation via a nebulizer. This route of delivery allows higher concentrations of drug in the lung sputum than can be achieved via systemic (e.g. oral) administration. QUINSAIR, as approved, is administered twice daily in 28-day cycles, using a hand-held nebulizer with a disposable handset known as the Zirela ® device, manufactured by our partner PARI Pharma GmbH, and configured specifically for use with QUINSAIR.

QUINSAIR is the first fluoroquinolone inhaled antibiotic to be approved in Canada and the EU for the treatment of chronic pulmonary infections due to Pseudomonas aeruginosa in cystic fibrosis (CF) patients. QUINSAIR was approved in the EU and Canada on the basis of three randomized, controlled studies, one Phase 2 and two Phase 3. In the EU, QUINSAIR is eligible for “new data” regulatory exclusivity of ten years after approval, a period which is concurrent with, and independent from, the period of any applicable patent.

We intend to discuss filing of a New Drug Application (“NDA”) with the FDA in 2016 for the treatment of Pseudomonas aeruginosa infection in CF based on the studies that were the basis for EU and Canadian marketing approvals. Depending on the feedback we receive, we may submit an NDA which, if approved, would enable us to market QUINSAIR in the United States.

About Pseudomonas aeruginosa infection in Cystic Fibrosis

CF is a rare, life-threatening genetic disease affecting approximately 70,000 people worldwide. CF is caused by a mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene. Defective or missing CFTR protein causes poor flow of salt and water into or out of the cell in several organs, including the lungs. This leads to the buildup of abnormally thick secretions that can cause chronic lung infections and progressive lung damage in many patients that eventually leads to death.

Patients with CF are highly susceptible to colonization with bacterial infections of the lung, largely because their pulmonary mucous secretions are thicker, stickier, and more difficult to expectorate than those of healthy individuals. This creates an environment in the lung that favors bacterial proliferation. As of 2014, approximately 50% of all patients with CF in the US were colonized with Pseudomonas aeruginosa, a gram-negative bacterial infection. Infection rates climb as patients age, with over 80% of patients colonized by adulthood. In the EU, infection rates vary

significantly from country to country, with a median of approximately 35% of patients colonized. These infections are currently treated primarily with inhaled antibiotics, including tobramycin, an aminoglycoside-class antibiotic sold by Novartis Pharmaceuticals Corporation as TOBI® or in dry-powder-inhalation format as TOBI Podhaler® and sold by others in generic form, and aztreonam, a monobacter-class antibiotic which is marketed in an inhaled formulation by Gilead Sciences, Inc. under the tradename Cayston®. Both tobramycin and aztreonam are primarily effective against gram-negative bacteria such as Pseudomonas aeruginosa. However, the prevalence of multi-drug-resistant Pseudomonas aeruginosa is growing. Thus, we believe there is an unmet need that might be addressed with a new class of inhaled antibiotic such as the fluoruquinolone class that levofloxacin represents.

CLINICAL DEVELOPMENT

RP103 Clinical Development

Huntington's Disease

Huntington's Disease ("HD") is a rare, inherited neurodegenerative disorder caused by an autosomal dominant mutation in a gene called huntingtin (Htt). The huntingtin gene encodes a protein that is also called "huntingtin." Expansion of a CAG triplet repeat beyond the normal range within the huntingtin gene results in a mutant form of the protein, which gradually damages cells in the brain. HD causes neuronal degeneration in the cerebral cortex and basal ganglia, which play a key role in movement and behavior control. The cumulative damage to these areas results in the hallmark symptoms of HD: a triad of movement, cognitive and neuropsychiatric symptoms which progress gradually in severity over 15-20 years, eventually causing severe physical and mental disability and premature death. The symptoms of HD usually become evident between ages 35-44 years, but the onset can also begin from childhood to late life (>75 years). The treatment options for HD patients are very limited, with no approved drugs that modify disease course. Recommended treatment strategies consist of drugs for symptomatic relief of chorea, an involuntary motor movement (with tetrabenazine, XENAZINE®, approved by the FDA) and mood disorder associated with HD as well as a variety of physical, occupational and dietary therapies.

RP103, enteric-coated delayed-release cysteamine bitartrate, is currently being evaluated as a potentially neuroprotective treatment for HD. Centre Hospitalier Universitaire d'Angers ("CHU d'Angers") in France, is conducting a Phase 2/3 clinical trial of RP103, referred to as CYST-HD (Clinicaltrials.gov Identifier:NCT02101957). This trial comprises an 18-month blinded, placebo-controlled phase, followed by an 18-month open-label phase in which all patients transitioned to RP103 and an extension phase for subjects who finished the 36 month trial and wish to continue on RP103. The primary endpoint of the trial was change from the baseline of the Total Motor Score ("TMS") of the Unified Huntington's Disease Rating Scale ("UHDRS") between RP103 and placebo treated patients. TMS, a validated rating scale, is comprised of approximately 15 different tests that evaluate gross and small motor function in patients with HD. The trial commenced in October 2010, with full enrollment achieved in June 2012. The study enrolled primarily Stage 1 patients showing early disease symptoms with a UHDRS TMS >5, Total Functional Capacity > 10 and a CAG repeat > 38. Due to the length of the study and the characteristic continuous progression of the disease, patients were allowed to continue their normal medication regime including taking antidepressants antipsychotics and neuroleptics. Tetrabenazine is approved as a treatment for chorea associated with HD, and chorea is a single measurement included in the TMS.

CYST-HD: 18 months results

In February 2014, we announced top line results from the planned 18-month analysis of the study. A total of 96 patients with HD were randomized to treatment with RP103 or placebo. A total of 89 patients completed the initial 18-month phase. A mixed model analysis of all 96 patients enrolled in the trial showed a trend towards slower progression of TMS in patients treated with RP103 versus those patients on placebo after 18 months treatment (4.51 vs. 6.68 respectively, p=0.19). While the results did not reach statistical significance, an overall positive trend was observed.

Patients were not stratified in the study based on concomitant medication use at baseline. We performed post-hoc statistical analyses to assess whether the TMS results were impacted by the effect of tetrabenazine on chorea. In 66 patients not taking tetrabenazine (32 under placebo and 34 under RP103), the results showed a statistically significant difference in the change in total motor score of 2.84 points of progression in the RP103 treatment arm versus 6.78 for the placebo group (p= 0.03).

There were no new or unusual variations from RP103's clinical safety profile with 48 of 52 patients experiencing at least one adverse event ("AE") during the 18-month interim evaluation versus 38 of 44 under placebo. There were slightly more patients under RP103 than under placebo reporting at least one gastrointestinal AE (61.5% RP103 versus 45.5% placebo), which consisted mostly of nausea, vomiting, abdominal pain, constipation, headache and breath odor. There were five patients treated with RP103 who experienced serious adverse events ("SAEs") compared with four patients treated with placebo. At the 18-month time point, seven patients had discontinued treatment, six in the RP103 arm and one in placebo. Three patients receiving RP103 discontinued for SAEs including one for lymphopenia, one for repetitive faintness and one for elevated liver enzymes. One SAE in the placebo group, anxiety, resulted in discontinuation.

CYST-HD: 36 months results

In December 2015, we announced top line results from the planned 36-month analysis of the study, which included subjects who crossed over from placebo to open-label treatment at the completion of month 18. The study examined the effect of RP103 in Huntington's disease subjects treated earlier, beginning at Month 0 (RP103/RP103) compared to subjects with a delayed start to treatment, beginning at Month 18 (placebo/RP103). The primary efficacy endpoint for this analysis was the change from baseline at 36 months in the TMS component of the UHDRS between placebo/RP103 and RP103/RP103-treated subjects. Analysis of this endpoint was also completed in the open-label phase of the study at 36 months. Key secondary endpoints evaluating function included

the UHDRS-TFC and Independence Scale. 88 subjects entered the open-label period and 78 subjects completed 36 months of treatment. The full analyses set included all randomized subjects from Month 0 to Month 36.

An evaluation of the change in the progression of the UHDRS-TMS at Month 36 from baseline in the full analyses set in the trial showed a 25% slower progression [10.0 (1.7) vs. 13.3 (1.8), respectively; p=0.18] in patients treated earlier with RP103 relative to those patients on a delayed start. In a completers analysis, these effects were more pronounced with a 35% slower progression [9.2(1.7) vs. 14.1(1.9), respectively p=0.06] in the earlier treatment with RP103 relative to those patients on a delayed start. The 25% treatment effect in TMS favoring subjects treated with RP103 for the full 36 months as compared to the placebo/RP103 arm, while not statistically significant, is regarded by clinical leaders in the field as clinically meaningful. These effects on the TMS were consistent with improvements in functional measures including the UHDRS-TFC and the Independence Scale. A 23% slowing in the rate of decline in TFC [-2.0 (0.33) vs. -2.6 (0.35); p=0.25] and a 46% slowing in the rate of deterioration on the Independence Scale [-6.9(1.45) vs. -12.7 (1.54); p=0.008] was observed, favoring earlier treatment relative to a delayed start of RP103. Subjects who completed the 36 months study period are allowed to continue receiving RP103 under an extension phase of the CYST-HD clinical trial.

The safety profile observed for RP103 after completion of the 36 month study was generally consistent with what has been previously reported. The most common adverse events included nausea, vomiting, diarrhea, headache and breath odor. Three deaths due to suicide occurred during the open-label period, including two deaths that occurred in subjects in the placebo/RP103 group and one death in the RP103/RP103 group. Deaths due to suicide were generally consistent with background rates, with over 25% of patients with Huntington's disease attempting suicide at least once and accounting for 5% to 7% of deaths, per published estimates. Suicides have not been observed in any other RP103 clinical trials or in any patients on clinical or commercial drug.

Regulatory Update

We initiated regulatory discussions with the FDA and the EMA in 2014 based on the 18-month data and most recently received feedback from the EMA in the fourth quarter of 2015 through a Scientific Advice procedure. The outcome of these interactions with both agencies indicated that additional data from a confirmatory study would be required to support an application for marketing authorization. We intend to update both regulatory agencies with the 36-month data and to discuss a trial design that would support marketing authorization.

Under our amended collaboration agreement with CHU d'Angers, we supply RP103 and placebo capsules for the clinical trial and open-label extension study and fund the third-party statistical analysis of clinical trial data in exchange for regulatory and commercial rights to the clinical trial data. Clinical expenses of the study are covered by a grant from the Programme Hospitalier de Recherche Clinique, which is funded by the French government.

In 2008, we received FDA orphan drug designation for cysteamine formulations, including RP103, for the potential treatment of HD. We have received orphan drug designation in the EU for the treatment of HD .

RP103 Mechanism in Huntington's Disease

In HD, mutant Htt aggregate formation and processing leads to neuronal, mitochondrial, cellular stress and dysfunction and death. The metabolism of cysteamine boosts systemic cysteine, which may induce several beneficial stress responses, including the production of glutathione, that in aggregate reduce cellular oxidative stress. A major deficiency of cystathionine c-lyase (CSE), the principal generator of endogenous cysteine from cystathionine, has been shown to mediate neurodegeneration in HD. The ability of CSE and cysteine to reverse oxidative stress and lethality in HD cells suggests that cysteine supplementation and intracellular mobilization through cysteamine therapy might be beneficial in treating HD. Through inhibition of intracellular enzymes, such as transglutaminase, cysteamine

inhibits protein aggregation, which are known to form in HD. Cysteamine also increases transcription and production of certain heat shock proteins, which may assist in clearing or repairing misfolded Htt and other proteins in neuronal cells. Cysteamine and its dimer cystamine have been shown in preclinical studies to increase levels of brain derived neurotropic factor, or BDNF. BDNF is induced by cortical neurons and helps support survival, growth and differentiation of new neurons and synapses. Two master genes, huntingtin, or Htt, and huntingtin-associated protein, or Hap1, govern BDNF axonal transport and secretion. Expression of the BDNF gene is reduced in both Alzheimer's and HD patients, and HD patients are believed to be deficient in BDNF. The BDNF gene may play a role in the regulation of stress response and in the biology of mood disorders. Finally, cysteamine's metal-chelating properties may assist in removing excess copper, a metal that has shown increased accumulation in brains of people with HD as well as other neurodegenerative disorders.

Mitochondrial Disorders including Leigh Syndrome

Leigh syndrome is a severe neurological disorder caused by genetic defects in mitochondrial or nuclear DNA affecting respiratory chain function that typically results in death within the first decade of life. The condition causes increased production of reactive oxygen species that disrupt mitochondrial electron transport and affect cellular function in a variety of tissues. Typically observed during the first year of life, Leigh syndrome is characterized by a failure to thrive, lack of coordination, involuntary and sustained muscle contraction, muscle wasting and multiple organ failure. The incidence of Leigh syndrome and similar mitochondrial disorders in the United States is estimated to be 1 in 40,000 newborns.

RP103 as a Treatment for Mitochondrial Disorders including Leigh Syndrome

In June 2014, we initiated a Phase 2 study in the United States designed to evaluate the safety, tolerability and efficacy of RP103 as a potential treatment for Leigh syndrome and other mitochondrial disorders. RP103 potentially increases mitochondrial glutathione which may act as a scavenging agent of reactive oxygen species and thereby reduce the mitochondrial oxidative stress typically associated with these disorders.

The clinical plan includes an open label, 24 week, Phase 2a study in 24 patients (up to a maximum of 32 patients). Patients with Leigh syndrome are expected to comprise approximately two-thirds of the enrolled population in the study. Employing a statistical plan based on an adaptive design, we will conduct interim analyses after four patients and again after 12 patients have completed the study. The primary endpoint of the study will be the change from baseline in the Newcastle Pediatric Mitochondrial Disease Scale, at 24 weeks. Secondary endpoints will include observations of myopathy, dystonia, seizures, motor development, dyskinesia, quality of life and activities of daily living. An interim analysis based on four subjects was conducted at the end of 2015. Evaluation of the safety data revealed no unexpected adverse events or adverse safety signal. Study enrollment is ongoing with data collection from 12 subjects for the second interim analysis per the statistical analysis plan expected inthe first quarter of 2016.

MP-376 Clinical Development

In addition to CF, MP-376 has development potential in two additional orphan diseases with significant unmet need: non-CF bronchiectasis (BE) and nontuberculous mycobacteria (NTM) lung infections. Currently, few therapeutic options exist for patients with these diseases. BE is characterized by abnormal dilatation and destruction of lung bronchi and bronchioles due to chronic recurring infection and long-term inflammation, which leads to frequent hospitalizations. NTM are a group of microbes that cause severe and recurrent lung infections, often in individuals who are immune-compromised or who have structural lung disease, such as bronchiectasis. We are evaluating the therapeutic potential of MP-376 in these indications and intend to pursue clinical programs in 2016 in non-CF related bronchiectasis and are also planning to do work in preparation to support further clinical development of MP-376 in NTM.

About non-CF Bronchiectasis (BE)

BE is a disease in which airways lose elasticity over time, which impairs the lung’s ability to clear out mucus,creating a highly favorable environment for bacteria. These bacterial infections typically result in inflammation that further damages bronchial tissue, creating a negative feedback loop and significant loss of lung function. BE can be due to a variety of causes, including but not limited to chronic obstructive pulmonary disease (COPD), smoking history, autoimmune disease, and triggering bacterial or viral infection.

Current standard of care is to reduce the number of exacerbations requiring critical care, with reduction of bacterial load considered to be highly important as a preventative measure. No antibiotic product is approved currently. There

is some evidence suggesting that drugs of the macrolide class are effective in treating infections in the context of BE, but these are associated with rapid development of bacterial resistance as well as side effects including hepatotoxicity, hearing loss, and cardiovascular events.

In in vitro studies, levofloxacin has demonstrated the ability to eradicate bacterial colonies of several types that are found with high frequency in the non-CF BE population. In addition, randomized, controlled studies have been conducted with inhaled ciprofloxacin, another drug in the same fluoroquinolone class as levofloxacin, showing increased time to exacerbations and improvements in bacterial load when compared to placebo. Levofloxacin is, in general, as potent as, or more potent in in vitro assays than ciprofloxacin. Thus, we believe it is a favorable candidate for development in BE.

About Non-Tuberculous Mycobacterium Infections (NTM)

NTM is a bacterial infection of the lung caused by bacteria of the mycobacterium family, but which do not result in tuberculosis. Infections of this type frequently result in progressive loss of lung function, and can be life-threatening if not treated. Symptoms of NTM include fever, weight loss, cough, lack of appetite, night sweats, and loss of energy. Approximately 60,000 patients exist in the United States, with another 30,000 found in the EU.

No treatment is currently approved specifically for use in NTM. Treatment guidelines suggest high doses of systemic (usually oral) antibiotics be used, typically with multiple active agents in a “cocktail” to cover a variety of bacterial strains. These regimens have a high rate of failure to clear the infection, and also cause significant side effects such as gastrointestinal distress, hearing impairment, flu-like reactions, and liver toxicity. Surgical resection of lung tissue is recommended in particularly symptomatic cases.

In in vitro studies, levofloxacin (the active agent in MP-376) has demonstrated the ability to inhibit bacterial colonies of several types that are found with high frequency in the NTM population, including m. abcessis and m. kansasii. Based on these results, and the demonstrated ability of MP-376 to reach certain concentrations in lung sputum of patients, as well as on feedback from medical providers and opinion leaders, we believe development of MP-376 for the treatment of this disease is appropriate.

Preclinical Product Candidates

Our preclinical programs include RP105 and RP106 being developed for a variety of rare diseases.

Future Activities

We expect that our near-term efforts will be focused on:

- Increasing product uptake and sales of PROCYSBI in the United States and continuing to provide comprehensive reimbursement and adherence support to commercial cystinosis patients in the United States;

- Increasing market penetration and sales of PROCYSBI in current markets in Europe, negotiating pricing and reimbursement in specific European countries, and accelerating launch in additional countries in Europe;
- Seeking approval for PROCYSBI from Health Canada;

- Launching QUINSAIR in Europe and Canada for treatment of chronic lung infection with Pseudomonas aeruginosa in CF patients;
- Pursuing NDA approval from the FDA for marketing of QUINSAIR in U.S. for treatment of Pseudomonas aeruginosa infection in CF patients;
- Pursuing clinical trials of MP-376 in non-CF BE;
- Design of a pediatric study of MP-376 for eradication of first infection with Pseudomonas aeruginosa in CF patients;
- Work in preparation to support further clinical development of MP-376 in NTM;
- Continuing a clinical trial to evaluate PROCYSBI in cysteamine-naïve cystinosis patients, as well as other supporting trials in underdeveloped markets;
- Screening for undiagnosed and unidentified late-onset adult nephropathic cystinosis patients;
- Supporting clinical programs and developing clinical and regulatory strategies for the use of RP103 as a potential treatment of HD;
- Supporting clinical programs evaluating RP103 for the potential treatment of mitochondrial disorders;
- Supporting our novel preclinical programs;
- Identifying promising in-licensing product and drug development candidates; and
- Exploring strategic partnerships for HD or our other potential product candidates.

Corporate Information

We are incorporated under the laws of the State of Delaware and our business was founded in May 2006. Our principal executive office is located at 7 Hamilton Landing, Suite 100, Novato, CA 94949. Our phone number is (415) 408-6200.

Intellectual Property

IP Protection for RP103 for Our Products and Product Candidates

We seek to protect our proprietary technology and other intellectual property that we believe is important to our business, including by seeking, maintaining and defending patents. We also rely on trade secrets and know-how to protect our business. We own certain of these intellectual property rights and have obtained licenses under other of our intellectual property rights.

Our intellectual property portfolio is directed to the composition of matter, or COM, the method of use, or MOU, and the composition for use, or CFU, of a formulation/pharmaceutical composition for our products, our product candidates, and other proprietary technologies and processes related to our product development candidates. As of February 25, 2016, our patent portfolio includes the patents and patent applications described below, which we own or have exclusively licensed from third parties, along with any patents that may issue from these patents and applications in the future.

With respect to PROCYSBI, we own, or exclusively license from the University of California,San Diego ("UCSD"), five issued patents and three pending patent applications in the United States, and own, or exclusively license from UCSD, three issued foreign patents, and numerous pending foreign patent applications directed to the formulation/composition, the MOU, and the CFU, of PROCYSBI for the treatment of cystinosis.

With respect to RP103 for indications other than nephropathic cystinosis, including HD and mitochondrial disorders, we own or hold, by exclusive license, six issued US patents and 18 foreign patents, as well as numerous pending applications in the United States and foreign jurisdictions.

IP Protection for QUINSAIR and MP-376

With respect to QUINSAIR, we currently hold seven issued U.S. patents, a Canadian patent and a European patent application that is allowable and is expected to issue in 2016.

General IP Protection

These patents will expire from 2019 to 2031, and additional patents issuing from pending patent applications or others that may be filed, if they issue, will expire after the standard 20-year term, subject to available patent term adjustments.

The term of individual patents depends upon the legal term of the patents in the countries in which they are obtained. In most countries in which we file, the patent term is 20 years from the date of filing the non-provisional application. In the United States, a patent's term may be lengthened by patent term adjustment, which compensates a patentee for administrative delays by the U.S. Patent and Trademark Office in granting a patent, or may be shortened if a patent is terminally disclaimed over an earlier-filed patent.

In addition, extensions of the term of a patent that covers an FDA-approved drug are available in the United States, in order to compensate for the patent term lost during the FDA regulatory review process. The Hatch-Waxman Act permits a patent term extension of up to five years beyond the expiration of the patent, based on the length of time the drug is under regulatory review, subject to certain limitations. Similar extensions are available in Europe and other foreign jurisdictions for patents that cover an approved drug. We expect to apply for available patent term extensions for patents covering our product candidates.

Despite the measures we take to protect our intellectual property, any of our patents or other proprietary rights could be challenged, invalidated, infringed or misappropriated or our intellectual property may not prove sufficient to provide us a competitive market advantage. See "Risk Factors-Risks Related to Intellectual Property and Competition".

Trademarks

Our trademark portfolio consists of several registered U.S. trademarks covering our company and our subsidiaries' names, the names of our products and services programs (which are additionally registered in additional territories as necessary to protect our rights to the names). Our trademark RAPTOR is registered in the United States, in the EU and

internationally generally and is currently pending registration in several other jurisdictions. Our trademark PROCYSBI is registered in the United States, the EU and several additional jurisdictions. It is pending registration in Canada. Our trademark QUINSAIR is registered in the EU and is pending registration in Canada and the United States.

All third-party trademarks and trade names identified in this Annual Report on Form 10-K are the property of their respective owners.

License Agreement with UCSD

In December 2007, by way of a merger with Encode Pharmaceuticals, Inc., ("Encode") we acquired certain patent rights licensed to Encode by UCSD pursuant to a license agreement dated October 2007, later amended in February 2008, amended and restated in December 2012, and further amended in March 2013 and December 2013. Pursuant to this agreement, we obtained an exclusive, worldwide, sublicenseable license under certain patent rights and know-how controlled by UCSD for the commercial development, use and sale, for human therapeutic purposes, of products covered by such patents or incorporating such know-how,

including RP103. This license is exclusive with respect to the licensed patent rights and non-exclusive with respect to the licensed know-how. Under the agreement, UCSD is obligated to diligently prosecute and maintain the licensed patent rights, conditioned upon our continued fulfillment of our obligation to reimburse UCSD for related costs incurred.

Pursuant to the license agreement, we are obligated to pay milestone payments (ranging in size for orphan and non-orphan indications), up to an aggregate total of $6,275,000, upon the occurrence of certain specified development-, regulatory- and commercial-related events during the term of the agreement. To date, we have paid UCSD approximately $2.2 million in total milestone payments. We are also obligated to pay UCSD a royalty on commercial net sales of licensed products, on a country-by-country basis, ranging in the low single-digit to mid-single-digit percentages, based on whether the licensed product sold is covered by the licensed patent rights in such country, as well as a percentage of sublicensing fees and sublicensing royalties we receive under the agreement, if any. In 2013, we began paying UCSD royalties based upon our net sales of PROCYSBI.

Unless earlier terminated, our license agreement with UCSD will expire upon the later of (i) on a country-by-country basis, the expiration of the last to expire of the licensed patent rights (in the applicable country), and (ii) ten years from the first commercial sale of any royalty-bearing product. We may terminate the agreement at any time upon a specified period of prior written notice to UCSD. In the event of our breach of an obligation under the agreement, which breach is not cured within a specified number of days after receiving notice of such from UCSD, UCSD may terminate the agreement or choose to convert the license into a non-exclusive license with respect to the indication for which we are in breach. We are currently behind in our developmental diligence obligations with respect to HD and non-alcoholic steatohepatitis under this agreement and are in discussions with UCSD to amend the agreement to conform to the product development timeline we expect to achieve. The agreement will immediately terminate if we file a claim asserting that any of the licensed patent rights are invalid or unenforceable.

Asset Purchase Agreement with Tripex

Asset Purchase Agreement

On August 20, 2015, we entered into an Asset Purchase Agreement with Tripex to purchase MP-376 or QUINSAIR and related intellectual property. At the closing of the asset acquisition pursuant to the Amended and Restated Asset Purchase Agreement dated October 2, 2015, which amended agreement provided for the assets to be acquired by our subsidiary, we made an upfront payment to Tripex of $35,370,000 in cash consideration, subject to certain deductions, and issued various Tripex stockholders 3,448,001 shares of our common stock. As additional consideration, Tripex may become entitled to receive contingent payments from us upon the achievement of certain milestones and variable royalty payments on the net sales of QUINSAIR-related products.

The contingent payments include:

- a one-time variable payment which may be as low as $40 million and up to $80 million if the FDA approves QUINSAIR for the treatment of Pseudomonas aeruginosa infections in cystic fibrosis with certain conditions for each level of payment;
- a one-time payment of $20 million if a second-indication registrational trial milestone for QUINSAIR is achieved;
- up to four milestone payments, totaling up to $250 million in the aggregate, payable upon achievement of first commercial sale of QUINSAIR in the United States and/or the European Union for up to two approved label indications in addition to cystic fibrosis; and
- certain royalties would become payable by us to Tripex based on net sales of QUINSAIR-related products by us and our sublicensees.

At our election, portions of the milestone payments may be paid in the form of shares of our common stock. In addition, in a change of control, the party acquiring us may be required to prepay portions of certain of our contingent payments if, after the change of control event, we have not met certain diligence obligations pertaining to QUINSAIR.

We are obligated to engage in specified levels of effort to undertake activities relevant to the contingent payments, each of which will be subject to various exceptions to performance.

PARI Letter Agreement

Under the purchase agreement with Tripex, we assumed rights and certain obligations under the Development and License Agreement, dated as of February 11, 2006, between PARI Pharma GmbH, a German corporation ("PARI"), and Mpex Pharmaceuticals, Inc., a prior owner of QUINSAIR. Pursuant to the Development and License Agreement, PARI granted Mpex a worldwide royalty-bearing license to develop, sell and otherwise exploit pharmaceutical preparations formulated for delivery via pulmonary administration, and the parties agreed to perform joint evaluation, research and development of potential formulations of

drug compounds for pulmonary delivery with customized PARI nebulizer devices. QUINSAIR was developed pursuant to the Development and License Agreement, and will continue to be developed and commercialized subject to the terms and conditions of the Development and License Agreement, as amended by the PARI Amendment (as defined and described below).

On August 20, 2015, we entered into a Letter Agreement with PARI, which provided that PARI and Raptor would enter into Amendment No. 1 to the Development and License Agreement (the "PARI Amendment") following the closing of our acquisition of QUINSAIR from Tripex. The PARI Amendment was entered into on October 4, 2015. Pursuant to the Development and License Agreement, as amended by the PARI Amendment, we will make payments due to PARI upon the achievement of milestones related to regulatory approval and commercialization activities. We are required to comply with diligence milestones related to development and commercialization of QUINSAIR in the United States, to spend a specified minimum amount per year on development activities in the United States until filing of the NDA for QUINSAIR in the United States, and will pay PARI tiered single digit royalties on net sales of QUINSAIR for a specified time period. We will have the right to buy down the royalties under certain conditions by paying an amount determined through a defined net present value calculation. The PARI Amendment further provides that in the event that we decide to cease the development or commercialization of QUINSAIR for exclusive delivery via the PARI nebulizer device in the United States, PARI shall have the right, in its sole discretion, to develop, and/or license its technology for use with other inhaled fluoroquinolones within the United States.

Orphan Drug Designation

We have been granted Orphan Drug Designation from the FDA for use of PROCYSBI to manage cystinosis for patients six years of age and older and separately in the pediatric population for two to six year olds, and the use of RP103 to potentially treat HD, pancreatic cancer and Batten Disease. The Orphan Drug Act of 1983 generally provides incentives, including marketing exclusivity, user fee waivers and tax benefits, to companies that undertake development and marketing of products to treat relatively rare diseases, which are defined as diseases for which there is a patient population of fewer than 200,000 persons in the United States or a patient population greater than 200,000 in the United States where there is no reasonable expectation that the cost of developing the drug will be recovered from sales in the United States. A drug that receives orphan drug designation may receive up to seven years of exclusive marketing in the United States for that indication, which means the FDA may not approve any other application to market the same drug for the same indication for a period of seven years, except in limited circumstances, such as a showing of clinical superiority over the product with orphan exclusivity or where the manufacturer is unable to assure sufficient product quantity. A drug may be entitled to an additional six months of exclusive marketing if it satisfies the requirements for pediatric exclusivity; we have applied for this additional six-month pediatric extension for PROCYSBI. See also "Orphan Designation and Exclusivity" and "Pediatric Studies and Exclusivity" below.

PROCYSBI has also been granted Orphan Drug Designation and awarded 10 years of data exclusivity and marketing protection by the EC for treatment of cystinosis, and RP103 has been granted Orphan Drug Designation by the EC for the treatment of HD. QUINSAIR has been awarded 10 years of data exclusivity and marketing protection by the EC for the treatment of Pseudomonas aeruginosa infection in CF patients and has been awarded Orphan Drug Designation by the FDA.

Competition

Cystinosis

Other than PROCYSBI, we are aware of two pharmaceutical products currently approved to treat cystinosis. Cystagon® (immediate-release cysteamine bitartrate capsules), is a systemic cystine-depleting therapy for cystinosis in the United States manufactured by Mylan N.V., and by Orphan Europe SARL in markets outside of the United States. Cystagon was approved by the FDA in 1994 and by the EC in 1997. Cystaran® (cysteamine ophthalmic solution) was approved by FDA in 2012 for treatment of corneal crystal accumulation in patients with cystinosis and is marketed by Sigma Tau Pharmaceuticals, Inc.

While we believe that PROCYSBI will continue to be well received in the market, Cystagon remains on the market and we expect it will compete with PROCYSBI for the foreseeable future. We are not aware of any pharmaceutical company with an active program to develop an alternative therapy for cystinosis. Academic researchers in the United States and Europe are pursuing gene therapy and stem cell therapy, as well as pro-drug and pegylated drug approaches as alternatives to cysteamine bitartrate. We believe that the development timeline to an approved product for these approaches is many years with substantial uncertainty.

Huntington’s Disease

We are not aware of any approved available treatments to slow the progression of HD. There is only one approved treatment available for specific symptoms of HD, Xenazine® to treat uncontrollable movements (chorea) that result from the disease. There are several pharmaceutical companies pursuing potential cures and disease modifying treatments for HD, as well as numerous academic

and foundation sponsored research efforts. Our product candidate, RP103, is in late-stage clinical development with the goal of slowing motor deterioration with potentially neuroprotective properties through specifically targeting deficient BDNF.

Companies with HD product candidates in development include Prana Biotechnology, Omeros, Teva (and formerly Auspex and Neurosearch), Ionis Pharmaceuticals/Roche, Eli Lilly & Co. and Pfizer. Several other companies have drug candidates in preclinical development. Additionally, nutritional supplements including creatine and coenzyme Q10 have been investigated as potential treatments for HD. The Huntington Study Group sponsors numerous studies of potential therapies for HD, including the recently completed trials evaluating coenzyme Q10 and the antibiotic minocycline.

·Pseudomonas Aeruginosa Infection in CF Patients
Currently, there are three products approved in the United States for treatment of chronic Pseudomonas aeruginosa lung infections in patients with CF. Tobramycin solution for inhalation is sold by Novartis as TOBI®, and is now also available as a generic from multiple sources. TOBI Podhaler®, a dry-powder inhalation formulation of tobramycin, is also sold by Novartis. Gilead Sciences sells Cayston®, a nebulized formulation of aztreonam. In the EU, an additional competitor, colistimethate, is available in addition to the products currently available in the United States.

Other programs that are in development for treatment of chronic pulmonary infections in CF patients include the inhaled amikacin product developed by Insmed, Inc., an inhaled vancomycin under development by Savara Pharmaceuticals and the tobramycin/fosfomycin treatment under development by CuRx, Inc.

·BE and NTM
No products are currently labeled for treatment of either non-CF BE or pulmonary NTM. Systemic antibiotics, labeled for other diseases, are frequently used off-label as first-line treatment. However, several inhaled antibiotic products are currently in development for either BE or NTM, including Insmed’s Arikayce (tm) (liposomal amikacin for inhalation), AG Bayer’s ciprofloxacin dry powder for inhalation, and Aradigm’s two inhaled ciprofloxacin product candidates, one of which has been licensed to Grifols, Inc.

Government Regulations of the Biotechnology Industry

Human therapeutic products are subject to extensive regulation by governmental authorities in the United States and foreign countries. Governmental authorities govern, among other things, the research, development, testing, manufacture, storage, recordkeeping, approval, labeling, promotion and marketing, distribution, post-approval monitoring and reporting, sampling, and import and export of pharmaceutical products. The nature and extent to which such regulation will apply to us will vary depending on the nature of any drug product candidates developed. Failure to comply with applicable governmental requirements may subject a company to a variety of administrative or judicial sanctions, such as refusal to approve pending applications, a clinical hold, warning letters, recall or seizure of products, partial or total suspension of production, withdrawal of the product from the market, injunctions, fines, civil penalties or criminal prosecution.

Governmental agency approval is required before any new unapproved drug or dosage form, including a new use of a previously approved drug, can be marketed in each jurisdiction in which the product is marketed. We anticipate that all of our drug product candidates will require regulatory approval by governmental agencies prior to commercialization.

In particular, human therapeutic products are subject to rigorous preclinical and clinical testing and other approval procedures of the FDA and similar regulatory authorities in other countries. Various federal statutes and regulations also govern or influence testing, manufacturing, safety, labeling, storage, record-keeping and marketing related to

such products. The process of obtaining these approvals and the subsequent compliance with the appropriate federal statutes and regulations requires substantial time and financial resources.

Before obtaining regulatory approvals for the commercial sale of any of our products under development, we must demonstrate through preclinical studies and clinical trials that the product is safe and efficacious for use in each target indication. The results from preclinical studies and early clinical trials might not be predictive of results that would be obtained in large-scale testing. Our clinical trials might not successfully demonstrate the safety and efficacy of any product candidates or result in marketable products, and failure can occur at any point in the testing process.

In order to clinically test, manufacture and market products for therapeutic use, we will have to comply with mandatory procedures and safety and effectiveness standards established by various regulatory bodies. In the United States, the Public Health Service Act and the Federal Food, Drug, and Cosmetic Act, as amended, or FDCA, and the regulations promulgated thereunder, and

other federal and state statutes and regulations govern, among other things, the testing, manufacture, labeling, storage, record keeping, approval, advertising, and promotion of our current and proposed product candidates. Product development and approval within this regulatory framework takes a number of years and involves the expenditure of substantial resources.

The steps required by the FDA before new drug products may be marketed in the United States include:

- Completion of extensive preclinical laboratory and animal studies performed in accordance with the FDA's Good Laboratory Practice, or GLP, regulations;
- The submission to the FDA of a request for authorization to conduct clinical trials in an investigational new drug application, or IND, which must become effective before clinical trials may commence;
- Approval by an independent institutional review board, or IRB, or ethics committee representing each clinical site before each clinical study may be initiated;
- Completion of adequate and well-controlled human clinical trials to establish and confirm the safety and efficacy of a drug candidate for the proposed indication;
- Completion of process validation, quality product release and stability;
- Submission to the FDA of a new drug application, or NDA, for the drug candidate for marketing approval;
- Potential review of the product application by an FDA advisory committee, where appropriate and if applicable;
- Satisfactory completion of an FDA pre-approval inspection of the manufacturing facilities where the proposed product is produced to assess compliance with the FDA's current Good Manufacturing Practice, or cGMP, requirement and to assure that the facilities, methods and controls are adequate to preserve the drugs' identity, strength and purity; and
- Review and approval of the NDA by the FDA before the product may be sold commercially.

The pre-clinical and clinical testing and approval process requires substantial time, effort and financial resources, and we cannot be certain that approvals for our product candidates will be granted on a timely basis, if at all. Preclinical testing includes laboratory evaluation and characterization of the safety and efficacy of a drug and its chemistry, formulation, stability and toxicity, as well as animal studies to assess the characteristics and potential safety and efficacy of the product. Preclinical testing results are submitted to the FDA as a part of an IND. Some pre-clinical testing may continue even after the IND is submitted. The IND automatically becomes effective 30 days after receipt by the FDA, unless the FDA, within the 30-day time period, raises concerns or questions relating to one or more proposed clinical trials and places a trial on clinical hold, including concerns that human research subjects will be exposed to unreasonable health risks. In such a case, the IND sponsor and the FDA must resolve any outstanding concerns before the clinical trial can begin. As a result, the submission of an IND may not result in FDA authorization to commence a clinical trial. A separate submission to an existing IND must also be made for each successive clinical trial conducted during product development. Further, an independent IRB, covering each site proposing to conduct the clinical trial must review and approve the plan for any clinical trial and informed consent information for subjects before the trial commences at that site and it must monitor the study until completed.

Clinical trials involve the administration of an investigational drug to human subjects under the supervision of qualified investigators in accordance with GCP requirements, which include the requirement that all research subjects provide their informed consent in writing for their participation in any clinical trial. Sponsors of clinical trials generally must register and report, at the NIH-maintained website ClinicalTrials.gov, key parameters of certain clinical trials. For purposes of an NDA submission and approval, human clinical trials are typically conducted in the following sequential phases, which may overlap or be combined. Phase 1 represents the initial administration of the drug to a small group of humans, either patients or healthy volunteers, typically to test for safety (adverse effects), dosage tolerance, absorption, distribution, metabolism, excretion and clinical pharmacology, and, if possible, to gain early evidence of effectiveness. Phase 2 involves studies in a small sample of the actual intended patient population to assess the efficacy of the drug for a specific indication, to determine dose tolerance and the optimal dose range and to gather additional information relating to safety and potential adverse effects. Multiple Phase 2 clinical trials may be

conducted by the sponsor to obtain information prior to beginning larger and more extensive Phase 3 clinical trials. Once an investigational drug is found to have some efficacy and an acceptable safety profile in the targeted patient population, Phase 3 studies are initiated to further establish clinical safety and efficacy of the therapy in a broader sample of the general patient population, in order to determine the overall risk-benefit ratio of the drug and to provide an adequate basis for any physician labeling. During all clinical studies, we must adhere to GCP or good clinical practices, standards. The results of the research and product development, manufacturing, preclinical studies, clinical studies and related information are submitted in an NDA to the FDA.

The FDA, the IRB or the clinical study sponsor may suspend or terminate a clinical study at any time on various grounds, including a finding that the research subjects are being exposed to an unacceptable health risk. Additionally, some clinical studies are overseen by an independent group of qualified experts organized by the clinical study sponsor, known as a data safety monitoring board or committee. This group provides authorization for whether or not a study may move forward at designated check points based

on access to certain data from the study. We may also suspend or terminate a clinical study based on evolving business objectives and/or competitive climate. The process of completing clinical testing and obtaining FDA approval for a new drug is likely to take a number of years and require the expenditure of substantial resources. If an application is submitted, there can be no assurance that the FDA will review and approve the NDA.

Assuming successful completion of all required testing in accordance with all applicable regulatory requirements, detailed investigational new drug product information is submitted to the FDA in the form of an NDA requesting approval to market the product for one or more indications. Under federal law, the submission of most NDAs is subject to a substantial application user fee. Applications for orphan drug products are exempt from the NDA user fees, unless the application includes an indication for other than a rare disease or condition.

An NDA must include all relevant data available from pertinent preclinical and clinical studies, including negative or ambiguous results as well as positive findings, together with detailed information relating to the product's chemistry, manufacturing, controls and proposed labeling, among other things. Data can come from company-sponsored clinical studies intended to test the safety and effectiveness of a use of a product, or from a number of alternative sources, including studies initiated by investigators. To support marketing approval, the data submitted must be sufficient in quality and quantity to establish the safety and effectiveness of the investigational new drug product to the satisfaction of the FDA.

Under federal law, the submission of an NDA is subject to a substantial application user fee, and the manufacturer and/or sponsor under an approved NDA are also subject to annual product and establishment user fees. The FDA has 60 days from its receipt of an NDA 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. The FDA may request additional necessary information rather than accept an NDA for filing. In this event, the NDA must be resubmitted with the additional information and may be subject to payment of additional user fees. The resubmitted application is also subject to review before the FDA accepts it for filing. Once the submission has been accepted for filing, the FDA begins an in-depth substantive review.

The FDA's goal is to review the application within 10 months after it accepts the application for filing, or, if the application relates to an unmet medical need in a serious or life-threatening indication, six months after the FDA accepts the application for filing. The review process is often significantly extended by FDA requests for additional information or clarification. In addition, an application may be referred to an advisory committee, which is a panel of independent experts, to review, evaluate and provide a recommendation to the FDA as to whether the application should be approved and under what conditions. The FDA is not bound by the recommendations of an advisory committee, but it typically follows such recommendations and considers them carefully when making approval decisions.

Before obtaining FDA approval for each product, the FDA typically will inspect the facility or facilities where the product is manufactured and will not approve an application unless it determines that the manufacturing processes and facilities are in compliance with cGMP requirements and adequate to assure consistent production of the product within required specifications. Additionally, before approving an NDA, the FDA will typically inspect one or more clinical sites to assure compliance with GCP requirements. Following approval, each product manufacturing establishment must be registered with the FDA and its quality control and manufacturing procedures must continue to conform and adhere at all times to the FDA's cGMP regulations. The FDA and other government agencies regularly inspect manufacturing facilities for compliance with these requirements. If, as a result of these inspections, the FDA determines that any equipment, facilities, laboratories or processes do not comply with applicable FDA regulations and conditions of product approval, the FDA may seek civil, criminal or administrative sanctions and/or remedies against us, including the suspension of the manufacturing operations. Manufacturers must expend substantial time, money and effort in the area of production and quality control to ensure full technical compliance with these

standards.

In some cases, the FDA may condition approval of an NDA for a product candidate on the sponsor's agreement to conduct additional clinical trials to further assess the drug's safety and effectiveness after NDA approval. Such post-approval trials are typically referred to as Phase 4 studies. In addition, even after initial FDA approval has been obtained, further studies would be required to gain approval for the use of a product as a treatment for clinical indications other than those for which the product was initially tested and approved. Once an NDA is approved, a product will be subject to pervasive and continuing regulation by the FDA, including, among other things, requirements relating to drug/device listing, recordkeeping, periodic reporting, product sampling and distribution, advertising and promotion and reporting of adverse experiences with the product. Results of post-marketing programs, including Phase 4 clinical studies or post-market surveillance, might limit or expand the further marketing of the products. Further, if there are any modifications to the drug, including changes in indication, manufacturing process, labeling or a change in manufacturing facility, submission and approval of an NDA supplement might be required. Drug manufacturers and other entities involved in the manufacture and distribution of approved drugs are required to register their establishments with the FDA and state agencies, and are subject to periodic unannounced inspections by the FDA and these state agencies for compliance with cGMP requirements. Changes to the manufacturing process are strictly regulated and generally require prior FDA approval before being implemented. FDA regulations also require investigation and correction of any deviations from cGMP or QSR and impose reporting and documentation

requirements upon us and any third-party manufacturers that we may decide to use. Accordingly, manufacturers must continue to expend time, money, and effort in the area of production and quality control to maintain cGMP or QSR compliance.

Failure to comply with applicable FDA requirements may result in a number of consequences that could materially and adversely affect us. Failure to adhere to approved trial standards and GCPs in conducting clinical trials could cause the FDA to place a clinical hold on one or more studies which would delay research and data collection necessary for product approval. Noncompliance with GCPs could also have a negative impact on the FDA's evaluation of an NDA. Failure to adhere to GCPs, cGMPs and other applicable requirements could result in FDA enforcement action and in civil and criminal sanctions, including but not limited to fines, seizure of product, refusal of the FDA to approve product approval applications, withdrawal of approved applications, and prosecution. Later discovery of previously unknown problems with a product, including adverse events of unanticipated severity or frequency, or with manufacturing processes, or failure to comply with regulatory requirements, may result in revisions to the approved labeling to add new safety information; imposition of post-market studies or clinical studies to assess new safety risks; or imposition of distribution restrictions or other restrictions under a Risk Evaluation and Mitigation Strategies, or REMS, program.

The FDA strictly regulates marketing, labeling, advertising, and promotion of products that are placed on the market pursuant to a number of complex regulations which include, among others, standards for direct-to-consumer advertising, off-label promotion, industry-sponsored scientific and educational activities, and promotional activities involving the internet. Drugs may be promoted only for the approved indications and in accordance with the provisions of the approved label. The FDA and other agencies actively enforce the laws and regulations prohibiting the promotion of off-label uses, and a company that is found to have improperly promoted off-label uses may be subject to significant liability. Indeed, the FDA has very broad enforcement authority under the FFDCA, and failure to abide by these regulations can result in penalties, including the issuance of a warning letter directing entities to correct deviations from FDA standards, a requirement that future advertising and promotional materials be pre-cleared by the FDA, and state and federal civil and criminal investigations and prosecutions.

Whether or not FDA approval has been obtained, approval of a product by regulatory authorities in foreign countries must be obtained prior to the commencement of marketing of the product in those countries. The requirements governing the conduct of clinical trials and product approvals vary widely from country to country, and the time required for approval might be longer or shorter than that required for FDA approval. Although there are some procedures for unified filings for some European countries, in general, each country at this time has its own procedures and requirements. There can be no assurance that any foreign approvals would be obtained.

In addition to the regulatory framework for product approvals, we and our collaborative partners must comply with federal, state and local laws and regulations regarding occupational safety, laboratory practices, the use, handling and disposition of radioactive materials, environmental protection and hazardous substance control, and other local, state, federal and foreign regulations. All facilities and manufacturing processes used by third parties to produce our drug candidates for clinical use in the United States must conform with cGMPs. These facilities and practices are subject to periodic regulatory inspections to ensure compliance with cGMP requirements. Their failure to comply with applicable regulations could extend, delay, or cause the termination of clinical trials conducted for our drug candidates or of manufacturing and sale of any of our products approved for sale. We cannot accurately predict the extent of government regulation that might result from future legislation or administrative action.

Expedited Review and Accelerated Approval Programs

A sponsor may seek approval of its product candidate under programs designed to accelerate FDA's review and approval of NDAs. For example, Fast Track Designation may be granted to a drug intended for treatment of a serious

or life-threatening disease or condition that has potential to address unmet medical needs for the disease or condition. The key benefits of fast track designation are the eligibility for priority review, rolling review (submission of portions of an application before the complete marketing application is submitted), and accelerated approval, if relevant criteria are met. Based on results of clinical studies submitted in an NDA, upon the request of an applicant, the FDA may grant the NDA priority review designation, which sets the target date for FDA action on the application at six months after the FDA accepts the application for filing. Priority review is granted where there is evidence that the proposed product would be a significant improvement in the safety or effectiveness of the treatment, diagnosis, or prevention of a serious condition. If criteria are not met for priority review, the application is subject to the standard FDA review period of 10 months after FDA accepts the application for filing. Priority review designation does not change the scientific/medical standard for approval or the quality of evidence necessary to support approval.

Under the accelerated approval program, the FDA may approve an NDA on the basis of either a surrogate endpoint that is reasonably likely to predict clinical benefit, or on a clinical endpoint that can be measured earlier than irreversible morbidity or mortality, that is reasonably likely to predict an effect on irreversible morbidity or mortality or other clinical benefit, taking into account the severity, rarity, or prevalence of the condition and the availability or lack of alternative treatments. Post-marketing studies or completion of ongoing studies after marketing approval are generally required to verify the drug’s clinical benefit in relationship to the surrogate endpoint or ultimate outcome in relationship to the clinical benefit. In addition, the Food and Drug Administration Safety

and Innovation Act, or FDASIA, which was enacted and signed into law in 2012, established the new Breakthrough Therapy designation. A sponsor may seek FDA designation of its product candidate as a Breakthrough Therapy if the drug is intended, alone or in combination with one or more other drugs, to treat a serious or life-threatening disease or condition and preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over existing therapies on one or more clinically significant endpoints, such as substantial treatment effects observed early in clinical development.

European Union Drug Review and Approval

In the EEA (which is comprised of the 28 Member States of the European Union plus Norway, Iceland and Liechtenstein), medicinal products can only be commercialized after obtaining a Marketing Authorization, or MA. There are two types of MA:

The Community MA, which is issued by the European Commission through the Centralized Procedure, based on the opinion of the CHMP of the EMA, is valid throughout the entire territory of the EEA. The Centralized Procedure is mandatory for certain types of products, such as biotechnology medicinal products, orphan medicinal products, and medicinal products containing a new active substance indicated for the treatment of AIDS, cancer, neurodegenerative disorders, diabetes and auto-immune and viral diseases. The Centralized Procedure is optional for products containing a new active substance not yet authorized in the EEA, or for products that constitute a significant therapeutic, scientific or technical innovation or which are in the interest of public health in the EU.

National MAs, which are issued by the competent authorities of the Member States of the EEA and only cover their respective territory, are available for products not falling within the mandatory scope of the Centralized Procedure. Where a product has already been authorized for marketing in a Member State of the EEA, this National MA can be recognized in other Member States through the Mutual Recognition Procedure. If the product has not received a National MA in any Member State at the time of application, it can be approved simultaneously in various Member States through the Decentralized Procedure.

Under the above described procedures, before granting the MA, the EMA or the competent authorities of the Member States of the EEA make an assessment of the risk-benefit balance of the product on the basis of scientific criteria concerning its quality, safety and efficacy.

Orphan Drug Designation and Exclusivity

The Orphan Drug Act provides incentives for the development of products intended to treat rare diseases or conditions. Under the Orphan Drug Act, the FDA may grant orphan designation to a drug intended to treat a rare disease or condition, which is generally a disease or condition that affects fewer than 200,000 individuals in the United States, or more than 200,000 individuals in the United States and for which there is no reasonable expectation that the cost of developing and making a drug product available in the United States for this type of disease or condition will be recovered from sales of the product. If a sponsor demonstrates that a drug is intended to treat rare diseases or conditions, the FDA will grant Orphan Drug Designation for that product for the orphan disease indication. Orphan Drug Designation must be requested before submitting an NDA. After the FDA grants Orphan Drug Designation, the identity of the therapeutic agent and its potential orphan use are disclosed publicly by the FDA.

Orphan Drug Designation provides manufacturers with research grants, tax credits and eligibility for orphan drug exclusivity. If a product that has Orphan Drug Designation subsequently receives the first FDA approval of the active moiety for that disease or condition for which it has such designation, the product is entitled to orphan drug exclusivity, which for seven years prohibits the FDA from approving another product with the same active ingredient for the same indication, except in limited circumstances. If a drug designated as an orphan product receives marketing

approval for an indication broader than the orphan indication for which it received the designation, it will not be entitled to orphan drug exclusivity. Orphan exclusivity will not bar approval of another product under certain circumstances, including if a subsequent product with the same active ingredient for the same indication is shown to be clinically superior to the approved product on the basis of greater efficacy or safety, or providing a major contribution to patient care, or if the company with orphan drug exclusivity is not able to meet market demand. Further, the FDA may approve more than one product for the same orphan indication or disease as long as the products contain different active ingredients. Moreover, competitors may receive approval of for the same product but for a different indication for which the orphan product has exclusivity. As a result, even if we obtain orphan exclusivity, we may still be subject to competition.

In the EU, the EMA's Committee for Orphan Medicinal Products, or COMP, grants Orphan Drug Designation to promote the development of products that are intended for the diagnosis, prevention or treatment of life-threatening or chronically debilitating conditions affecting not more than five in 10,000 persons in the European Union and for which no satisfactory method of diagnosis, prevention, or treatment has been authorized (or the product would be a significant benefit to those affected). Additionally, designation is granted for products intended for the diagnosis, prevention, or treatment of a life-threatening, seriously debilitating or serious and chronic condition and when, without incentives, it is unlikely that sales of the drug in the EU would be sufficient to justify the necessary investment in developing the medicinal product. In the EU, Orphan Drug Designation entitles a party to financial incentives such as reduction of fees or fee waivers and 10 years of data exclusivity is granted following medicinal product approval.

This period may be reduced to six years if the Orphan Drug Designation criteria are no longer met after five years, including where it is shown that the product is sufficiently profitable not to justify maintenance of data exclusivity.

Orphan Drug Designation must be requested before submitting an application for marketing approval. Orphan Drug Designation does not convey any advantage in, or shorten the duration of, the regulatory review and approval process.

Pediatric Studies and Exclusivity

NDAs must contain data (or a proposal for post-marketing activity) to assess the safety and effectiveness of an investigational new drug product for the claimed indications in all relevant pediatric populations in order to support dosing and administration for each pediatric subpopulation for which the drug is safe and effective. The FDA may, on its own initiative or at the request of the applicant, grant deferrals for submission of some or all pediatric data until after approval of the product for use in adults or full or partial waivers if certain criteria are met. The requirements for pediatric data do not apply to any drug for an indication for which orphan designation has been granted.

Pediatric exclusivity is another type of non-patent exclusivity in the United States and, if granted, provides for the attachment of an additional six months of marketing protection to the term of any existing regulatory exclusivity, including the five-year and three-year non-patent and orphan exclusivity. This six-month exclusivity may be granted if an NDA or Biologic License Application sponsor submits pediatric data that fairly respond to a written request from the FDA for such data. The data do not need to show the product to be effective in the pediatric population studied; rather, if the clinical study is deemed to fairly respond to the FDA's request, the additional protection is granted. If reports of FDA-requested pediatric studies are submitted to and accepted by the FDA within the statutory time limits, whatever statutory or regulatory periods of exclusivity or patent protection cover the product are extended by six months. This is not a patent term extension, but it effectively extends the regulatory period during which the FDA cannot approve another application relying on the NDA sponsor's data. We have applied for this additional six-month pediatric extension for PROCYSBI.

Hatch-Waxman Amendments and Exclusivity

As an alternative path to FDA approval for modifications to formulations or uses of products previously approved by the FDA, an applicant may submit an NDA under Section 505(b)(2) of the FDCA. Section 505(b)(2) was enacted as part of the Hatch-Waxman Amendments and 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. If the 505(b)(2) applicant can establish that reliance on FDA's previous findings of safety and effectiveness is scientifically appropriate, it may eliminate the need to conduct certain preclinical or clinical studies of the new product. The FDA may also require companies to perform additional studies or measurements, including clinical trials, to support the change from the approved branded reference drug. The FDA may then approve the new product candidate for all, or some, of the label indications for which the branded reference drug has been approved, as well as for any new indication sought by the 505(b)(2) applicant.

In seeking approval for a drug through an NDA, including a 505(b)(2) NDA, applicants are required to list with the FDA certain patents whose claims cover the applicant's product. Upon approval of an NDA, each of the patents listed in the application for the drug is then published in the Orange Book. Any applicant who files an abbreviated new drug application, or ANDA, seeking approval of a generic equivalent version of a drug listed in the Orange Book or a 505(b)(2) NDA referencing a drug listed in the Orange Book must satisfy a number of conditions prior to FDA approval and marketing of the generic product. Initially, an ANDA filer must certify to the FDA that (1) no patent information on the drug product that is the subject of the application has been submitted to the FDA; (2) such patent has expired; (3) the date on which such patent expires; or (4) such patent is invalid or will not be infringed upon by the manufacture, use or sale of the drug product for which the application is submitted. This last certification is known as

a paragraph IV certification. A notice of the paragraph IV certification must be provided to each owner of the patent that is the subject of the certification and to the holder of the approved NDA to which the ANDA or 505(b)(2) application refers. In certain limited circumstances in which the Orange Book only lists patents for methods of using the drug product, the applicant may instead choose to submit a “section viii” statement (instead of a paragraph IV certification) stating that its proposed label does not describe the patented method of use.

Following notice of a Paragraph IV certification, the NDA holder and patent owners can block FDA approval of the ANDA by filing a lawsuit against the ANDA filer asserting that the generic product infringes one or more of the Orange Book listed patents. As long as the patent infringement suit is filed within 45 days of the receipt of the paragraph IV certification notice, the FDA is automatically prohibited from approving the application for 30 months from the receipt of the paragraph IV certification unless (i) the patents expire, (ii) the ANDA filer receives a verdict in its favor, or (iii) the parties settle the lawsuit. Further, if the NDA holder's suit is successful, the FDA will be barred from approving the ANDA until all of the asserted patents have expired. The FDA also cannot approve an ANDA or 505(b)(2) application until all applicable non-patent exclusivities listed in the Orange Book for the branded reference drug have expired. For example, a pharmaceutical manufacturer may obtain five years of non-patent exclusivity upon NDA

approval of a new chemical entity, (NCE), which is a drug containing an active moiety that has not been approved by FDA in any other NDA. An “active moiety” is defined as the molecule responsible for the drug substance’s physiological or pharmacologic action. During that five-year exclusivity period, the FDA cannot accept for filing (and therefore cannot approve) any ANDA seeking approval of a generic version of that drug or any 505(b)(2) NDA that relies on the FDA's approval of the drug, provided that that the FDA may accept an ANDA four years into the NCE exclusivity period if the ANDA applicant also files a paragraph IV certification.

A drug, including one approved under Section 505(b)(2), may obtain a three-year period of exclusivity for a particular condition of approval, or change to a marketed product, such as a new formulation for a previously approved product, if one or more new clinical studies (other than bioavailability or bioequivalence studies) was essential to the approval of the application and was conducted/sponsored by the applicant. Should this occur, the FDA would be precluded from approving any ANDA or 505(b)(2) application for the protected modification until after that three-year exclusivity period has run. However, unlike NCE exclusivity, the FDA can accept an application and begin the review process during the exclusivity period.

Coverage and Reimbursement

The commercial success of PROCYSBI, QUINSAIR and our drug candidates and our ability to commercialize those products successfully will depend in part on the extent to which governmental payor programs , including Medicare and Medicaid in the United States with respect to PROCYSBI, provincial and federa1 governmental authorities in Canada and European regional and national governmental authorities throughout Europe, with respect to QUINSAIR, private health insurers and other third-party payors provide adequate coverage and reimbursement. These third-party payors generally develop their own policies as to which drugs they will pay for and the reimbursement levels for the drugs. For example, governmental programs in the United States often require manufacturers to pay certain rebates or otherwise provide discounts to secure coverage of drug products. To control healthcare expenditures generally, in the United States, the EU and other potentially significant markets for PROCYSBI, QUINSAIR and our drug candidates, government authorities and third party payors are increasingly attempting to limit or regulate the price of medical products and services, particularly for new and innovative products and therapies. The measures taken often have resulted in lower average selling prices. Further, the increased emphasis on managed healthcare in the United States and on country and regional pricing and reimbursement controls in the EU places additional pressure on product pricing, reimbursement and usage, which may adversely affect our future product sales and results of operations. These pressures can arise from rules and practices of managed care groups, judicial decisions and governmental laws and regulations related to Medicare, Medicaid and healthcare reform, as well as drug coverage and reimbursement policies and pricing in general.

Some of the additional requirements and restrictions on coverage and reimbursement levels imposed by third-party payors influence the purchase of healthcare services and products. For example, there may be limited coverage to specific drug products on an approved list, or formulary, which, in the United States, might not include all of the FDA-approved drug products for a particular indication. There may also be formulary placements that result in lower reimbursement levels and higher cost-sharing borne by patients. Further, third-party payors are increasingly examining the medical necessity and cost-effectiveness of medical products and services, in addition to their safety and efficacy. We may need to conduct expensive pharmacoeconomic studies in order to demonstrate the medical necessity and cost-effectiveness of our products, in addition to the costs required to obtain the FDA, EMA and Health Canada approvals. Our products may not be considered medically necessary or cost-effective. Even if a third-party payor determines to provide coverage for a drug product, adequate reimbursement may not be available to enable us to maintain price levels sufficient to realize an appropriate return on our investment in drug development. In some countries in Europe, pricing and reimbursement are separate processes; thus, an authority may approve PROCYSBI or QUINSAIR but deny national reimbursement for it. In the EU and Canada, reimbursement rates may be determined by comparison to approved therapeutic competitors, review of pricing of the same product in other countries and, in

some circumstances, through health technology assessments that seek to quantify how the expected benefits at a price may influence the cost and quality of patient care. Because we have just begun the process of providing guidance to the relevant pricing and reimbursement authorities for QUINSAIR in anticipation of our launch of that product in the EU and Canada, we cannot predict what cost containment measures such third party payors may seek to apply. Whereas the majority of health authorities in Europe have supported patient access to inhaled antibiotics, budget constraints may affect the pricing we are able to achieve, and because inhaled levofloxacin has not previously been marketed in Europe, the lack of external reference data contributes to the difficulty in predicting pricing and reimbursement outcomes.

Healthcare legislative proposals to reform healthcare or reduce costs under government insurance programs may also result in lower reimbursement for our drugs and drug candidates or exclusion of our drugs and drug candidates from coverage altogether. The cost containment measures that healthcare payors and providers are instituting and any healthcare reform could significantly reduce our revenues from the sale of PROCYSBI, QUINSAIR and any of our approved drug candidates. We cannot provide any assurances that we will be able to obtain and maintain third party coverage or adequate reimbursement for PROCYSBI, QUINSAIR or any of our approved drug candidates in whole or in part.

Healthcare Reform

With respect to legislative reform, in the United States, there have been and continue to be a number of significant legislative initiatives to contain healthcare costs. For example, in March 2010, the Affordable Care Act was passed, which substantially changes the way health care is financed by both governmental and private insurers, and significantly impacts the U.S. pharmaceutical industry. The Affordable Care Act, among other things, subjects biologic products to potential competition by lower-cost biosimilars, addresses a new methodology by which rebates owed by manufacturers under the Medicaid Drug Rebate Program are calculated for drugs that are inhaled, infused, instilled, implanted or injected, increases the minimum Medicaid rebates owed by manufacturers under the Medicaid Drug Rebate Program and extends the rebate program to individuals enrolled in Medicaid managed care organizations, establishes annual fees and taxes on manufacturers of certain branded prescription drugs, and a new Medicare Part D coverage gap discount program, in which manufacturers must agree to offer 50% point-of-sale discounts off negotiated prices of applicable brand drugs to eligible beneficiaries during their coverage gap period, as a condition for the manufacturer's outpatient drugs to be covered under Medicare Part D.

In addition, other legislative changes have been proposed and adopted in the United States since the Health Care Reform Law was enacted. On August 2, 2011, the Budget Control Act of 2011 among other things, created measures for spending reductions by Congress. A Joint Select Committee on Deficit Reduction, tasked with recommending a targeted deficit reduction of at least $1.2 trillion for the years 2013 through 2021, was unable to reach required goals, thereby triggering the legislation's automatic reduction to several government programs. This includes aggregate reductions of Medicare payments to providers of 2% per fiscal year, which went into effect in April 2013, due to subsequent legislative amendments to the statute, and will remain in effect through 2025 unless additional Congressional action is taken.

We expect that additional state and federal healthcare reform measures could be adopted in the future, any of which could limit the amounts that federal and state governments will pay for healthcare products and services, which could result in reduced demand for our product candidates or additional pricing pressures.

Other Healthcare Laws

We are also subject to healthcare regulation and enforcement by the federal government and the states and foreign governments in which we conduct our business. These laws include, without limitation, state and federal anti-kickback, fraud and abuse, false claims, privacy and security and physician sunshine laws and regulations.

The federal Anti-Kickback Statute prohibits, among other things, any person from knowingly and willfully offering, soliciting, receiving or providing remuneration, directly or indirectly, to induce either the referral of an individual, for an item or service or the purchasing or ordering of a good or service, for which payment may be made under federal healthcare programs such as the Medicare and Medicaid programs. The Anti-Kickback Statute is subject to evolving interpretations. In the past, the government has enforced the Anti-Kickback Statute to reach large settlements with healthcare companies based on sham consulting and other financial arrangements with physicians. A person or entity does not need to have actual knowledge of the statute or specific intent to violate it in order to have committed a violation. 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 federal False Claims Act. The majority of states also have anti-kickback laws which establish similar prohibitions and in some cases may apply to items or services reimbursed by any third-party payor, including commercial insurers.

Additionally, the civil False Claims Act prohibits knowingly presenting or causing the presentation of a false, fictitious or fraudulent claim for payment to the United States government. Actions under the False Claims Act may be brought by the Attorney General or as a qui tam action by a private individual in the name of the government.

Violations of the False Claims Act can result in very significant monetary penalties and treble damages. The federal government is using the False Claims Act, and the accompanying threat of significant liability, in its investigation and prosecution of pharmaceutical and biotechnology companies throughout the country, for example, in connection with the promotion of products for unapproved uses and other sales and marketing practices. The government has obtained multi-million and multi-billion dollar settlements under the False Claims Act in addition to individual criminal convictions under applicable criminal statutes. Given the significant size of actual and potential settlements, it is expected that the government will continue to devote substantial resources to investigating healthcare providers' and manufacturers' compliance with applicable fraud and abuse laws.

The federal Health Insurance Portability and Accountability Act of 1996, or HIPAA, also created new federal criminal statutes that prohibit among other actions, knowingly and willfully executing, or attempting to execute, a scheme to defraud any healthcare benefit program, including private third-party payors, knowingly and willfully embezzling or stealing from a healthcare benefit program, willfully obstructing a criminal investigation of a healthcare offense, and knowingly and willfully falsifying, concealing or covering up a material fact or making any materially false, fictitious or fraudulent statement in connection with the delivery of or

payment for healthcare benefits, items or services. Similar to the federal Anti-Kickback Statute, a person or entity does not need to have actual knowledge of the statute or specific intent to violate it in order to have committed a violation.

In addition, a person who offers or transfers to a Medicare or Medicaid beneficiary any remuneration, including waivers of co-payments and deductible amounts (or any part thereof), that the person knows or should know is likely to influence the beneficiary's selection of a particular provider, practitioner or supplier of Medicare or Medicaid payable items or services may be liable for civil monetary penalties of up to $10,000 for each wrongful act. Moreover, in certain cases, providers who routinely waive copayments and deductibles for Medicare and Medicaid beneficiaries can also be held liable under the Anti-kickback Statute and civil False Claims Act, which can impose additional penalties associated with the wrongful act. One of the statutory exceptions to the prohibition is non-routine, unadvertised waivers of copayments or deductible amounts based on individualized determinations of financial need or exhaustion of reasonable collection efforts. The Office of Inspector General of the Department of Health and Human Services emphasizes, however, that this exception should only be used occasionally to address special financial needs of a particular patient. Although this prohibition applies only to federal healthcare program beneficiaries, the routine waivers of copayments and deductibles offered to patients covered by commercial payers may implicate applicable state laws related to, among other things, unlawful schemes to defraud, excessive fees for services, tortious interference with patient contracts and statutory or common law fraud. To the extent our patient assistance programs are found to be inconsistent with applicable laws, we may be required to restructure or discontinue such programs, or be subject to other significant penalties.

There has also been a recent trend of increased federal and state regulation of payments made to physicians and other healthcare providers. The Patient Protection and Affordable Care Act, as amended by the Health Care and Education Reconciliation Act, or collectively, the Affordable Care Act, among other things, imposes new reporting requirements on drug manufacturers for payments made by them to physicians and teaching hospitals, as well as ownership and investment interests held by physicians and their immediate family members. Failure to submit required information may result in civil monetary penalties of up to an aggregate of $150,000 per year (or up to an aggregate of $1 million per year for "knowing failures"), for all payments, transfers of value or ownership or investment interests that are not timely, accurately and completely reported in an annual submission. Drug manufacturers were required to begin collecting data on August 1, 2013 and submit reports to the government by March 31, 2014 and June 30, 2014, and the 90th day of each subsequent calendar year. Certain states also mandate implementation of compliance programs, impose restrictions on drug manufacturer marketing practices and/or require the tracking and reporting of gifts, compensation and other remuneration to physicians.

We may also be subject to data privacy and security regulation by both the federal government and the states in which we conduct our business. HIPAA, as amended by the Health Information Technology and Clinical Health Act, or HITECH, and their respective implementing regulations, including the final omnibus rule published on January 25, 2013, imposes specified requirements relating to the privacy, security and transmission of individually identifiable health information. Among other things, HITECH makes HIPAA's privacy and security standards directly applicable to "business associates," defined as independent contractors or agents of covered entities that create, receive, maintain or transmit protected health information in connection with providing a service for or on behalf of a covered entity. HITECH also increased the civil and criminal penalties that may be imposed against covered entities, business associates and possibly other persons, and gave state attorneys general new authority to file civil actions for damages or injunctions in federal courts to enforce the federal HIPAA laws and seek attorney's fees and costs associated with pursuing federal civil actions. In addition, state laws govern the privacy and security of health information in certain circumstances, many of which differ from each other in significant ways, thus complicating compliance efforts.

The shifting commercial compliance environment and the need to build and maintain robust and expandable systems to comply with different compliance and/or reporting requirements in multiple jurisdictions increase the possibility

that a healthcare company may violate one or more of the requirements. If our operations are found to be in violation of any of such laws or any other governmental regulations that apply to us, we may be subject to penalties, including, without limitation, civil and criminal penalties, damages, fines, the curtailment or restructuring of our operations, exclusion from participation in federal and state healthcare programs and imprisonment, any of which could adversely affect our ability to operate our business and our financial results.

Manufacturing

PROCYSBI drug product and the active pharmaceutical ingredient (API), cysteamine bitartrate, are manufactured on a contract basis by third parties. QUINSAIR drug product, and its API, levofloxacin, and the Zirela nebulizer device are all manufactured on a contract basis by third parties. We believe that our third party manufacturers all have sufficient manufacturing capacity to support our commercial and clinical demands for PROCYSBI for the foreseeable future as well as the clinical and commercial requirements for the initial launch of QUINSAIR.

In general we expect to continue to contract with outside providers for manufacturing services, including API and drug product manufacture, encapsulation, vialing and packaging. Third-party manufacturers' facilities are subject to periodic inspections to confirm compliance with applicable law and must be GMP certified. We are aware that the EMA plans to inspect the manufacturing facilities

of our PROCYSBI drug product manufacturer in the first half of 2016. Although we have never experienced a material disruption in supply from our contract manufacturers, we cannot assure that such a disruption will not occur in the future.

Research and Development

We have an active research and development effort. We plan to focus our research and development efforts in the discovery, research, preclinical and clinical development of our drug candidates in order to provide therapies that we believe will be safer, less intrusive and more effective than current approaches in treating a wide variety of disorders. During the years ended December 31, 2015, 2014, and 2013, we incurred approximately $58.6 million, $43.5 million, and $29.2 million, respectively, in research and development expenses.

Operating Segment and Geographic Information

Operating segments are components of an enterprise for which separate financial information is available and is evaluated regularly by a company in deciding how to allocate its resources and to assess its performance. We have reviewed how we allocate our resources and analyze performance worldwide and have determined that, because employees work on integrated programs in the United States and in Europe, encompassing all stages of product development and commercialization, we operate in one segment.

Compliance with Environmental Laws

We estimate the annual cost of compliance with environmental laws, comprised primarily of hazardous waste removal, will not be material.

Employees

As of December 31, 2015, we had 158 full time employees (126, 30, and 2 in the United States, EU and Canada, respectively). Of the 158 employees, 49 are sales and marketing, and 44 are general and administrative personnel, 6 are in manufacturing, 15 in quality control and assurance, and 44 are in research and development. Based on our current plan, over the next 12-month period we intend to expand our employee base across most functions in the Company. None of our employees are represented by a collective bargaining unit.

Facilities

Our primary offices are located at 7 Hamilton Landing, Suite 100, Novato, CA 94949. Our main phone number is (415) 408-6200 and our facsimile number is (415) 382-8002. Our European headquarters are located at Naritaweg 165, 1043 BW Amsterdam, Netherlands and we have administrative offices in Utrecht, Netherlands.

Website

Our corporate website is located at www.raptorpharma.com. Any information contained in, or that can be accessed through, our website is not incorporated by reference into this Annual Report on Form 10-K.

Available Information

Our annual reports on Form 10-K, quarterly reports on Form 10-Q, current reports on Form 8-K, and amendments to those reports filed or furnished pursuant to Section 13(a) or 15(d) of the Exchange Act may be accessed through the SEC’s website at www.sec.gov and on our website at www.raptorpharma.com free of charge. Such filings are placed

on our website as soon as reasonably practicable after they are filed with the SEC. Our code of business conduct and ethics, audit committee charter, corporate governance and nominating committee charter and compensation committee charter are also posted on our website.

ITEM 1A: RISK FACTORS

Investing in our common stock involves a high degree of risk. Before deciding whether to invest in our common stock, you should consider carefully the risk factors described below, together with the other information contained in this Annual Report on Form 10-K and other documents we file with the SEC, such as our quarterly reports on Form 10 Q, our current reports on Form 8 K and any public announcements we make from time to time. If any of these risks actually occur, it may materially harm our business, financial condition, operating results or cash flow. As a result, the market price of our common stock could decline, and you could lose all or part of your investment. Additional risks and uncertainties that are not yet identified or that we think are immaterial may also materially harm our business, operating results and financial condition and could result in a complete loss of your investment.

Risks Associated with Commercialization and Product Development

Our revenues currently depend on the success of our only current commercial drug, PROCYSBI, for the management of nephropathic cystinosis.

PROCYSBI is our only currently marketed product and as a result, our net revenue and operating results substantially depend on the continued commercial success of PROCYSBI. We commenced marketing for PROCYSBI in the United States in June 2013 and Europe in April 2014. In the United States, we are permitted to market PROCYSBI for the management of nephropathic cystinosis in adults and children two years and older. In September 2013, we received marketing authorization from the European Commission ("EC") to commercialize PROCYSBI for the treatment of proven nephropathic cystinosis in the European Economic Area ("EEA"). We commenced commercial sales of PROCYSBI in Germany in April 2014 and have launched commercial sales in select additional countries in Europe. We have no assurance of securing reimbursement or subsequently launching in additional countries in the EEA. We believe that our results of operations and, in particular, our net product sales of PROCYSBI will affect the trading price of our common stock substantially. If PROCYSBI sales do not meet market expectations, our stock price may significantly decrease.

Our ability to successfully commercialize our current and any other future drug products will depend on multiple factors, including:

- our ability to provide acceptable evidence of the safety and efficacy of our products;
- compliance with regulatory requirements, including fulfilling post-approval commitments;
- our ability to obtain approval by regulatory agencies in other countries, including appropriate product labeling;
- the effect of current and future healthcare laws;
- the manufacture and supply of adequate quantities of our products in compliance with current good manufacturing practices as needed to meet commercial demand;
- adequate coverage and reimbursement for our products from commercial health plans and government health programs, which we refer to collectively as "third-party payors";
- our ability to obtain acceptable prices in EEA countries and other select territories, including acceptable reimbursement at the country-specific price;
- limitations or warnings currently contained in or as may later be required in approved labeling and the breadth of product labeling or product insert requirements;
- our ability to enter into agreements with wholesalers, distributors and pharmacies on commercially reasonable terms; and
- the protection, development and maintenance of intellectual property and other commercial product protection for our products.

If we fail to grow sales of PROCYSBI in existing markets, to successfully sell PROCYSBI in other countries or to successfully commercialize QUINSAIR or any other future products within a reasonable time period, we will have reduced financial resources and will be unable to fully execute our business plans, and our results of operations and financial condition will be materially adversely affected.

Our ability to generate significant product sales from our products is dependent upon market acceptance among physicians, patients, patient families, third-party payors and the healthcare community.

Our current and any future drug products may not attain or maintain market acceptance among physicians, patients, patient families, third-party payors or the healthcare community compared to the current and evolving standards of care and to standards of care from new competitors. We believe that the degree of market acceptance and our ability to generate significant product sales of our current and any future drug products will depend on a number of factors, including:

- the efficacy, safety, availability and ease of administration of our products relative to alternative treatments;
- the price of our products, both in absolute terms and relative to the quality of therapeutic benefits and price of alternative treatments;
- the timing of market introductions of our products and product lines relative to competitive treatments;
- the nature of publicity related to our products relative to the publicity related to our competitors' products;
- the prevalence and severity of adverse side effects of our current and any future products relative to competitive products;

- good patient compliance to therapy;
- availability of coverage and adequate reimbursement from third-party payors;
- provision of affordable out-of-pocket costs to patients and/or other programs to ensure patient access to our products; and
- the identification of currently diagnosed and undiagnosed patients and continued growth of the cystinosis and cystic fibrosis markets and the markets for any other future products.

Our efforts to educate patients, physicians, parents, the medical community and third-party payors on the benefits of our products may require significant resources and may not be successful at the levels planned. If our products do not achieve and maintain significant market acceptance among physicians, patients, patient families, third-party payors and the healthcare community, our business, results of operations and financial condition will be materially adversely affected.

The amount of our product sales in the EEA is dependent in part upon the pricing and reimbursement decisions adopted in each of the EEA countries, which may not be at acceptable levels to us.

One or more EEA countries may not support pricing within our target pricing and reimbursement range for our products due to budgetary decisions made by regional, national and local health authorities and third-party payors in the EEA, which would negatively affect our revenues. The pricing and reimbursement process in EEA countries can be lengthy, involved and difficult to predict.. Failure to timely complete the pricing and reimbursement process in the EEA countries will delay our ability to market PROCYSBI, to bring QUINSAIR to market in the EEA and to derive revenues from those countries.

We may be subject to penalties and litigation and large incremental expenses if we fail to comply with regulatory requirements or experience problems with our products.

Even after we achieve regulatory approvals, we are subject to ongoing obligations and continued regulatory review with respect to many operational aspects including our manufacturing processes, labeling, packaging, distribution, storage, adverse event monitoring and reporting, dispensation, advertising, promotion and recordkeeping. These requirements include submissions of safety and other post-marketing information and reports, ongoing maintenance of product registration and continued compliance with good manufacturing practices, or GMPs, good clinical practices, or GCPs, good pharmacovigilance practice, or GVPs, good distribution practices, or GDPs, and good laboratory practices, or GLPs. We are in the process of implementing corrective and preventive actions that we expect will complete in the first quarter of 2016 related to our pharmacovigilance system to address findings issued in August 2015 following a routine inspection from a European regulatory authority in June 2015 and our own internal reviews of our internal processes.

If we, our products or product candidates, or the third-party manufacturing facilities for our products or product candidates fail to comply with applicable regulatory requirements, a regulatory agency may:

- impose injunctions or restrictions on the marketing, manufacturing or distribution of a product, suspend or withdraw product approvals, revoke necessary licenses or suspend product reimbursement;
- issue warning letters, show cause notices or untitled letters describing alleged violations, which may be publicly available;
- suspend any ongoing clinical trials or delay or prevent the initiation of clinical trials;
- delay or refuse to approve pending applications or supplements to approved applications we have filed;
- refuse to permit drugs or precursor or intermediary chemicals to be imported or exported to or from the United States;
- suspend or impose restrictions or additional requirements on operations, including costly new manufacturing quality or pharmacovigilance requirements;

- seize or detain products or require us to initiate a product recall; and/or
- commence criminal investigations and prosecutions.

Moreover, existing regulatory approvals and any future regulatory approvals that we obtain will be subject to limitations on the approved indicated uses and patient populations for which our products may be marketed, the conditions of approval, requirements for potentially costly, post-market testing and requirements for surveillance to monitor the safety and efficacy of the products. In the EEA, the advertising and promotion of pharmaceuticals is strictly regulated. The direct-to-consumer promotion of prescription pharmaceuticals is not permitted, and some countries in the EEA require the notification and/or prior authorization of promotional or advertising materials directed at healthcare professionals. The FDA, European Medicines Agency (“EMA”), EC and other authorities in the EEA countries strictly regulate the promotional claims that may be made about prescription products, and our product labeling,

advertising and promotion are subject to continuing regulatory review. Physicians nevertheless may prescribe our products to their patients in a manner that is inconsistent with the approved label or that is off-label. Positive clinical trial results in any of our product development programs increase the risk that approved pharmaceutical forms of the same active pharmaceutical ingredients may be used off-label in those indications. Our investigational product candidate RP103 is comprised of the same active pharmaceutical ingredient ("API") as PROCYSBI. If we are found to have improperly promoted off-label uses of approved products, we may be subject to significant sanctions, civil and criminal fines and injunctions prohibiting us from engaging in specified promotional conduct.

In addition, engaging in improper promotion of our products for off-label uses in the United States can subject us to false claims litigation under federal and state statutes. These false claims statutes in the United States include the federal False Claims Act, which allows any individual to bring a lawsuit against a pharmaceutical company on behalf of the federal government alleging submission of false or fraudulent claims or causing to present such false or fraudulent claims for payment by a federal program such as Medicare or Medicaid. Growth in false claims litigation has increased the risk that a pharmaceutical company will have to defend a false claim action, pay civil money penalties, settlement fines or restitution, agree to comply with burdensome reporting and compliance obligations and be excluded from Medicare, Medicaid and other federal and state healthcare programs.

The regulations, policies or guidance of regulatory agencies may change and new or additional statutes or government regulations may be enacted that could prevent or delay regulatory approval of our product candidates or further restrict or regulate post-approval activities. For example, the Food and Drug Administration Safety and Innovation Act ("FDASIA"), requires the FDA to issue new guidance describing its policy regarding internet and social media promotion of regulated medical products, and the FDA may soon specify new restrictions on this type of promotion. In January 2014, the FDA released draft guidance on how drug companies can fulfill their regulatory requirements for post-marketing submission of interactive promotional media, and though the guidance provided insight into how the FDA views a company's responsibility for certain types of social media promotion, there remains a substantial amount of uncertainty. We cannot predict the likelihood, nature or extent of adverse government regulation that may arise from pending or future legislation or administrative action, either in the United States or abroad. If we are unable to achieve and maintain regulatory compliance, we will not be permitted to market our drugs, which would materially adversely affect our business, results of operations and financial condition.

If we are unable to expand the use of RP103 or MP-376 pursuant to regulatory approval for additional clinical indications or geographic territories, or are unable to obtain regulatory approval for other product candidates, we may delay or terminate some of our product development activities. This would adversely affect the long term value of RP103, MP-376 or other product candidates as well as our growth prospects.

The research, testing, manufacturing, clinical development, labeling, approval, sale, marketing and distribution of drug products, among other things, are subject to extensive regulation by the FDA and other regulatory authorities in the United States and by similar foreign governmental regulatory entities. We are not permitted to market any of our drug product candidates unless we obtain and maintain appropriate marketing approvals from regulatory agencies in each of the markets in which we intend to market our products. Once approved, we may only market our products for the specific uses that are reflected in the product's approved labeling. A product's approved labeling may contain limitations or warnings or may be for different patient populations or for fewer or more limited indications than we request in our pre-market approval application, which could result in limiting reimbursement, access for intended use or the commercial profile of a drug. In the United States, we are permitted to market the active pharmaceutical ingredient of RP103 in the formulation of a final drug product and in the doses approved under the brand name PROCYSBI only for the management of nephropathic cystinosis in adults and children two years and older. We are permitted to market PROCYSBI in the EEA as an orphan medicinal product for the treatment of proven nephropathic cystinosis. MP-376 has been approved for marketing in Canada and the European Union ("EU") under the specific indication as a medicinal product for the management of chronic pulmonary infections due to Pseudomonas

aeruginosa in adults 18 years and older with cystic fibrosis. Neither RP103 nor MP-376 has been approved in any other market or for any other disease indication. There can be no assurance that we will obtain regulatory approval for any other uses for our product candidates or that, even if we obtained additional approvals, we would be able to commercialize the product candidates successfully.

A new drug application ("NDA"), submitted to the FDA, or a marketing authorization application ("MAA"), submitted to the EMA, must be supported by extensive clinical and preclinical data, as well as extensive information regarding chemistry, manufacturing and controls. This information must demonstrate the safety and efficacy of the applicable product candidate for the management of each individual indication to the satisfaction of the applicable regulatory authority. Obtaining approval of an NDA, MAA or any other filing for marketing authorization in a foreign country for a drug product candidate is an extensive, expensive and uncertain process. The time required to obtain approval by the FDA and comparable foreign authorities is unpredictable but typically takes many years following the commencement of clinical trials and depends upon numerous factors, including the substantial discretion of the regulatory authorities. The FDA, EC, EMA or other regulatory authorities may delay, limit or deny approval of RP103, MP-376 or our future drug product candidates for many reasons, including:

- the results of clinical trials may not meet the level of statistical or clinical significance required by regulatory authorities for approval;
- regulatory authorities may disagree with the number, design, size, conduct or implementation of our clinical trials; they may change the requirements for approval even after having reviewed and commented on the design for our clinical trials;
- regulatory authorities may not find the data from preclinical studies and clinical trials sufficient to demonstrate that product candidates have adequate clinical and other benefits or adequate safety profiles, even if they achieve their specified endpoints in clinical trials; or they may disagree with our interpretation of data from preclinical studies or clinical trials and/or require that we conduct additional trials;
- regulatory authorities may not accept data generated at our clinical trial sites;
- if requested by us, regulatory authorities may not hold an advisory committee meeting in a timely manner or at all, or, if an advisory committee is convened it may recommend against approval of our application or may recommend that the regulatory agency require, as a condition of approval, additional preclinical studies or clinical trials; approval may also be contingent on a Risk Evaluation and Mitigation Strategy, which limits the labeling, distribution or promotion of a drug product;
- regulatory authorities may require additional preclinical or clinical studies or other data prior to granting approval, and we may not be able to generate the required data on a timely basis, if at all;
- regulatory authorities may identify deficiencies in the manufacturing processes or in the facilities of our third-party suppliers and/or contract manufacturers or may require us to manufacture additional validation batches or change our submitted regulatory documents, process, specifications or third-party suppliers or contract manufacturers; and
- we may not be able to validate manufacturing processes to the satisfaction of the regulatory authorities.

With respect to QUINSAIR, the FDA has indicated in previous written communications that it believes the data submitted in connection with EMA's subsequent approval of MP-376 for the management of chronic pulmonary infections due to Pseudomonas aeruginosa in adults with cystic fibrosis does not provide substantial evidence of efficacy and safety to support FDA approval of MP-376 for treatment of patients with cystic fibrosis. The FDA identified a number of limitations with the design of the pivotal trial upon which approval of QUINSAIR in the EU and Canada was based that, in the FDA's view, impacts its ability to be used as a pivotal efficacy study. The FDA also questioned whether patients in the study achieved any overall benefit, as the primary endpoint in the study was not met. We intend to discuss potential registration strategies with the FDA. We may not agree with the developmental pathway that the FDA recommends or be able to conduct the clinical trials that the FDA requests, which would limit our ability to seek regulatory approval for MP-376 in the United States.

If we fail to gain regulatory approval for RP103 or MP-376 for other indications, in additional geographic jurisdictions, or for our other future drug product candidates, we will have to delay or terminate some or all of our research product development programs, and our business, results of operations and financial condition will be materially adversely affected.

We do not have internal manufacturing capabilities. In the near term, we expect to continue to rely on a single source supplier for our API for PROCYSBI and a single third-party manufacturer for the conversion to finished commercial drug product. Similarly, we expect to utilize single source suppliers for the QUINSAIR API, drug product and delivery device, upon commercial launch. We also rely on third parties for the distribution and pharmaceutical services of PROCYSBI in the United States and the EEA. If we are unable to rely on these third parties, our revenue will be delayed or diminished and our business, results of operations and financial condition will be materially adversely affected.

We do not own or operate manufacturing facilities and currently lack the in-house capability to manufacture our current products or product candidates. As a result, we currently contract with external contract manufacturing organizations ("CMOs"), for commercial and clinical quantities of our products for the indications under development. We rely on a single source supplier for our cysteamine API. While we have procured additional manufacturing support with a second provider for clinical supply of PROCYSBI,

we will continue to rely on a single third-party manufacturer for supply of finished commercial product. Our ability to obtain sufficient quantities of PROCYSBI and RP103 is constrained by limited supplies of raw materials and the limited capacity and output of these third parties. Furthermore, any reduction, delay or interruption in our supply of APIs from the single source supplier or of our supply of finished goods from our CMOs could result in significant additional operating costs, interruptions in product supply, delays in sales of PROCYSBI, delays in the commercial launch of QUINSAIR, and delays in developing RP103 and MP-376 for additional indications. In addition, supply arrangements from alternative sources not currently under contract may not be available on acceptable economic terms, if at all.

The manufacture of pharmaceutical products requires significant expertise and capital investment, including the development of advanced manufacturing techniques and process controls. Pharmaceutical products have stringent specifications for product quality including stability that must be maintained within product specifications. Manufacturers of pharmaceutical products often encounter difficulties in production, particularly in scaling up initial production volume to commercial requirements as more batches are produced and usually at greatly increased scale per batch. Assessing process capability takes time after launch of a pharmaceutical product as process experience grows with manufacturing experience and products are periodically evaluated for improvements or specification revisions. Moreover, cysteamine bitartrate is difficult to manufacture because the molecule is labile and can be sensitive to process and stability conditions. Difficulties may arise related to internal processes, production costs and yields, quality control, including stability of the product and quality control testing, sourcing scarcities, resource constraints, equipment problems, shortages of qualified personnel, labor disputes, severe weather events, unstable political environments or financial difficulties at foreign facilities, as well as compliance with strictly enforced federal, state and foreign regulations. Manufacturers may breach their agreements with us or may terminate or decline to renew their agreements with us, whether due to our breach of the relevant agreements or based on their own business priorities. In addition, due to our small patient population, the manufacture of our drug may be given lower priority on the production line if manufacturing priority is decided by scale. As a result of the above-discussed issues, contract manufacturers may decide that the business risk associated with products such as ours is not justified.

Manufacturers and suppliers are subject to regulatory requirements covering, among other things, manufacturing, process controls, testing, quality control and record keeping and are subject to ongoing inspections by regulatory agencies. We have no direct control over the ability of our contract manufacturing parties to maintain adequate quality control, quality assurance and qualified personnel, and while final outputs are reviewed by our own internal quality control, we depend on our third-party supplier and manufacturers for compliance with the FDA's current cGMP requirements and other FDA requirements, the Drug Enforcement Administration's regulations and other rules and regulations prescribed by applicable non-U.S. regulatory authorities. If our contract manufacturing partners cannot successfully manufacture material that conforms to our specifications and the strict regulatory requirements of the FDA or other regulatory authorities, they will not be able to supply manufactured product to us and they will not be able to secure and/or maintain regulatory approval for their manufacturing facilities, and we may experience long delays and interruptions to our manufacturing supply and increased costs.

Pursuant to ongoing obligations from the NDA for PROCYSBI, we are required to collect and submit data to the FDA regularly regarding our currently observed clinical and commercial product profile and overall product safety assessment. Similarly, pursuant to obligations in the MAA for QUINSAIR, we will be required to conduct post-marketing clinical studies in cystic fibrosis patients and submit data to the EMA regularly regarding observed clinical product profile and safety assessment. In addition, we intend to continue to evaluate our product specification limits, and any changes to our product specifications may require additional review and approval by regulators in the United States and Europe. If there are material delays in any such review and approval process, or if regulators reject any proposals for changes in product specifications or require additional data to support the updated specifications, we may experience an inventory shortfall, which would have a material adverse effect on sales of our products.

If we or our third-party suppliers and manufacturers fail to comply with applicable regulatory requirements, we could experience significant delays or interruptions to our manufacturing supply that may result in the delay or suspension of our preclinical or clinical trials. In addition, a regulatory agency could issue warning letters or untitled letters, seek an injunction, impose civil or criminal penalties or monetary fines, suspend or withdraw regulatory approval, require specification changes, suspend any ongoing clinical trials, refuse to approve pending applications or supplements to applications, suspend or impose restrictions on operations, including costly new manufacturing requirements, seize or detain products or request or require that we initiate a product recall.

We also rely on a third-party logistics provider and specialty pharmacy to distribute PROCYSBI to patients in the United States and to pharmacies in the EEA and to collect from insurance companies and government agencies in the United States and from pharmacies in the EEA. We plan to employ a similar network of third-party services providers to distribute QUINSAIR in the EU and Canada. Our ability to collect from a particular logistics provider is not only subject to such provider’s credit worthiness but is also dependent, in part, on its ability to arrange for full reimbursement from third-party payors. The outsourcing of our distribution function is complex, and we may experience difficulties that could reduce, delay or stop shipments of our products. If we encounter such distribution problems, and we are unable to quickly enter into a similar agreement with another specialty distributor on substantially similar terms, if at all, the distribution of our products could become disrupted, resulting in reduced revenues, healthcare

provider dissatisfaction and/or patient dissatisfaction, which may materially adversely affect our business, results of operations and financial condition.

If any of these events were to occur, our reputation would be harmed, revenues from sales of our products would be delayed or diminished and our business, results of operations and financial condition would be materially adversely affected.

If serious adverse side effects become associated with our current or future products, our business, results of operations and financial condition will be materially adversely affected.

The prescribing information for both PROCYSBI and QUINSAIR include several warnings relating to observed adverse reactions of the active pharmaceutical ingredient usage. The FDA may require products approved under Section 505(b)(2) of the Federal Food, Drug and Cosmetic Act (the "FDCA") to bear the same or similar warning statements as the reference product used in the approval. We expect to update adverse reactions listed in the prescribing information for our products based on continued commercial use and additional clinical trials. If additional adverse reactions emerge, or if there is a pattern of severe or persistent previously observed side effects in the relevant patient populations, the FDA, the EMA or other regulatory agencies could modify or revoke our marketing approvals, require us to modify our labels or require us to suspend production, require a product recall, or we may choose to withdraw a product from the market.

Regulatory authorities could also require us to change the way our products are administered or modify a product in some other way, or they could require us to conduct additional clinical trials or costly post-marketing testing and surveillance to monitor the safety or efficacy of our products. If this were to occur, we may be unable to maintain marketing approvals in our approved indications and/or obtain marketing approval in other indications. In addition, patients or their representatives may bring claims against us alleging serious adverse side effects or harm suffered as a result of use of our products. Any such side effects or related claims could have a material adverse effect on our business, results of operations and financial condition. See also the risk factor titled "We may be subject to product liability claims."

If we fail to demonstrate safety or efficacy in our preclinical studies or clinical trials or to keep to the terms of a product development program, our future business prospects for our drug product candidates will be materially adversely affected.

Clinical trials are very expensive, time consuming and difficult to design and implement. The outcome of clinical trials is uncertain, and results of earlier studies and trials may not be predictive of future trial results. Delays in the commencement or completion of clinical or preclinical testing for RP103 or MP-376 or any of our other product candidates could significantly affect our product development costs and business plan.

Preclinical studies involve testing in multiple non-human disease models to demonstrate efficacy and safety. Regulatory agencies evaluate these data carefully as part of their determination whether to authorize clinical testing in humans. If certain preclinical data reveal potential safety issues or if the results are inconsistent with an expectation of the drug product candidate's efficacy in humans, the regulatory agencies may require additional testing before allowing human clinical trials. This additional testing will increase program expenses and extend timelines. There are many potential preclinical models to test for different disease states, and we could fail to choose the best or a predictive preclinical model to determine proof of concept, safety and efficacy of our drug product candidates. We may decide to suspend further testing on our drug product candidates or technologies if, in the judgment of our management and advisors, the preclinical test results do not support further development. Following successful preclinical testing, drug product candidates must be tested in a clinical development program to provide data on safety and efficacy in humans prior to becoming eligible for product approval and licensure by regulatory agencies. Success in preclinical testing and

early clinical trials does not ensure that later clinical trials will be successful. Product candidates in later stages of clinical trials may fail to show the desired safety and efficacy traits despite having progressed through preclinical studies and initial clinical trials.

Clinical trials may also be delayed or repeated as a result of ambiguous or negative interim results or unforeseen complications in testing. A number of companies in the biopharmaceutical industry have suffered significant setbacks in advanced clinical trials due to lack of efficacy or adverse safety profiles, notwithstanding promising results in earlier trials. The clinical trial process may fail to demonstrate with statistical significance that our drug product candidates are safe for humans and effective for indicated uses. This failure may cause us to abandon a drug product candidate and may delay development of other drug product candidates. For example, we announced in September 2015, based on information then available, that we would not advance our program for the treatment of pediatric non-alcoholic steatohepatitis (NASH) with RP103 after topline results from a Phase 2b trial which failed to show efficacy as measured by the trial’s primary endpoints. Unless the full data set, which we expect to receive later this year, provides a compelling rationale for us to continue the NASH program, our decision will remain unchanged. Any delay in, or termination of, our preclinical testing or clinical trials will delay the filing of relevant marketing applications with regulatory agencies and, ultimately, our ability to commercialize our drug product candidates and generate revenues from related products.

The rate of completion of any clinical trials will be dependent upon, among other factors, the rate of patient enrollment. Patient enrollment is a function of many factors, including the size of the patient population, the nature of the trial, the nature of the disease or medical condition being studied, the availability of alternative therapies, drugs and competing clinical trials of potential alternative therapeutics, the proximity of patients to clinical sites and the eligibility criteria for the study. Delays in planned patient enrollment may result in increased costs and delays. In addition, because many of our clinical trials involve small patient populations, the results of these early clinical trials may not be indicative of future results. Further, the timing of regulatory approval of clinical trial applications by local regulatory agencies or ethics committees may also affect the initiation of trial sites and therefore the rate of patient enrollment.

Under the Prescription Drug User Fee Act, the FDA seeks to respond to NDAs within ten months of the filing date, but this timeframe is often extended. For example, a sponsor may seek FDA designation of a drug candidate as a "fast track product." Fast track products are those products intended for the treatment of a serious or life-threatening disease or condition and which demonstrate the potential to address unmet medical needs for such disease or condition. If fast track designation is obtained, the FDA may initiate review of sections of an NDA before the application is complete. This "rolling review" is available if the applicant provides and the FDA approves a schedule for the remaining information. In addition, FDASIA established a new category of drugs referred to as "breakthrough therapies," which are defined as drugs intended, alone or in combination with one or more other drugs, to treat a serious or life-threatening disease or condition where preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over existing therapies on one or more clinically significant endpoints, such as substantial treatment effects observed early in clinical development. In the future, we may request breakthrough designation or fast track designation from the FDA for our other drug product candidates, but there can be no assurance that we will obtain such designations. Moreover, even if we obtain breakthrough designation or fast track designation from the FDA, the designations do not guarantee that the FDA will approve our NDA, that the development program or review timeline will ultimately be shorter than if we had not obtained the designations or that the FDA will not request additional information, including additional clinical studies, during its review.

We do not know whether our investigational new drug, or IND, applications for future products or the protocols for any future clinical trials will be accepted by the FDA or EMA. We do not know if our clinical trials will begin or be completed on schedule or at all. Even if completed, we do not know if these trials will produce clinically meaningful results sufficient to support an application for marketing approval. The commencement and completion of our planned clinical trials could be substantially delayed or prevented by several factors, including:

- a limited number of, and competition for, suitable patients with particular types of disease for enrollment in clinical trials;
- delays or failures in obtaining regulatory clearance to commence a clinical trial;
- delays or failures in obtaining sufficient clinical materials;
- inability to design appropriate clinical trial protocols;
- delays or failures in reaching agreement on acceptable clinical trial agreement terms or clinical trial protocols with the Institutional Review Boards at prospective sites;
- inability of our clinical research organizations ("CROs"), or other third-party contractors to comply with all contractual requirements or to perform their services in a timely or acceptable manner;
- inability by us, our CROs or their employees to conduct the clinical trial in accordance with all applicable FDA, Drug Enforcement Administration or other regulatory requirements or our clinical protocols;
- lack of efficacy during, or other unfavorable results from, clinical trials or preclinical studies;
- discovery of serious or unexpected toxicities or side effects experienced by study participants or other unforeseen safety issues;
- failure of patients to complete the clinical trial, or inability or unwillingness of patients or medical investigators to follow our clinical trial protocols;

- inability to monitor patients adequately during or after treatment;
- regulatory action by the FDA or other regulatory authorities; and/or
- lack of adequate funding to continue the clinical trial, including the incurrence of any unforeseen costs.

In addition, changes in applicable regulatory requirements and guidance may occur, and we may need to amend clinical trial protocols to reflect these changes. Amendments may require us to resubmit our clinical trial protocols to Institutional Review Boards for reexamination, which may affect the costs, timing or successful completion of a clinical trial.

Sales of our products outside of the United States are also subject to foreign regulatory requirements governing clinical trials, manufacturing and marketing approvals. Even if the FDA and EC grant marketing approval for a product candidate, comparable regulatory authorities of foreign countries must also approve the manufacturing and marketing of our product candidates in those countries. Approval procedures vary among jurisdictions and can involve requirements and administrative review periods different from, and greater than, those in the United States, including additional preclinical studies or clinical trials or manufacturing and control requirements. In many countries outside the United States, a product candidate must be approved for reimbursement before it can be approved for sale in that country. In many cases, the price that we propose to charge for our products is also subject to approval by individual countries before we can launch our product candidates in those countries. Obtaining foreign regulatory approvals, complying with foreign regulatory requirements and gaining approved pricing and reimbursement could result in significant delays, difficulties and costs for us and could delay or prevent the introduction of our products in certain countries. Further, clinical trials conducted in one country may not be accepted by regulatory authorities in other countries. Regulatory approval in one country does not ensure approval in any other country, while a failure or delay in obtaining regulatory approval in one country may have a negative effect on the regulatory approval process in others.

Any delay in our preclinical or clinical programs or the failure to demonstrate safety or efficacy in our clinical trials would have a material adverse effect on our business, results of operations and financial condition.

If we fail to obtain or maintain orphan drug or other regulatory exclusivity for our products or to obtain and maintain exclusivity for our orphan drug product candidates relative to competitive products, our competitors may sell products to treat the same conditions, possibly at lower prices, and our revenues will be significantly reduced.

PROCYSBI received marketing approval from the FDA for the management of nephropathic cystinosis in adults and children two years and older and seven years of market exclusivity as an orphan drug in the United States through the year 2020 for the treatment of patients six years and older and separately received orphan designation with market exclusivity through the year 2022 for patients ages two to six years. PROCYSBI has also received approval as an orphan medicinal product for the management of proven nephropathic cystinosis and 10 years of market exclusivity in the EEA. QUINSAIR received marketing approval from the EMA in 2015 and has also received 10 years of market exclusivity for management of chronic pulmonary infections due to Pseudomonas aeruginosa in adults with cystic fibrosis. In the United States, the FDA has designated QUINSAIR as an orphan drug for treatment of pulmonary infections due to Pseudomonas aeruginosa and other bacteria in patients with cystic fibrosis. As part of our business strategy, we intend to develop RP103 and MP-376, and potentially other drugs, for additional therapeutic indications that may be eligible for FDA and EMA orphan drug designation.

Under the Orphan Drug Act, the FDA may designate a product as an orphan drug if it is a drug intended to treat a rare disease or condition, defined as a patient population of less than 200,000 in the United States, or a patient population greater than 200,000 in the United States where there is no reasonable expectation that the cost of developing the drug will be recovered from sales in the United States. In the United States, orphan drug designation entitles a party to financial incentives such as opportunities for grant funding towards clinical trial costs, tax advantages and user-fee waivers. The company that first obtains FDA approval for a designated orphan drug for a given rare disease receives marketing exclusivity for use of that drug for the stated condition for a period of seven years, plus an additional six months if designated for a pediatric indication.

In the EU, the EMA’s Committee for Orphan Medicinal Products grants orphan drug designation to promote the development of products that are intended for the diagnosis, prevention or treatment of life-threatening or chronically debilitating conditions affecting not more than five in 10,000 persons in the EU and for which no satisfactory method of diagnosis, prevention or treatment has been authorized (or if the product would be a significant benefit to those affected). In addition, designation is granted for products intended for the diagnosis, prevention or treatment of a

life-threatening, seriously debilitating or serious and chronic condition as well as when it is unlikely that sales of the drug in the EU would be sufficient to justify the necessary investment in developing the medicinal product without incentives. An EU orphan drug designation entitles a party to financial incentives such as reduced fees or fee waivers, and 10 years of market exclusivity is granted following medicinal product approval. This period may be reduced to six years if the orphan drug designation criteria are no longer met after five years, including where it is shown that the product is sufficiently profitable not to justify maintenance of market exclusivity. An applicant must request orphan drug designation before submitting an application for marketing approval. Orphan drug designation does not convey any advantage in, or shorten the duration of, the regulatory review and approval process. Even though we have been granted orphan drug designation in the United States and in the EU prior to the approval of RP103 for the treatment of Huntington's Disease ("HD"), and even if we obtain orphan drug designation for our future drug product candidates, we may not fulfill the criteria for exclusivity, or we may not be the first to obtain marketing approval for any orphan indication. Further, even if we obtain orphan drug exclusivity for a particular product, that exclusivity may not effectively protect the product from competition because different drugs can be approved for the same condition. Even after an orphan drug is approved, the FDA can subsequently approve a drug for the same condition if the FDA concludes that the later drug is safer, more effective or makes a major contribution to patient care. Orphan drug exclusive marketing rights may also be lost if the FDA later determines that the request for designation was materially defective, if a subsequent product is deemed clinically superior or if the manufacturer is unable to deliver sufficient quantities of the drug.

Because the extent and scope of patent protection for some of our drug products may be particularly limited, orphan drug designation is especially important for our eligible products and we plan to rely on the orphan or other regulatory exclusivity period to maintain a competitive position. However, if we do not obtain and/or maintain orphan drug exclusivity for our drug products, or if our drug products do not have strong patent protection, our competitors may sell the same drug to treat the same condition, possibly at lower prices, and our revenues will be reduced. Also, without strong patent protection, competitors may sell a generic version of our products upon the expiration of orphan exclusivity if our patent position is not upheld or physicians may prescribe a generic version of our product off-label when our orphan status or marketing exclusivity has expired with respect to one indication, but not others.

If our competitors succeed in developing products and technologies that are more effective than our own, or if scientific developments change our understanding of the potential scope and utility of our drug product candidates, then our technologies and future drug product candidates may be rendered less competitive.

We face significant competition from industry participants that are pursuing technologies similar to those that we are pursuing and are developing pharmaceutical products that are competitive with our products or our product candidates. Many of the pharmaceutical companies in areas competitive with us have greater capital resources, larger overall research and development staff and facilities and a longer history in drug discovery, development, regulatory approval, manufacturing and marketing than we do. With these additional resources and experience, our competitors may be able to respond to rapid and significant technological changes in the biotechnology and pharmaceutical industries faster than we can.

We expect that the technologies associated with biotechnology research and development will continue to develop rapidly. Our future success will depend in large part on our ability to maintain a competitive position with respect to these technologies. Rapid technological development, as well as new scientific developments, may result in our compounds, drug products, drug product candidates or processes becoming obsolete before we can recover any or all of the expenses incurred to develop them. For example, changes in our understanding of the appropriate population of patients who should be treated with a targeted therapy like those we are developing may limit the drug’s market potential if it is subsequently demonstrated that only certain subsets of patients should be treated with the targeted therapy.

No clinical data have been generated for the use of MP-376 to treat non-cystic fibrosis bronchiectasis (“BE”) or non-tuberculous mycobacteria infection (“NTM”)..

We plan to pursue a Phase 2 clinical trial of MP-376 for use in the indication of BE not associated with cystic fibrosis in 2016 and also plan to do work in preparation to support its further clinical development in the treatment of pulmonary NTM, based on third-party data generated pertaining to the susceptibility of certain pathogens to treatment with levofloxacin and other fluoroquinolone molecules. No clinical data have been generated with MP-376 in patients with BE or with NTM infections, either by us or by other parties. This creates substantial uncertainty as the efficacy of MP-376 in these indications. Successful completion of well-controlled clinical trials of adequate size and design is a prerequisite to submitting an NDA to the FDA and, consequently, the ultimate approval and commercial marketing of MP-376 or any other potential product candidate in these indications. A failure of one or more clinical trials can occur at any stage of testing. The outcome of preclinical testing and early clinical trials may not be predictive of the success of later preclinical testing or clinical trials, and interim results of a clinical trial do not necessarily predict final results. Moreover, preclinical and clinical data are often susceptible to varying interpretations and analyses, and many companies that have believed their product candidates performed satisfactorily in preclinical studies and clinical trials have nonetheless failed to obtain marketing approval for their products from regulatory authorities.

The approval of any product or product candidate, including QUINSAIR, in any given market does not ensure approval in any other market.

In order to market any product candidate for a specific indication, we must establish and comply with numerous regulatory requirements on a country-by-country basis regarding safety and efficacy. Clinical trials conducted in one country may not be accepted by regulatory authorities in other countries, and regulatory approval in one country does not guarantee regulatory approval in any other country. Approval processes vary among countries and can involve additional product testing and validation, and additional administrative review periods. As a result, international regulatory requirements could delay or prevent the introduction of our products and product candidates across different countries. For example, approval of QUINSAIR for use in CF patients with Pseudomonas aeruginosa in the EU and Canada does not ensure approval by the FDA or regulatory authorities in other countries or jurisdictions, nor does it ensure approval for the same conditions of use. Further, seeking U.S. regulatory approval for QUINSAIR for a specific indication could result in difficulties and costs for us and require additional preclinical studies or clinical trials which could be costly and time consuming. If we fail to comply with regulatory requirements in international markets or to obtain and maintain required approvals, or if regulatory approvals in international markets are delayed, our target market will be reduced and our ability to realize the full market potential of our products and product candidates will be unrealized.

We have obligations to Tripex to conduct certain regulatory and development activities with respect to QUINSAIR. Delays or other factors that prevent us from completing these regulatory and development activities may put us in breach of our obligations to Tripex.

The terms of our asset purchase agreement for the acquisition of QUINSAIR require us to pursue commercially reasonable efforts to initiate, and subsequently to complete, an additional clinical trial in a non-cystic-fibrosis patient population within a specified period of time. These terms also require us to progress toward filing an NDA for approval of QUINSAIR in the United States in all or part of the cystic fibrosis patient population within a specified period of time. These obligations are subject to certain exceptions due to, for example, manufacturing delays not under our control, or delays caused by the FDA. If we fail to properly exercise such efforts to initiate and complete an appropriate clinical trial, or fail to file an NDA for U.S. approval in the cystic fibrosis patient population, during the time periods specified in the asset purchase agreement, we may be subject to various claims by Tripex and parties affiliated with Tripex.

Because the target patient populations for our products and some of our drug product candidates are small, we must achieve significant market share and obtain sufficient per-patient prices for our products to achieve meaningful gross and operating profits.

PROCYSBI, QUINSAIR and clinical development of RP103 and MP-376 target rare diseases with small patient populations, including cystinosis, cystic fibrosis, mitochondrial disorders including Leigh's Disease, NTM, BE and HD. To successfully commercialize a drug product for these indications, we must identify patients and a targeted prescriber base for each drug product. Due to small patient populations, we believe that we would need to have significant market penetration to achieve meaningful revenues. In addition, the per-patient prices at which we sell our current products for these indications will need to be relatively high in order for us to generate meaningful gross and net operating profits because we must recoup our investment in our product development programs, which programs often require ongoing investment after a product's approval. Patients who discontinue therapy or do not fill prescriptions are not easily replaced by new patients because of the limited patient populations. There can be no assurance that we will successfully obtain or maintain sufficient market share or per-patient prices. Because our current potential target populations are very small, even if we obtain significant market share for our current or future products and product candidates, we may never achieve profitability despite obtaining such significant market share.

If we fail to comply with our reporting and payment obligations under the Medicaid Drug Rebate Program or other governmental pricing programs in the United States, we could be subject to additional reimbursement requirements, penalties, sanctions and fines, which could have a material adverse effect on our business, results of operations and financial condition.

We participate in the Medicaid Drug Rebate Program, as administered by the Centers for Medicare & Medicaid Services ("CMS"), and other federal and state government pricing programs in the United States, and we may participate in additional government pricing programs in the future. These programs generally require us to pay rebates or otherwise provide discounts to government payors in connection with drugs, including PROCYSBI, that are dispensed to beneficiaries of these programs. In some cases, such as with the Medicaid Drug Rebate Program, the rebates are based on pricing and rebate calculations that we report on a monthly and quarterly basis to the government agencies that administer the programs. Pricing and rebate calculations are complex, vary among products and programs, and are often subject to interpretation by governmental or regulatory agencies and the courts. The terms, scope and complexity of these government pricing programs change frequently. Responding to current and future changes may increase our costs and the complexity of compliance will be time consuming.

In addition, the Office of Inspector General has recently increased its focus on the methodologies used by manufacturers to calculate average manufacturer price ("AMP"), and best price ("BP"), to assess manufacturer compliance

with reporting requirements under the Medicaid Drug Rebate Program. We are liable for errors associated with our submission of pricing data and for any overcharging of government payors. For example, failure to submit monthly/quarterly AMP and BP data on a timely basis could result in a civil monetary penalty of $10,000 per day for each day the submission is late beyond the due date. Failure to make necessary disclosures and/or to identify overpayments could result in allegations against us under the Federal False Claims Act and other laws and regulations.

Any required refunds to the U.S. government or responding to a government investigation or enforcement action would be expensive and time consuming and could have a material adverse effect on our business, results of operations and financial condition. In the event that the CMS were to terminate our rebate agreement, no federal payments would be available under Medicaid or Medicare for our covered outpatient drugs.