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UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
Washington, D.C. 20549

FORM 10-K

(Mark One)

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

For the fiscal year ended December 31, 2017

OR

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

For the transition period from _____ to _____

Commission File Number 0-30739

INSMED INCORPORATED
(Exact name of registrant as specified in its charter)

Virginia	**54-1972729**
(State or other jurisdiction of incorporation or organization)	**(I.R.S. employer identification no.)**
10 Finderne Avenue, Building 10 Bridgewater, New Jersey 08807	**(908) 977-9900**
(Address of principal executive offices)	**(Registrant's telephone number including area code)**

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

Title of each class	**Name of each exchange on which registered**
Common Stock, par value $0.01 per share	**Nasdaq Global Select Market**

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

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

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 [ ] No [✓]

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 [✓] No [ ]

Indicate by check mark whether the registrant has submitted electronically and posted on its corporate Web site, if any, every Interactive Data File required to be submitted and posted pursuant to Rule 405 of Regulation S-T (§ 232.405 of this chapter) during the preceding 12 months (or for such shorter period that the registrant was required to submit and post such files). Yes [✓] No [ ]

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

Indicate by check mark whether the registrant is a large accelerated filer, an accelerated filer, a non-accelerated filer, a smaller reporting company, or an emerging growth company (See the definitions of "large accelerated filer," "accelerated filer," "smaller reporting company" and "emerging growth company" in Rule 12b-2 of the Exchange Act). Large accelerated filer [✓] Accelerated filer [ ] Non-accelerated filer (Do not check if a smaller reporting company) [ ] Smaller reporting company [ ] Emerging growth company [ ]

If an emerging growth company, indicate by check mark if the registrant has elected not to use the extended transition period for complying with any new or revised financial accounting standards provided pursuant to Section 13(a) of the Exchange Act [ ]

Indicate by check mark whether the registrant is a Shell Company (as defined in Rule 12b-2 of the Exchange Act). Yes [ ] No [✓]

The aggregate market value of the voting and non-voting common equity held by non-affiliates of the registrant on June 30, 2017, was $1,057 million (based on the closing price for shares of the registrant's common stock as reported on the Nasdaq Global Select Market on that date). In determining this figure, the registrant has assumed solely for this purpose that all of its directors, executive officers, persons beneficially owning 10% or more of the registrant's outstanding common stock and certain other stockholders of the registrant may be considered to be affiliates. This assumption shall not be deemed conclusive as to affiliate status for this or any other purpose.

On February 1, 2018, there were 76,617,946 shares of the registrant's common stock, $0.01 par value, outstanding.

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DOCUMENTS INCORPORATED BY REFERENCE

Portions of the registrant's definitive Proxy Statement for its 2018 Annual Meeting of Shareholders to be filed with the Securities and Exchange Commission no later than May 1, 2018 and to be delivered to shareholders in connection with the 2018 Annual Meeting of Shareholders, are herein incorporated by reference in Part III of this Form 10-K.

INSMED INCORPORATED

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Unless the context otherwise indicates, references in this Form 10-K to “Insmed Incorporated” refers to Insmed Incorporated, a Virginia corporation, and “Company,” “Insmed,” “we,” “us” and “our” refer to Insmed Incorporated together with its consolidated subsidiaries. INSMED, CONVERT and ARIKAYCE are trademarks of Insmed Incorporated. This Form 10-K also contains trademarks of third parties. Each trademark of another company appearing in this Form 10-K is the property of its owner.

CAUTIONARY NOTE REGARDING FORWARD-LOOKING STATEMENTS

This Annual Report on Form 10-K contains forward-looking statements that involve substantial risks and uncertainties. "Forward-looking statements," as that term is defined in the Private Securities Litigation Reform Act of 1995, are statements that are not historical facts and involve a number of risks and uncertainties. Words herein such as "may," "will," "should," "could," "would," "expects," "plans," "anticipates," "believes," "estimates," "projects," "predicts," "intends," "potential," "continues," and similar expressions (as well as other words or expressions referencing future events, conditions or circumstances) identify forward-looking statements.

Forward-looking statements are based on our current expectations and beliefs, and involve known and unknown risks, uncertainties and other factors, which may cause our actual results, performance and achievements and the timing of certain events to differ materially from the results, performance, achievements or timing discussed, projected, anticipated or indicated in any forward-looking statements. Such risks, uncertainties and other factors include, among others, the following:

- *risks that the full six-month data from the CONVERT study (the CONVERT study or the 212 study) or subsequent data from the remainder of the study's treatment and off-treatment phases will not be consistent with the top-line six-month results of the study;*
- *uncertainties in the research and development of our existing product candidates, including due to delays in data readouts, such as the full data from the CONVERT study, patient enrollment and retention or failure of our preclinical studies or clinical trials to satisfy pre-established endpoints, including secondary endpoints in the CONVERT study and endpoints in the CONVERT extension study (the 312 study);*
- *risks that subsequent data from the 312 study will not be consistent with the interim results;*
- *failure to obtain, or delays in obtaining, regulatory approval from the US Food and Drug Administration (FDA), Japan's Ministry of Health, Labour and Welfare (MHLW) and Pharmaceuticals and Medical Devices Agency (PMDA), the European Medicines Agency (EMA), and other regulatory authorities for our product candidates or their delivery devices, such as the eFlow Nebulizer System, including due to insufficient clinical data, selection of endpoints that are not satisfactory to regulators, complexity in the review process for combination products or inadequate or delayed data from a human factors study required for US regulatory approval;*
- *failure to maintain regulatory approval for our product candidates, if received, due to a failure to satisfy post-approval regulatory requirements, such as the submission of sufficient data from confirmatory clinical studies;*
- *safety and efficacy concerns related to our product candidates;*
- *lack of experience in conducting and managing preclinical development activities and clinical trials necessary for regulatory approval, including the regulatory filing and review process;*
- *failure to comply with extensive post-approval regulatory requirements or imposition of significant post-approval restrictions on our product candidates by regulators;*
- *uncertainties in the rate and degree of market acceptance of product candidates, if approved;*
- *inability to create an effective direct sales and marketing infrastructure or to partner with third parties that offer such an infrastructure for distribution of our product candidates, if approved;*
- *inaccuracies in our estimates of the size of the potential markets for our product candidates or limitations by regulators on the proposed treatment population for our product candidates;*
- *failure of third parties on which we are dependent to conduct our clinical trials, to manufacture sufficient quantities of our product candidates for clinical or commercial needs, including our raw materials suppliers, or to comply with our agreements or laws and regulations that impact our business;*
- *inaccurate estimates regarding our future capital requirements, including those necessary to fund our ongoing clinical development, regulatory and commercialization efforts as well as milestone payments or royalties owed to third parties;*

- *failure to develop, or to license for development, additional product candidates, including a failure to attract experienced third-party collaborators;*
- *uncertainties in the timing, scope and rate of reimbursement for our product candidates;*
- *changes in laws and regulations applicable to our business and failure to comply with such laws and regulations;*
- *inability to repay our existing indebtedness or to obtain additional capital when needed on desirable terms or at all;*
- *failure to obtain, protect and enforce our patents and other intellectual property and costs associated with litigation or other proceedings related to such matters;*
- *restrictions imposed on us by license agreements that are critical for our product development, including our license agreements with PARI Pharma GmbH (PARI) and AstraZeneca AB (AstraZeneca), and failure to comply with our obligations under such agreements;*
- *competitive developments affecting our product candidates and potential exclusivity related thereto;*
- *the cost and potential reputational damage resulting from litigation to which we are or may be a party, including, without limitation, the class action lawsuit against us that recently was dismissed without prejudice;*
- *loss of key personnel; and*
- *lack of experience operating internationally.*

We may not actually achieve the results, plans, intentions or expectations indicated by our forward-looking statements because, by their nature, forward-looking statements involve risks and uncertainties because they relate to events and depend on circumstances that may or may not occur in the future. You should carefully read the factors discussed in Risk Factors, Item 1A of Part I of this Annual Report on Form 10-K, as well as the discussion and analysis of our financial condition and financial statements contained in this Annual Report on Form 10-K for additional discussion of the risks and uncertainties that could cause our actual results to differ materially from those in our forward-looking statements. We caution readers not to place undue reliance on any such forward-looking statements, which speak only as of the date they are made. We disclaim any obligation, except as specifically required by law and the rules of the Securities and Exchange Commission (SEC), to publicly update or revise any such statements to reflect any change in our expectations or in events, conditions or circumstances on which any such statements may be based, or that may affect the likelihood that actual results will differ from those set forth in the forward-looking statements.

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PART I

ITEM 1. BUSINESS

Business Overview

Insmed is a global biopharmaceutical company focused on the unmet needs of patients with rare diseases. Our lead product candidate is amikacin liposome inhalation suspension (ALIS) (formerly known as liposomal amikacin for inhalation), which is in late-stage development for adult patients with treatment refractory nontuberculous mycobacteria (NTM) lung disease caused by Mycobacterium avium complex (MAC), a rare and often chronic infection that can cause irreversible lung damage and can be fatal. Our earlier clinical-stage pipeline includes INS1007 and INS1009. INS1007 is a novel oral, reversible inhibitor of dipeptidyl peptidase 1 (DPP1), an enzyme responsible for activating neutrophil serine proteases, which are implicated in the pathology of chronic inflammatory lung diseases, such as non-cystic fibrosis (non-CF) bronchiectasis. INS1009 is an inhaled nanoparticle formulation of a treprostinil prodrug that may offer a differentiated product profile for rare pulmonary disorders, including pulmonary arterial hypertension (PAH).

The table below summarizes the current status and anticipated milestones for our principal product candidates: ALIS, INS1007, and INS1009.

Product Candidate/Target Indications	Status	Next Expected Milestones
ALIS for NTM lung infections	• We announced top-line data for the CONVERT study on September 5, 2017. Based on top-line results, the CONVERT study met its primary endpoint of culture conversion, which we defined as three consecutive negative monthly sputum cultures by month six with statistical and clinical significance, with 29% of patients in the ALIS plus current guideline-based therapy (GBT) arm achieving culture conversion, compared to 9% of patients in the GBT-only arm ($p<0.0001$). • We announced interim data from the CONVERT study and the 312 extension study on January 3, 2018. The recent data included interim long-term durability data for the CONVERT study and interim efficacy data for the 312 study. • The CONVERT study is a randomized, open-label global phase 3 clinical study of ALIS in adult patients with treatment refractory NTM lung disease caused by MAC. The 312 study is a 12-month extension study of patients who completed six months of treatment in the CONVERT study, but did not demonstrate culture conversion by month six. • The FDA has designated ALIS as an orphan drug, a breakthrough therapy, and a qualified infectious disease product (QIDP). • The European Commission has granted an orphan designation for ALIS for the treatment of NTM lung disease.	• We plan to pursue accelerated approval of ALIS pursuant to Section 506(c) of the Federal Food Drug and Cosmetic Act and 21 C.F.R. Part 314 Subpart H (Accelerated Approval of New Drugs for Serious or Life-Threatening Illnesses) (Subpart H) based on the six-month data from the CONVERT study. We plan to file a new drug application (NDA) for approval of ALIS with the US Food and Drug Administration (FDA) before the end of March 2018. • We intend to seek marketing approvals for ALIS in certain countries outside the US, such as Japan, when sufficient data are available. If approved, we expect ALIS would be the first inhaled antibiotic specifically indicated for the treatment of NTM lung disease caused by MAC in North America, Japan and Europe. • If approved, we plan to commercialize ALIS in the US, Japan, certain countries in Europe, and certain other countries.
INS1007 (oral reversible inhibitor of DPP1) for non-CF bronchiectasis and other rare diseases	• We are enrolling patients in the WILLOW study, a global phase 2, randomized, double-blind, placebo-controlled, parallel-group, multi-center clinical study to assess the efficacy, safety and tolerability, and pharmacokinetics of INS1007 administered once daily for 24 weeks in subjects with non-CF bronchiectasis. • We are currently assessing regulatory strategies which could expedite the development and regulatory reviews of INS1007 in the US and the EU.	• We expect to advance enrollment in the WILLOW clinical study of INS1007 during 2018. • We are exploring the potential of INS1007 in various neutrophil-driven inflammatory conditions.
INS1009 (inhaled nanoparticle formulation of a treprostinil prodrug) for rare pulmonary disorders	• The results of our phase 1 study of INS1009 were presented at the European Respiratory Society international congress in September 2016. • The phase 1 study was a randomized, double-blind, placebo-controlled, single ascending dose study of INS1009 for inhalation to determine its safety, tolerability, and pharmacokinetics in healthy volunteers.	• We believe INS1009 may offer a differentiated product profile for rare pulmonary disorders, including PAH, and we are currently evaluating our options to advance its development including exploring its use as an inhaled dry powder formulation.

Our earlier-stage pipeline includes preclinical compounds that we are evaluating in multiple rare diseases of unmet medical need, including methicillin-resistant staph aureus (MRSA) and NTM. To complement our internal research and development, we actively evaluate in-licensing and acquisition opportunities for a broad range of rare diseases.

Corporate History

We were incorporated in the Commonwealth of Virginia on November 29, 1999. On December 1, 2010, we completed a business combination with Transave, Inc. (Transave), a privately held New Jersey-based company focused on the development of differentiated and innovative inhaled pharmaceuticals for the site-specific treatment of serious lung diseases.

Our Strategy

Our strategy focuses on the needs of patients with rare diseases. We are currently primarily focused on the development and commercialization of ALIS. We are not aware of any approved inhaled therapies specifically indicated to treat NTM lung disease in North America, Japan or Europe. While we believe that ALIS has the potential to treat a number of different bacterial infections, we are prioritizing securing US regulatory approval of ALIS for adult patients with treatment refractory NTM lung disease caused by MAC. We are also advancing earlier-stage programs in other rare pulmonary disorders.

Our current priorities are as follows:

- Completing the CONVERT study and the 312 study;
- Preparing an NDA for submission under Subpart H to the FDA for ALIS based on the six-month data from the CONVERT study;
- Ensuring our product supply chain will support the commercialization, if approved, and future life cycle management programs of ALIS;
- Preparing for potential commercialization of ALIS in the US, Japan, certain countries in Europe, and certain other countries;
- Developing the core value dossier to support the global reimbursement of ALIS;
- Supporting further research and lifecycle management strategies for ALIS, including exploring the potential use of ALIS as part of a front-line, multi-drug regimen and as maintenance monotherapy to prevent recurrence (defined as true relapse or reinfection) of NTM lung disease;
- Enrolling patients in the WILLOW phase 2 study of INS1007 in non-CF bronchiectasis;
- Exploring INS1009 for use as an inhaled dry powder formulation and generating preclinical findings from our earlier-stage program(s); and
- Expanding our rare disease pipeline through corporate development.

Product Pipeline

ALIS for Patients with NTM Lung Disease

Our lead product candidate is ALIS, a novel, once-daily liposomal formulation of amikacin that is in late-stage clinical development for adult patients with treatment refractory NTM lung disease caused by MAC, a rare and often chronic infection that can cause irreversible lung damage and can be fatal. Amikacin solution for parenteral administration is an established drug that has activity against a variety of NTM; however, its use is limited by the need to administer it intravenously and by toxicity to hearing, balance, and kidney function (Peloquin et al., 2004). Unlike amikacin solution for intravenous administration, our advanced liposome technology uses charge-neutral liposomes to deliver amikacin directly to the lung where it is taken up by the lung macrophages where the NTM infection resides. This technology prolongs the release of amikacin in the lungs, while minimizing systemic exposure thereby, offering the potential for decreased systemic toxicities. ALIS's ability to deliver high levels of amikacin directly to the lung distinguishes it from intravenous amikacin. ALIS is administered once-daily, using a portable aerosol delivery system, via an optimized, investigational eFlow® Nebulizer System manufactured by PARI Pharma GmbH (PARI).

The FDA has designated ALIS as an orphan drug, a breakthrough therapy, and a QIDP for NTM lung disease. Orphan designated drugs are eligible for seven years of exclusivity for the orphan indication. QIDP designation features an additional five years of exclusivity for the designated indication. As a result, if ALIS is approved in the US, we expect FDA to grant a total of 12 years of exclusivity in the indication for which ALIS is approved. A QIDP-designated product is eligible for fast

track status and is often granted priority review status. A priority review designation for a drug which is not a new molecular entity (NME) means the FDA's goal is to take action on the NDA within six months following the receipt of the NDA.

The CONVERT Study and 312 Study

CONVERT Top-Line Efficacy Data

We announced top-line data for the CONVERT study on September 5, 2017. The CONVERT study enrolled 336 adult patients with NTM lung disease caused by MAC who were refractory to at least six months of treatment on current GBT of a multi-drug regimen. After a screening period of up to 10 weeks, eligible patients were randomized 2:1 to once-daily ALIS plus GBT or GBT only. The primary endpoint of the study was the proportion of patients achieving culture conversion, which we defined as three consecutive monthly negative sputum cultures, by month six. Based on top-line results, the CONVERT study met its primary endpoint, with 29% of patients in the ALIS plus GBT arm achieving culture conversion, compared to 9% of patients in the GBT-only arm ($p<0.0001$).

We also reported top-line data for certain secondary and exploratory endpoints for the first six months of the study. Top-line data for the six-minute walk test indicated no statistically significant difference between patients in the two arms of the study. However, an analysis of these data (per a pre-specified exploratory endpoint) showed that patients who achieved culture conversion in either arm demonstrated an improvement in six-minute walk distance when compared to patients who did not culture convert ($p=0.0108$). Top-line data for the secondary endpoint of time to conversion demonstrated that patients in the GBT-only arm took approximately 30% longer to convert when compared to patients on ALIS plus GBT ($p<0.0001$). We are continuing our analysis of the impact of conversion on a variety of other clinical measures.

The protocol for the CONVERT study incorporates feedback from the FDA and the EMA via its scientific advice working party process, as well as local health authorities in other countries, including Japan's PMDA. Because the CONVERT study met the primary endpoint of culture conversion at month six based on the top-line results, we plan to submit an NDA for ALIS to the FDA by the end of March 2018 pursuant to Subpart H, which permits the FDA to approve a product candidate based on a surrogate or intermediate endpoint subject to the requirement that we conduct post-approval studies to verify and describe the clinical benefit of the product. We expect to receive a six-month priority review from the FDA. We believe that efficacy data from the CONVERT study at month six will be sufficient to support the accelerated approval of ALIS. We expect that full approval would be contingent on FDA review of, among other things, the final analyses of durability of culture conversion for converters.

CONVERT Top-Line Safety and Tolerability Data

Approximately 98% of patients in the ALIS plus GBT arm of the CONVERT study experienced at least one treatment-emergent adverse event (TEAE), compared to 91% of patients in the GBT-only arm, with most events being mild or moderate in severity. A greater percentage of patients in the ALIS plus GBT arm than in the GBT-only arm experienced TEAEs involving dysphonia, cough, haemoptysis, dyspnoea, oropharyngeal pain, diarrhea, nausea, and fatigue. Based on our review of the top-line study safety data, the incidence of dysphonia, cough and dyspnoea among patients in the ALIS plus GBT arm generally decreased after the second study month. Approximately 20% and 18% of patients in the ALIS plus GBT arm and GBT-only arm of the study, respectively, experienced at least one serious treatment emergent adverse event (STEAE). The table below provides additional information regarding certain STEAEs experienced by patients in the CONVERT study.

		2:1 Randomization	
Patients Reporting STEAEs >3% in Either Arm		**ALIS + GBT (n=223)**	**GBT (n=112)**
Patients Reporting At Least One STEAE		20.2% (45)	17.9% (20)
System Organ Class	**Preferred Term**		
Respiratory, Thoracic, Mediastinal Disorders		11.7% (26)	9.8% (11)
	Hemoptysis	2.7% (6)	4.5% (5)
	COPD (exacerbation)	3.1% (7)	0.9% (1)
Infections and Infestations		9.0% (20)	5.4% (6)
	Pneumonia	3.6% (8)	1.8% (2)
Cardiac Disorders		0.4% (1)	4.5% (5)
Patient Deaths		2.7% (6)	4.5% (5)

There were no distinctions between treatment arms for adverse events of hearing loss or renal impairment, side effects commonly associated with the intravenous use of amikacin. As of September 2017, the overall dropout rate in the CONVERT study was 16.1%, with an 8.9% dropout rate in the GBT-only arm and a 19.6% dropout rate in the ALIS plus GBT arm. As of December 2017, the overall dropout rate in the CONVERT study was 18% (n=60/336).

CONVERT Long-Term Durability Data

We also recently announced interim data on the durability of culture conversion, as defined by patients that have completed treatment and continued in the CONVERT study off all therapy for three months, which we expect will be the endpoint necessary to support full regulatory approval in the US. The following data are interim results observed through December 2017, and have not been further analyzed. As of December 2017, of the 75 patients achieving culture conversion in the CONVERT study, 53 of these patients were evaluable for durability of culture conversion three months after the completion of treatment. Interim data for durability of culture conversion as of December 2017 on these 53 patients are detailed below:

	Evaluable Number of Patients as of December 2017 (At Least Three Months Post Treatment)*	**Percent with Durable Culture Conversion Three Months After Completion of All Treatment**
Converters in the ALIS + GBT arm (n=65)	46	60.9% (28/46)
Converters in the GBT-only arm (n=10)	7	0.0% (0/7)

* Evaluable number of patients includes all patients who reached three months post-treatment and all patients who discontinued prior to three months post-treatment.

312 Study

All non-converters in the CONVERT study, as determined at the month eight visit, may be eligible to enter the 312 study which is a separate 12-month, single-arm, open-label study. The purpose of the 312 study is to evaluate the safety and tolerability of longer-term treatment with ALIS added to GBT. The secondary endpoints of the 312 study include evaluating the proportion of patients achieving culture conversion (three consecutive monthly negative sputum cultures) by month six and the proportion of patients achieving culture conversion by month 12 (end of treatment).

312 Study Interim Efficacy Data

We recently announced interim data for the 312 study, which enrolled 163 adult patients with NTM lung disease caused by MAC who completed six months of treatment in the CONVERT study, but did not demonstrate culture conversion by Month 6. The following data are interim results observed through December 2017, and have not been further analyzed. Patients in the ALIS plus GBT arm of the CONVERT study and patients in the GBT-only arm of the CONVERT study who did not achieve culture conversion by Month 6 had the option to enroll in the 312 study at Month 8. Under the study protocol, patients from both arms of the CONVERT study will receive 12 months of ALIS plus GBT in the 312 study. We will also use the data from this trial to further assess the impact of the addition of ALIS to background GBT on sputum culture conversion, by Month 6.

As of December 2017, of the 163 patients enrolled in the 312 study, 124 patients were evaluable for culture conversion. Descriptive interim culture conversion data as of December 2017 for these 124 patients are detailed below. The interim culture conversion data has not been statistically analyzed.

	Number of Patients Completing Six Months of Treatment in the 312 study as of December 2017 **	Percent Achieving Sputum Culture Conversion by Month 6 in the 312 study
Patients who received GBT only in the 212 study and crossed over to receive six months of treatment with ALIS + GBT (n=90)	67	28.4% (19/67)
Patients who received ALIS + GBT in the 212 study and crossed over to continue treatment in the 312 study, to receive a combined total of 14 months of ALIS + GBT treatment in both studies (n=73)	57	12.3% (7/57)

** Includes all patients completing six months of treatment, all patients who discontinued prior to six months and for all ongoing patients prior to six months who completed two months of treatment.

312 Study Interim Safety and Tolerability Data

We have not yet performed a final analysis of any safety data for the 312 study. However, based on an interim review of data available from the 312 study, we believe that STEAEs were similar to the STEAEs we reported in September 2017 as part of our top-line data results for the 212 study. As of December 2017, the overall dropout rate in the 312 study was 24% (n=39/163).

Phase 2 Study (or 112 Study)

Our completed phase 2 study (or 112 study) was a randomized, double-blind, placebo-controlled study that evaluated the efficacy and safety of ALIS in adults with NTM lung disease due to MAC or *M. abscessus* that was refractory to guideline-based therapy. In October 2016, the results from the phase 2 study were published online in the *American Journal of Respiratory and Critical Care Medicine* (Olivier et al. 2016).

The study included an 84-day double-blind phase in which patients were randomized 1:1 either to ALIS once-daily plus a multi-drug regimen or to placebo (empty liposomes) once-daily plus a multi-drug regimen. After completing the 84-day double-blind phase, patients had the option of continuing in an 84-day open-label phase during which all patients received ALIS plus the same multi-drug regimen. The study also included 28-day and 12-month off-ALIS follow-up assessments. Eighty-nine (89) patients were randomized and dosed in the study. Of the 80 patients who completed the 84-day double-blind phase, 78 patients entered the open-label phase and received ALIS plus the same multi-drug regimen for 84 days. Seventy-six (76) percent (59/78) of patients who entered the open-label phase of the study completed the open-label study.

The primary efficacy endpoint of the study was the change from baseline (Day 1) to the end of the double-blind phase of the trial (Day 84) in a semi-quantitative measurement of mycobacterial density on a seven-point scale. ALIS did not meet the pre-specified level for statistical significance although there was a positive trend (p=0.072) in favor of ALIS. The p-value for the key secondary endpoint of culture conversion to negative at Day 84 was 0.003, in favor of ALIS. A shorter time to first negative sputum culture was also observed with ALIS relative to placebo during the double-blind phase (p=0.013).

The microbiologic outcomes from the 112 study were also explored post hoc using a more stringent definition of culture conversion, which was defined as at least three consecutive monthly sputum samples that test negative for NTM, consistent with the definition of culture conversion in the ATS/IDSA Guidelines and in clinical practice. Twenty-three (23) patients achieved at least three consecutive negative monthly sputum samples by the 28-day follow-up assessment, of which four started to convert at baseline prior to administration of study drug. For the other 19 patients who achieved culture conversion, 17 achieved culture conversion after receiving ALIS (10 during the double-blind phase and seven after entering the open-label phase, of which six received ALIS for the first time in the open-label phase). Two patients achieved culture conversion while receiving placebo during the double-blind phase. The majority of patients who achieved culture conversion (three consecutive negative monthly sputum samples) during the double-blind phase continued to have negative cultures through the open-label and follow-up phases.

At the end of the double-blind phase, the ALIS group improved from baseline in mean distance walked in the six-minute walk test. At the end of the open-label phase, patients in the ALIS group continued to improve in the mean distance

walked in the six-minute walk test, while the patients who previously received placebo in the double-blind phase and subsequently received ALIS in the open-label phase demonstrated a reduced rate of decline from baseline.

Approximately 90% of patients in both treatment groups experienced at least one treatment-emergent adverse event, with most events either mild or moderate in severity. During the double-blind phase a greater percentage of patients treated with ALIS experienced, among others, dysphonia, bronchiectasis exacerbation, cough, oropharyngeal pain, fatigue, chest discomfort, wheezing, and infective pulmonary exacerbation of cystic fibrosis (CF). No clinically relevant changes were detected in laboratory values and vital signs.

Further Research and Lifecycle Management for ALIS

We are currently exploring and supporting research and lifecycle management programs for ALIS beyond refractory NTM lung infections caused by MAC. Specifically, we are evaluating future study designs focusing on the MAC disease treatment pathway, including front-line treatment and monotherapy maintenance to prevent recurrence (defined as true relapse or reinfection) of NTM lung disease. In addition, we are evaluating non-MAC NTM species, such as *M. abscessus*. If the data from the CONVERT study are sufficient to support our marketing authorization applications (MAAs) and regulatory bodies approve ALIS, such lifecycle management studies could enable us to reach more potential patients. These initiatives may include new clinical studies sponsored by us or investigator-initiated studies, which are clinical studies initiated and sponsored by physicians or research institutions with funding from us.

Market Opportunity for ALIS in NTM Lung Disease in 2018

NTM lung disease is associated with increased rates of morbidity and mortality, and MAC is the predominant pathogenic species in NTM lung disease in the US, Japan and Europe. The prevalence of NTM lung disease has increased over the past two decades, and we believe it is an emerging public health concern worldwide. Based on currently available information from external sources, including market research funded by us and third parties, and internal analyses and calculations, we estimate potential patient populations in the US, Japan and EU5 (comprised of France, Germany, Italy, Spain and the United Kingdom) for 2018 as follows:

Potential Market	Estimated Number of Patients with Diagnosed NTM Lung Disease	Estimated Number of Patients Treated for NTM Lung Disease Caused by MAC	Estimated Number of Patients Refractory to Treatment
United States	75,000-105,000	40,000-50,000	10,000-15,000
Japan	125,000-145,000	60,000-70,000	15,000-18,000
EU5	14,000	4,400	1,400

We are not aware of any approved inhaled therapies specifically indicated for NTM lung disease in North America, Japan or Europe. Current guideline-based approaches for NTM lung disease, including those from the American Thoracic Society and Infectious Diseases Society of America, involve multi-drug regimens not approved for the treatment of NTM lung disease and treatment that could last two years or more. Based on a burden of illness study that we conducted in the US with a major medical benefits provider, we previously concluded that patients with NTM lung disease are costly to healthcare plans, while a recent claims-based study in the US has shown that patients with NTM lung disease have higher resource utilization and costs than their age and gender-matched controls. Accordingly, we believe that a significant market opportunity for ALIS in NTM lung disease exists in the US and internationally.

We are currently exploring the NTM market opportunity for ALIS in Japan. The CONVERT study included a comprehensive pharmacokinetic sub-study in Japanese subjects in lieu of a separate local pharmacokinetic study in Japan, as agreed with the PDMA. If the data from the CONVERT study are sufficient to support our MAAs, and the FDA approves ALIS, we expect our first regulatory filing after the US to be in Japan. We have established a Japanese legal entity and plan to hire local employees in 2018 to closely manage our regulatory and pre-commercial activities.

INS1007

INS1007 is a small molecule, oral, reversible inhibitor of DPP1, which we licensed from AstraZeneca in October 2016. DPP1 is an enzyme responsible for activating neutrophil serine proteases in neutrophils when they are formed in the bone marrow. Neutrophils are the most common type of white blood cell and play an essential role in pathogen destruction

and inflammatory mediation. Neutrophils contain the neutrophil serine proteases, neutrophil elastase, proteinase 3, and cathepsin G, that have been implicated in a variety of inflammatory diseases. In chronic inflammatory lung diseases, neutrophils accumulate in the airways and release active neutrophil serine proteases in excess that cause lung destruction and inflammation. INS1007 may decrease the damaging effects of inflammatory diseases, such as non-CF bronchiectasis, by inhibiting DPP1 and its activation of neutrophil serine proteases. Non-CF bronchiectasis is a progressive pulmonary disorder in which the bronchi become permanently dilated due to chronic inflammation and infection. Currently, there is no cure, and we are not aware of any FDA-approved therapies specifically indicated for non-CF bronchiectasis.

The WILLOW Study

The WILLOW study, a global phase 2, randomized, double-blind, placebo-controlled, parallel group, multi-center clinical study to assess the efficacy, safety and tolerability, and pharmacokinetics of INS1007 administered once daily for 24 weeks in subjects with non-CF bronchiectasis. We commenced enrollment in the WILLOW study in December 2017. In addition, we are exploring the potential of INS1007 in various neutrophil-driven inflammatory conditions.

Phase 1 Study Results

In a phase 1 study of healthy volunteers conducted by AstraZeneca, INS1007 (previously AZD7986) was well tolerated and demonstrated inhibition of the activity of the neutrophil serine protease neutrophil elastase in a dose and concentration dependent manner. In preclinical studies, it was shown to reversibly inhibit DPP1 and the activation of neutrophil serine proteases within maturing neutrophils.

INS1009

INS1009 is an investigational sustained-release inhaled treprostinil prodrug nanoparticle formulation that has the potential to address certain of the current limitations of existing prostanoid therapies. We believe that INS1009 prolongs duration of effect and may provide PAH patients with greater consistency in pulmonary arterial pressure reduction over time. Current inhaled prostanoid therapies must be dosed four to nine times per day for the treatment of PAH. Reducing dose frequency has the potential to ease patient burden and improve compliance. Additionally, we believe that INS1009 may be associated with fewer side effects, including elevated heart rate, low blood pressure, and severity and/or frequency of cough, associated with high initial drug levels and local upper airway exposure when using current inhaled prostanoid therapies. We believe INS1009 may offer a differentiated product profile for rare pulmonary disorders, including PAH, and we are currently evaluating our options to advance its development, including exploring its use as an inhaled dry powder formulation.

Phase 1 Study Results

In late 2014, we had a pre-IND meeting with the FDA for INS1009 and clarified that, subject to final review of the preclinical data, INS1009 could be eligible for an approval pathway under Section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) (505(b)(2) approval). Like a traditional NDA that is submitted under Section 505(b)(1) of the FDCA, a 505(b)(2) NDA must establish that the drug is safe and effective, but unlike a traditional NDA, the applicant may rely at least in part on studies not conducted by or for the applicant and for which the applicant does not have a right of reference. The ability to rely on existing third-party data to support safety and/or effectiveness can reduce the time and cost associated with traditional NDAs.

We have completed a phase 1 study of INS1009. The phase 1 study was a randomized, double-blind, placebo-controlled single ascending dose study of INS1009 for inhalation to determine its safety, tolerability, and pharmacokinetics in healthy volunteers. Twenty-four (24) patients were enrolled and received INS1009 with cohorts of eight patients receiving doses of 85 micrograms (mcg), 170 mcg, 340 mcg or placebo. Participants in the first cohort (8 patients) received a single dose of open label treprostinil (Tyvaso®) at 54 mcg 24 hours prior to receiving INS1009 at 85 mcg. The 85 mcg dose of INS1009 provides an equivalent amount of treprostinil on a molar basis as the 54 mcg dose of Tyvaso. The peak treprostinil serum concentration was approximately 90% lower after INS1009 administration compared with Tyvaso, which could indicate a reduced future adverse event (AE) profile. The pharmacokinetic characteristics also supported once- or twice-daily dosing. The longer half-life of treprostinil for INS1009 was likely due to a sustained pulmonary release. The AE profile was consistent with other inhaled prostanoids. These data were presented at the European Respiratory Society international congress in September 2016.

Research and Development

Research and development expenses consist of salaries, benefits and other related costs, including stock-based compensation, for personnel serving in our research and development functions, including medical affairs. Expenses also

include other internal operating expenses, the cost of manufacturing our drug candidate(s) for clinical study, the cost of conducting clinical studies, and the cost of conducting preclinical and research activities. In addition, our R&D expenses include payments to third parties for the license rights to products in development (prior to marketing approval), such as for INS1007. Our expenses related to manufacturing our drug candidate(s) for clinical study are primarily related to activities at contract manufacturing organizations (CMOs) that manufacture our product candidates for our use, including purchases of active pharmaceutical ingredients. Our expenses related to clinical trials are primarily related to activities at contract research organizations that conduct and manage clinical trials on our behalf. We incurred approximately $109.7 million, $122.7 million, and $74.3 million for research and development expenses in the years ended December 31, 2017, 2016, and 2015, respectively.

Corporate Development

In October 2016, we exclusively licensed global rights to INS1007 from AstraZeneca and we plan to continue to develop, acquire, in license or co-promote complementary products that address rare diseases. We are focused broadly on rare disease therapeutics and prioritizing those areas that best align with our core competencies.

Manufacturing

We do not have any in-house manufacturing capability other than for small-scale pre-clinical development programs, and depend completely on a small number of third-party manufacturers and suppliers for the manufacture of our product candidates for use in clinical trials. We plan to rely on third-party manufacturers and suppliers for the commercial manufacture and supply of any product candidates that we may commercialize. ALIS is manufactured currently by Therapure Biopharma Inc. (Therapure) in Canada at a 200 kilogram (kg) scale and by Ajinimoto Althea, Inc. (Althea) in the US at a 50 kg scale. For additional information about our agreements with Therapure and Althea, see *License and Other Agreements—ALIS-Related Agreements*. In order to meet potential commercial demand, if ALIS is approved, we funded the manufacturing expansion at Therapure in Canada that operates at a larger scale than Althea. We have also identified certain second source suppliers for our supply chain and plan to enter into supply and quality agreements with certain of these second source suppliers in preparation for commercialization of ALIS. In addition, we have entered into a commercialization agreement with PARI, the manufacturer of our drug delivery nebulizer for ALIS, to address our commercial supply needs (Commercialization Agreement).

In October 2017, we entered into certain agreements with Patheon UK Limited (Patheon) related to increasing our long-term production capacity for ALIS commercial inventory. The agreements provide for Patheon to manufacture and supply ALIS for our anticipated commercial needs. Under these agreements, we are required to deliver to Patheon the required raw materials, including active pharmaceutical ingredients, and certain fixed assets needed to manufacture ALIS. The investment in the long-term production capacity build-out, including these agreements, and related agreements or purchase orders with third parties for raw materials and fixed assets, is estimated to be approximately $60.0 million and will be incurred over the next three to four years.

In May 2017, we entered into a commercial supply agreement with AstraZeneca related to certain short-term production needs for INS1007. We expect our future requirements for INS1007, beyond phase 2, will be manufactured by a CMO.

We currently produce INS1009 and plan to utilize third parties to manufacture INS1009 at a larger scale and to manufacture the nebulizer used to deliver the drug.

Intellectual Property

We own or license rights to more than 350 issued patents and pending patent applications in the US and in foreign countries, including more than 175 issued patents and pending patent applications related to ALIS. Our success depends in large part on our ability to maintain proprietary protection surrounding our product candidates, technology and know-how; to operate without infringing the proprietary rights of others; and to prevent others from infringing our proprietary rights. We actively seek patent protection by filing patent applications, including on inventions that are important to the development of our business in the US, Japan, Europe, Canada, and selected other foreign markets that we consider key for our product candidates. These international markets generally include Australia, China, India, Israel, and Mexico.

Our patent strategy includes obtaining patent protection, where possible, on compositions of matter, methods of manufacture, methods of use, methods of treatment, dosing and administration regimens and formulations. We also rely on trade secrets, know-how, continuing technological innovation, in-licensing and partnership opportunities to develop and maintain our proprietary position.

We monitor for activities that may infringe our proprietary rights, as well as the progression of third-party patent applications that may have the potential to create blocks to our products or otherwise interfere with the development of our business. We are aware, for example, of US patents, and corresponding international counterparts, owned by third parties that

contain claims related to treating lung infections using inhaled antibiotics. If any of these patents were to be asserted against us, we do not believe that our proposed products would be found to infringe any valid claim of these patents.

Reflecting our commitment to safeguarding proprietary information, we require our employees, consultants, advisors, collaborators and other third-party partners to sign confidentiality agreements to protect the exchange of proprietary materials and information. We also seek to preserve the integrity and confidentiality of our data and trade secrets by maintaining physical security of our premises and physical and electronic security of our information technology systems.

ALIS Patents and Trade Secrets

Of the patents and applications related to ALIS, there are eight issued US patents and one allowed US patent application that cover the ALIS composition and its use in treating NTM. Upon approval of ALIS for the treatment of NTM, these patents may be eligible for listing in the FDA Orange Book. These patents and their expiration dates are as follows:

- US Patent No. 7,718,189 (expires June 6, 2025)
- US Patent No. 8,226,975 (expires August 15, 2028)
- US Patent No. 8,632,804 (expires December 5, 2026)
- US Patent No. 8,802,137 (expires April 8, 2024)
- US Patent No. 8,679,532 (expires December 5, 2026)
- US Patent No. 8,642,075 (expires December 5, 2026)
- US Patent No. 9,566,234 (expires January 18, 2034)
- US Patent No. 9,827,317 (expires April 8, 2024)
- US Patent No. 9,895,385 (expires May 15, 2035)

In addition, we own six pending US patent applications that cover the ALIS composition and/or its use in treating NTM. We also own a pending US application that covers methods for making ALIS. Upon approval of ALIS for the treatment of refractory NTM lung disease caused by MAC, these patent applications, if issued as patents, may be eligible for listing in the FDA Orange Book.

Four patents have been granted by the European Patent Office (EPO) (European Patent Nos. 1581236, 1909759, 1962805 and 2363114) that relate to ALIS and its use in treating NTM. In addition, we have five applications pending before the EPO that relate to ALIS and its use in treating NTM lung disease. We also have a pending European application that describes certain methods of making ALIS. More than 40 patents have also been issued in other major foreign markets, e.g., Japan, China, Korea, Australia, and India, that relate to ALIS and/or methods of using ALIS for treating various pulmonary disorders, including NTM lung disease. More than 60 foreign patent applications are pending that relate to the ALIS composition and/or its use in treating various pulmonary disorders, including NTM lung disease. We anticipate that in the US, we will have potential patent coverage for ALIS and its use in treating NTM lung disease, through May 15, 2035.

European Patent No. 2363114 was opposed by Generics (UK) Ltd, a wholly-owned subsidiary of Mylan NV, and was revoked in November 2017. We intend to appeal that decision, and the patent remains enforceable during the appeal. European Patent No. 1909759, owned by us, was previously opposed by Generics (UK) Ltd. An oral hearing was held on October 19, 2015, during which we submitted amended claims. The European Patent Office Opposition Division (EPOOD) maintained the patent as amended. This decision is currently under appeal by Generics (UK) Ltd.

Through our agreements with PARI, we have license rights to US and foreign patents and applications that cover the eFlow Nebulizer System medical device through January 18, 2034. We have rights to use the nebulizers in clinical trials, and we have entered into a commercial supply agreement with PARI.

The basic terms of utility patents issued in the US are the longer of 17 years from the issue date or 20 years from the earliest effective filing date, if the patent was in force on or was issued from a patent application that was filed prior to June 8, 1995; or 20 years from the earliest effective filing date, if the patent application was filed on or after June 8, 1995. All ALIS patent applications have earliest effective filing dates falling after June 8, 1995. The basic term of foreign utility patents may vary in accordance with provisions of applicable local law, but is typically 20 years from the earliest effective filing date.

INS1007 Patents

Through our agreement with AstraZeneca, we have licensed US Patent Nos. 9,522,894 and 9,815,805, which have claims directed to INS1007 and methods for using INS1007. Each expires January 21, 2035 (not taking into account any potential patent term extension). Counterpart patent applications are pending throughout the world and a continuation application is pending in the US.

INS1009 Patents

We own US Patent No. 9,255,064 (expires October 24, 2034), which is the first patent to issue with claims covering hexadecyl-treprostinil, the treprostinil component of INS1009. Other treprostinil prodrugs are also claimed and described in the

patent. We also own US Patent No. 9,469,600, which has claims directed to INS1009 and other treprostinil prodrug nanoparticle formulations and expires October 24, 2034. Counterpart patent applications to US Patent Nos. 9,255,064 and 9,469,600 are pending in Europe, Japan and other foreign jurisdictions.

We own pending patent applications that relate to methods for using treprostinil prodrugs and nanoparticle formulations comprising the same, including INS1009 in treating patients with PAH and other diseases, as well as methods for manufacturing such treprostinil prodrugs and nanoparticle formulations.

Trademarks

In addition to our patents and trade secrets, we have filed applications to register certain trademarks in the US and/or abroad, including INSMED and ARIKAYCE. At present, we have received either a registration or a notice of allowance for the INSMED and ARIKAYCE marks from the US Patent and Trademark Office. We have also received foreign notices of allowance or registrations for the INSMED and ARIKAYCE marks, among others. The EMA has indicated it has no objection to our use of the name ARIKAYCE, and the FDA has conditionally approved our use of the name ARIKAYCE as the proposed trade name for ALIS. Our ability to obtain and maintain trademark registrations will in certain geographical locations depend on making use of the mark in commerce on or in connection with our products and approval of the trademarks for our products by regulatory authorities in each country.

License and Other Agreements

ALIS-related Agreements

We currently rely, and will continue to rely, on agreements with a number of third parties in connection with the development and manufacture of ALIS.

PARI Pharma GmbH

We have a licensing agreement with PARI for use of the optimized eFlow Nebulizer System for delivery of ALIS in treating patients with NTM lung infections, CF and bronchiectasis. Under the licensing agreement, we have rights under several US and foreign issued patents, and patent applications involving improvements to the optimized eFlow Nebulizer System, to exploit such system with ALIS for the treatment of such indications, but we cannot manufacture such nebulizers except as permitted under our Commercialization Agreement with PARI. We currently have rights to use the nebulizers in clinical trials. The eFlow Nebulizer System is labeled as investigational for use in our clinical trials in the US, Japan, Canada and Australia and must receive regulatory approval before we can market ALIS; the eFlow Nebulizer System has been approved for use in the EU.

We have certain obligations under this licensing agreement in relation to specified licensed indications. With respect to CF, we are obligated to use commercially reasonable efforts to develop, obtain regulatory and reimbursement approval, market and sell ALIS in two or more major European countries. With respect to NTM, CF and bronchiectasis, we have specific obligations to use commercially reasonable efforts to achieve certain developmental and regulatory milestones by set deadlines. Additionally, for NTM, we are obligated to use commercially reasonable efforts to achieve certain commercial milestones in the US, Europe and Canada. The consequences of our failing to use commercially reasonable efforts to achieve these milestones are context-specific, but include ending PARI's non-compete obligation, making the license non-exclusive and terminating the license, in each case with respect to the applicable indication. Termination of the licensing agreement or loss of exclusive rights may occur if we fail to meet our obligations, including payment of royalties to PARI, or if we do not meet certain milestones contained in the licensing agreement such as obtaining marketing approval or achieving the first commercial sale of ALIS.

Under the licensing agreement, we paid PARI an upfront license fee and PARI is entitled to receive milestone payments up to an aggregate of €4.3 million either in cash, qualified stock or a combination of both, at PARI's discretion, based on achievement of certain future milestone events including first acceptance of MAA submission (or equivalent) in the US of ALIS and the device, first receipt of marketing approval in the US for ALIS and the device, and first receipt of marketing approval in a major EU country for ALIS and the device. In addition, PARI is entitled to receive royalty payments in the mid-single digits on the annual global net sales of ALIS pursuant to the licensing agreement, subject to certain specified annual minimum royalties. In October 2017, we exercised an option to buy-down the future royalties that will be payable to PARI.

This license agreement will remain in effect on a country-by-country basis until the final royalty payments have been made with respect to the last country in which ALIS is sold, or until the agreement is otherwise terminated by either party. We have the right to terminate this license agreement upon written notice for PARI's uncured material breach, if PARI is the subject of specified bankruptcy or liquidation events, or if PARI fails to reach certain specified obligations. PARI has the right to terminate this license agreement upon written notice for our uncured material breach, if we are the subject of specified bankruptcy or liquidation events, if we assign or otherwise transfer the agreement to a third party that does not agree to assume all of our rights and obligations set forth in the agreement, or if we fail to reach certain specified milestones.

In July 2014, we entered into a Commercialization Agreement with PARI for the manufacture and supply of eFlow nebulizer systems and related accessories (the Device) as optimized for use with ALIS. Under the Commercialization Agreement, PARI manufactures the Device except in the case of certain defined supply failures, when we will have the right to make the Device and have it made by third parties (but not certain third parties deemed under the Commercialization Agreement to compete with PARI). The Commercialization Agreement has an initial term of 15 years from the first commercial sale of ALIS pursuant to the licensing agreement (the Initial Term). The term of the Commercialization Agreement may be extended by us for an additional five years by providing written notice to PARI at least one year prior to the expiration of the Initial Term.

Althea

In September 2015, we entered into a Commercial Fill/Finish Services Agreement (the Fill/Finish Agreement) with Althea to produce, on a non-exclusive basis, ALIS in finished dosage form at a 50 kg scale. We are obligated to pay a minimum of $2.7 million for the batches of ALIS produced by Althea each calendar year during the term of the Fill/Finish Agreement. The Fill/Finish Agreement became effective as of January 1, 2015, and had an initial term that was to end on December 31, 2017. In 2016, we signed an extension of the Fill/Finish Agreement through December 31, 2019, and it may be extended for additional two-year periods upon mutual written agreement of us and Althea at least one year prior to the expiration of its then-current term. The Company has expensed at least the required minimum in each year of the contract.

Either we or Althea may terminate the Fill/Finish Agreement upon the occurrence of certain events, including (i) material breach of the Fill/Finish Agreement by either party, provided such breach is not cured within 30 days after receipt by the breaching party of written notice of the breach or (ii) insolvency or bankruptcy of the other party. In addition, we may terminate the Fill/Finish Agreement without cause with 12 months' prior written notice to Althea, and Althea may terminate the Agreement without cause with 24 months' prior written notice to us.

Therapure

In February 2014, we entered into a contract manufacturing agreement with Therapure for the manufacture of ALIS at a 200 kg scale. Pursuant to the agreement, we collaborated with Therapure to construct a production area for the manufacture of ALIS in Therapure's existing manufacturing facility in Mississauga, Ontario, Canada. Therapure manufactures ALIS for us on a non-exclusive basis. The agreement has an initial term of five years from the first date on which Therapure delivers ALIS to us after we obtain permits related to the manufacture of ALIS, and will renew automatically for successive periods of two years each, unless terminated by either party by providing the required two years' prior written notice to the other party. Notwithstanding the foregoing, the parties have rights and obligations under the agreement prior to the commencement of the initial term. Under the agreement, we are obligated to pay certain minimum amounts for the batches of ALIS produced each calendar year. The agreement allows for termination by either party upon the occurrence of certain events, including (i) the material breach by the other party of any provision of the agreement or the quality agreement expected to be entered into between the parties, and (ii) the default or bankruptcy of the other party. In addition, we may terminate the agreement for any reason upon no fewer than 180 days' advance notice.

Patheon & related agreements

In October 2017, we entered into certain agreements with Patheon related to increasing our long-term production capacity for ALIS commercial inventory. The agreements provide for Patheon to manufacture and supply ALIS for our anticipated commercial needs. Under these agreements, we are required to deliver to Patheon the required raw materials, including active pharmaceutical ingredients, and certain fixed assets needed to manufacture ALIS. Patheon's supply obligations will commence once certain technology transfer and construction services are completed. Our manufacturing and supply agreement with Patheon will remain in effect for a fixed initial term, after which it will continue for successive renewal terms unless either we or Patheon have given written notice of termination. The technology transfer agreement will expire when the parties agree that the technology transfer services have been completed. The agreements may also be terminated under certain other circumstances, including by either party due to a material uncured breach of the other party or the other party’s insolvency. These early termination clauses may reduce the amounts due to the relevant parties. The investment in our long-term production capacity build-out, including under the Patheon agreements and related agreements or purchase orders with third parties for raw materials and fixed assets, is estimated to be approximately $60.0 million and will be incurred over the next three to four years.

SynteractHCR, Inc. (Synteract)

We entered into a services agreement with Synteract pursuant to which we retained Synteract to perform implementation and management services in connection with the 212 study. We may terminate the services agreement or any work order for any reason and without cause with 30 days' written notice. Either party may terminate the agreement in the event of a material breach or, bankruptcy petition by the other party or, if any approval from a regulatory authority is revoked, suspended or expires without renewal. We anticipate that aggregate costs relating to all work orders for the 212 study will be

approximately $45 million over the period of the study. In April 2015, we entered into a work order with Synteract to perform implementation and management services for the 312 study. We anticipate that aggregate costs relating to all work orders for the 312 study will be approximately $25 million over the period of the study.

Cystic Fibrosis Foundation Therapeutics, Inc. (CFFT)

In 2004 and 2009, we entered into research funding agreements with CFFT whereby we received $1.7 million and $2.2 million for each respective agreement in research funding for the development of ALIS. If ALIS becomes an approved product for CF in the US, we will owe a payment to CFFT of up to $13.4 million that is payable over a three-year period after approval as a commercialized drug in the US. Furthermore, if certain global sales milestones are met within five years of the drug commercialization, we would owe an additional payment of $3.9 million. Under the 2009 agreement, in the event we terminate development of ALIS for CF prior to first commercial sale of a product containing ALIS for a period of 360 continuous days, and such termination is not for reasons outside of our reasonable control, then at CFFT's election and within 180 days of such termination, CFFT (1) may elect to develop ALIS for CF and (2) will have the right to receive from us an exclusive (subject to certain exceptions), royalty-free, sub-licensable license to use, develop, sell and commercialize a product containing ALIS in the treatment of certain infections in CF patients or pulmonary disease associated with CF.

INS1007-related License Agreement

In October 2016, we entered into the AZ License Agreement, pursuant to which AstraZeneca granted us exclusive global rights for the purpose of developing and commercializing AZD7986 (renamed INS1007). In consideration of the licenses and other rights granted by AstraZeneca, we made an upfront payment of $30.0 million in late October 2016. We are obligated to make a series of contingent milestone payments to AstraZeneca totaling up to an additional $85.0 million upon the achievement of clinical development and regulatory filing milestones. If we elect to develop INS1007 for a second indication, we will be obligated to make an additional series of contingent milestone payments totaling up to $42.5 million. We are not obligated to make any additional milestone payments for additional indications. In addition, we have agreed to pay AstraZeneca tiered royalties ranging from a high single-digit to mid-teen on net sales of any approved product based on INS1007 and one additional payment of $35.0 million upon the first achievement of $1 billion in annual net sales. The AZ License Agreement provides AstraZeneca with the option to negotiate a future agreement with us for commercialization of INS1007 in chronic obstructive pulmonary disease or asthma. If we fail to comply with our obligations under our agreements with AstraZeneca (including, among other things, if we fail to use commercially reasonable efforts to develop and commercialize a product based on INS1007, or we are subject to a bankruptcy or insolvency), AstraZeneca would have the right to terminate the license.

Competition

The biotechnology and pharmaceutical industries are highly competitive. We face potential competitors from many different areas including commercial pharmaceutical, biotechnology and device companies, academic institutions and scientists, other smaller or earlier stage companies and non-profit organizations developing anti-infective drugs and drugs for respiratory diseases. Many of these companies have greater human and financial resources and may have product candidates in more advanced stages of development and may reach the market before our product candidates. Competitors may develop products that are more effective, safer or less expensive or that have better tolerability or convenience. We also may face generic competitors where third-party payers will encourage use of the generic products. Although we believe that our formulation delivery technology, respiratory and anti-infective expertise, experience and knowledge in our specific areas of focus provide us with competitive advantages, these potential competitors could reduce our commercial opportunity. Additionally, there currently are, and in the future there may be, already-approved products for certain of the indications for which we are developing, or in the future may choose to develop, our product candidates. For instance, PAH is a competitive indication with established products, including other formulations of treprostinil.

NTM lung disease competitive overview

In the NTM lung disease market, our major competitors include pharmaceutical and biotechnology companies that have approved therapies or therapies in development for the treatment of chronic lung infections. While some companies have expressed interest in studying their products for NTM, we are not aware of any companies that are currently conducting clinical trials for the treatment of refractory NTM lung disease or of any approved inhaled therapies specifically indicated for refractory NTM lung infections in North America, Europe or Japan, but, as previously described, there is an ATS/IDSA-recommended treatment regimen that is utilized.

Government Regulation

Orphan Drug Designation

United States

Under the Orphan Drug Act (ODA), the FDA may grant orphan drug designation to drugs intended to treat a rare disease or condition (for the purposes of the ODA, "rare" is defined as a disease or condition for which the drug is intended

affects fewer than 200,000 people in the US) if it meets certain criteria specified by the ODA and FDA. After the FDA grants orphan drug designation, the drug and the specific intended use(s) for which it has obtained designation are listed by the FDA in a publicly-accessible database. The FDA has designated ALIS as an orphan drug for treatment of (i) infections caused by NTM, (ii) bronchiectasis in patients with *Pseudomonas* aeruginosa or other susceptible microbial pathogens and (iii) bronchopulmonary *Pseudomonas* aeruginosa infections in CF patients.

Orphan drug designation qualifies the sponsor for various development incentives of the ODA, including tax credits for qualified clinical testing, and a waiver of the NDA user fee (unless the application seeks approval for an indication not included in the orphan drug designation). Orphan drug designation also affords the company a period of exclusivity for the orphan indication upon approval of the drug. Specifically, the first NDA applicant with an FDA orphan drug designation for a particular active moiety to receive FDA approval of the drug for an indication covered by the orphan designation is entitled to a seven-year exclusive marketing period, often referred to as orphan drug exclusivity, in the US for that drug in that indication. A product that has several separate orphan designations may have several separate exclusivities for separate orphan indications. During the orphan drug exclusivity period, the FDA may not approve any other applications to market the same drug for the same indication for use, except in limited circumstances, such as a showing of clinical superiority to the product that has orphan drug exclusivity. Orphan drug exclusivity does not prevent the FDA from approving a different drug for the same disease or condition or the same drug for a different disease or condition, and it does not alter the timing or scope of the regulatory review and approval process; the sponsor must still submit evidence from clinical and non-clinical studies sufficient to demonstrate the safety and effectiveness of the drug.

Japan

The MHLW may, after hearing the opinion of the Pharmaceutical Affairs and Food Sanitation Council, grant orphan drug designation to a drug intended to treat a rare disease or condition if the drug meets the following conditions: (i) the number of target patients is less than 50,000 in Japan, (ii) the necessity of orphan drug designation is high from a medical point of view, (iii) there are sufficient theoretical grounds to use the drug for the target disease, and (iv) the plan for development of the drug is appropriate. Even if a drug is granted orphan drug designation, however, it does not always receive the manufacturing and marketing approval that is necessary for the drug to be sold or marketed in Japan.

Pharmaceutical manufacturers or distributors who have received orphan drug designation for a drug may be entitled to: (i) subsidies from the Japanese government through the National Institutes of Biomedical Innovation, Health and Nutrition (NIBIOHN); (ii) guidance and/or advice from the MHLW, PMDA and NIBIOHN for the study research of the drug; (iii) in principle, tax deductibility of 20% of the total research and research expenditures for the drug; (iv) priority review of their application; and (v) a re-examination interval period of 10 years (in general, drugs are subject to reexamination by the MHLW every eight years after receiving manufacturing/marketing approval).

European Union

The European Commission grants orphan drug designation to promote the development of drugs or biologics (1) for life-threatening or chronically debilitating conditions affecting not more than five in 10,000 people in the EU, or (2) for life threatening, seriously debilitating or serious and chronic condition in the EU where, without incentives, sales of the drug in the European Economic Area (the European Union plus Iceland, Lichtenstein, and Norway) (EEA) are unlikely to be sufficient to justify its development. Orphan drug designation is available either if no other satisfactory method of diagnosing, preventing or treating the condition is approved in the EEA or if such a method does exist but the proposed orphan drug will be of significant benefit to patients. The European Commission has granted an orphan designation for ALIS for the treatment of NTM lung disease.

If a drug with an orphan drug designation subsequently receives a marketing authorization for a therapeutic indication which is covered by such designation, the drug is entitled to orphan exclusivity. Orphan exclusivity means that the EMA or a national medicines agency may not accept another application for authorization, or grant an authorization, for a same or similar drug for the same therapeutic indication. Competitors may receive such a marketing authorization despite orphan exclusivity, provided that they demonstrate that the existing orphan product is not supplied in sufficient quantities or that the 'second' drug or biologic is clinically superior to the existing orphan product. The 'second' drug may but need not have an orphan designation as well. The period of orphan exclusivity is ten years, which can be extended by two years where an agreed pediatric investigation plan has been implemented. The exclusivity period may also be reduced to six years if the designation criteria are no longer met, including where it is shown that the product is sufficiently profitable not to justify maintenance of market exclusivity. Each orphan designation carries the potential for one market exclusivity for all the therapeutic indications that are covered by the designation. A product that has several separate orphan designations may have several separate market exclusivities.

Orphan drug designation also provides opportunities for free protocol assistance and fee reductions for access to the centralized regulatory procedure or fee exemptions for companies with a small and medium enterprises status. In addition,

Member States may provide national benefits to orphan drugs, such as early access to the reimbursement procedure or exemption from any turnover tax imposed on pharmaceutical companies.

The orphan designation may be applied for at any time during the development of the drug but before the application for marketing authorization. At the time of marketing authorization, the criteria for orphan designation are examined again, and the Commission decides on the maintenance of the orphan designation. The non-maintenance of the orphan designation means that the drug loses its orphan status and thus no longer benefits from orphan exclusivity, fee reductions or exemptions, and national benefits.

Drug Approval

United States

In the US, pharmaceutical products are subject to extensive regulation by the FDA and other government bodies. The FDCA and other federal and state statutes and regulations 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. Failure to comply with applicable US requirements at any time during product development, approval, or after approval may subject a company to a variety of administrative or judicial sanctions, such as imposition of clinical holds, FDA refusal to file or approve new drug applications, warning letters, product recalls, product seizures, total or partial suspension of production or distribution, injunctions, fines, refusals of government contracts, restitution, disgorgement, civil penalties, and criminal prosecution. The description below summarizes the current approval process in the US for our product candidates.

Preclinical Studies

Preclinical studies include laboratory evaluation of product chemistry, formulation and toxicity, and pharmacology, as well as animal trials to assess the characteristics and potential safety and efficacy of the product. The conduct of the preclinical tests must comply with federal regulations and requirements including the FDA's good laboratory practices (GLP) regulations and the US Department of Agriculture's regulations implementing the Animal Welfare Act. An IND sponsor must submit the results of the preclinical tests, together with manufacturing information, analytical data, any available clinical data or literature, and a proposed clinical trial protocol, among other things, to the FDA as part of an IND application. Certain non-clinical tests, such as animal tests of reproductive toxicity and carcinogenicity, may continue even after the IND is submitted. An IND automatically becomes effective 30 days after receipt by the FDA, unless before that time the FDA raises concerns or questions related to one or more proposed clinical trials and places the clinical trial on a clinical hold. In such a case, the IND sponsor and the FDA must resolve any outstanding concerns before the clinical trial can begin. As a result, submission of an IND may not result in the FDA allowing clinical trials to commence.

Clinical Trials

Clinical trials involve the administration of the investigational new drug to human subjects (healthy volunteers or patients) under the supervision of a qualified investigator. Clinical trials must be conducted (i) in compliance with all applicable federal regulations and guidance, including those pertaining to good clinical practice (GCP) standards that are meant to protect the rights, safety, and welfare of human subjects and to define the roles of clinical trial sponsors, investigators, and monitors as well as (ii) under protocols detailing, among other things, the objectives of the trial, the parameters to be used in monitoring safety, and the effectiveness criteria to be evaluated. Each protocol involving testing of a new drug in the US (whether in patients or healthy volunteers) must be included as a submission to the IND, and the FDA must be notified of subsequent protocol amendments, including new protocols. In addition, the protocol must be reviewed and approved by an institutional review board (IRB), and all study subjects must provide informed consent. Typically, before any clinical trial, each institution participating in the trial will require review of the protocol before the trial commences at that institution. Progress reports detailing the results of the clinical trials must be submitted at least annually to the FDA and there are additional, more frequent reporting requirements for certain adverse events.

A study sponsor might choose to discontinue a clinical trial or a clinical development program for a variety of reasons. The FDA may impose a temporary or permanent clinical hold, or other sanctions, if it believes that the clinical trial either is not being conducted in accordance with the FDA requirements or presents an unacceptable risk to the clinical trial subjects. An IRB may also require the clinical trial at the site to be halted, either temporarily or permanently, for failure to comply with the IRB's requirements, or may impose other conditions.

Clinical trials to support NDAs for marketing approval are typically conducted in three sequential pre-approval phases, but the phases may overlap or be combined. In Phase 1, short term (typically less than a few months) testing is conducted in a small group of subjects (typically 20-100), who may be patients with the target disease or condition or healthy volunteers, to evaluate its safety, determine a safe dosage range, and identify side effects. In Phase 2, the drug is given to a larger group of subjects (typically up to several hundred) with the target condition to further evaluate its safety and gather preliminary evidence of efficacy. Phase 3 studies typically last between several months and two years. In Phase 3, the drug is

given to a large group of subjects with the target disease or condition (typically several hundred to several thousand), often at multiple geographical sites, to confirm its effectiveness, monitor side effects, and collect data to support drug approval. Only a small percentage of investigational drugs complete all three phases of development and obtain marketing approval.

NDA

After completion of the required clinical testing, an NDA can be prepared and submitted to the FDA. FDA approval of the NDA is required before marketing of the product may begin in the US. The NDA is a large submission that must include, among other things, the results of all preclinical, clinical and other testing and a compilation of data relating to the product's pharmacology, chemistry, manufacture, and controls. The application also includes representative samples, copies of the proposed product labeling, patent information, and a financial certification or disclosure statement. The cost of preparing and submitting an NDA is substantial. Additionally, under federal law (as amended by the most recent reauthorization of the Prescription Drug User Fee Act (PDUFA VI) in the FDA Reauthorization Act of 2017 (FDARA)), most NDAs are subject to a substantial application fee and, upon approval, the applicant will be assessed an annual prescription drug program fee, both of which are adjusted annually. NDAs for orphan drugs are not subject to an application fee, unless the application includes an indication other than the orphan-designated indication. FDA also has the authority to grant waivers of certain user fees, pursuant to the FDCA.

The FDA has 60 days from its receipt of an NDA to determine whether the application is accepted for filing based on the FDA's threshold determination that it is sufficiently complete to permit substantive review. Once the submission is accepted for filing, the FDA begins a substantive review. The FDA may refer applications for novel drug products or drug products that present difficult questions of safety or efficacy to an advisory committee, typically a panel that includes outside clinicians and other experts, for review, evaluation and a recommendation as to whether the application should be approved. The FDA is not bound by the recommendation of an advisory committee, but it generally follows such recommendations.

Before approving an NDA, the FDA will typically inspect one or more clinical sites to assure compliance with GCP. Additionally, the FDA will typically inspect the facility or the facilities at which the drug is manufactured. FDA will not approve the product unless compliance with current good manufacturing practices (cGMP) is satisfactory and the NDA contains data that provide substantial evidence of effectiveness for the proposed indication, generally consisting of adequate and well-controlled clinical investigations, and that the drug is safe for use under the conditions of use in the proposed labeling. The FDA also reviews the proposed labeling submitted with the NDA and typically requires changes in the labeling text.

After the FDA evaluates the NDA and the manufacturing and testing facilities, it issues either an approval letter or a complete response letter. Complete response letters generally outline the deficiencies in the submission and delineate the additional testing or information needed in order for the FDA to reconsider the application. If and when those deficiencies have been addressed to the FDA's satisfaction in a resubmission of the NDA, the FDA will issue an approval letter. An approval letter, which may specify post approval requirements, authorizes commercial marketing of the drug for the approved indication or indications and the other conditions of use set out in the approved prescribing information. Once granted, product approvals may be withdrawn if compliance with regulatory standards is not maintained or problems are identified following initial marketing. Under priority review status, the FDA has 180 days from either the 60 day filing date (in the case of NME NDA submissions) or the date of receipt of the NDA (in the case of non-NME original NDA submissions) to issue either an approval letter or a complete response letter, unless the review period is adjusted by mutual agreement between the FDA and the applicant or as a result of the applicant submitting a major amendment. The FDA's current performance goals call for the FDA to complete review of 90 percent of standard (non-priority) NDAs within 10 months and priority NDAs within six months of filing.

As a condition of NDA approval, the FDA may require substantial post-approval testing, known as phase 4 studies, to be conducted in order to gather additional information on the drug's effect in various populations and any side effects associated with long-term use. Beyond routine post marketing safety surveillance, the FDA may require specific additional surveillance to monitor the drug's safety or efficacy and may impose other conditions, including labeling restrictions that can materially affect the potential market and profitability of the drug. As a condition of approval, or after approval, the FDA also may require submission of a risk evaluation and mitigation strategy (REMS) to mitigate any identified or suspected serious risks. The REMS may include medication guides, physician communication plans, assessment plans, and elements to assure safe use, such as restricted distribution methods, patient registries, or other risk minimization tools. Further post-approval requirements are discussed below.

Expedited Review and Approval of Eligible Drugs

Under the FDA's accelerated approval program, the FDA may approve certain drugs for serious or life-threatening conditions on the basis of a surrogate or intermediate endpoint that is reasonably likely to predict clinical benefit, which can substantially reduce time to approval. A surrogate endpoint used for accelerated approval is a marker—a laboratory measurement, radiographic image, physical sign or other measure that is thought to predict clinical benefit, but is not itself a measure of clinical benefit. An intermediate clinical endpoint is a clinical endpoint that can be measured earlier than

irreversible morbidity and mortality (IMM) that is reasonably likely to predict an effect on IMM or other clinical benefit. The FDA bases its decision on whether to accept the proposed surrogate or intermediate clinical endpoint on the scientific support for that endpoint.

As a condition of accelerated approval, the FDA typically requires certain post-marketing clinical studies to verify and describe clinical benefit of the product, and may impose restrictions on distribution to assure safe use. Post marketing studies would usually be required to be studies already underway at the time of the accelerated approval. In addition, promotional materials for an accelerated approval drug to be used in the first 120 days post-approval must be submitted to the FDA prior to approval, and materials to be used after that 120-day period must be submitted 30 days prior to first use. If the required post-marketing studies fail to verify the clinical benefit of the drug, or if the applicant fails to perform the required post-marketing studies with due diligence, the FDA may withdraw approval of the drug under streamlined procedures in accordance with the agency's regulations. The agency may also withdraw approval of a drug if, among other things, the promotional materials for the product are false or misleading, or other evidence demonstrates that the drug product is not shown to be safe or effective under its conditions of use.

The FDA also has various programs—fast track designation, priority review, and breakthrough designation—that are intended to expedite or streamline the process for the development and FDA review of drugs that meet certain qualifications. The purpose of these programs is to provide important new drugs to patients earlier than under standard FDA review procedures. The programs each have different eligibility criteria and provide different benefits, and can be applied either alone or in combination depending on an applicant's circumstances. Fast track designation applies to a drug that is intended to treat a serious condition and for which nonclinical or clinical data demonstrate the potential to address unmet medical need. It should be requested at the time of IND submission or ideally no later than the pre-NDA meeting. The FDA must respond to requests for fast track designation within 60 days of receipt of the request. If granted, the applicant is eligible for actions to expedite development and review, such as frequent interaction with the review team, as well as for rolling review, meaning that the applicant may submit sections of the application as they are available. The timing of FDA's review of these sections depends on a number of factors, and the review clock does not start running until the agency has received a complete NDA submission. The FDA may withdraw fast track designation if the agency determines that the designation is no longer supported by data emerging in the clinical trial process.

Priority review applies to an application (both original and efficacy supplement) for a drug that treats a serious condition and that, if approved, would provide a significant improvement in safety or effectiveness. It also applies to any supplement that proposes a labeling change pursuant to a report on a pediatric study. A request for priority review is submitted at the time of NDA or supplemental NDA submission. The FDA must respond within 60 days of receipt of the request. If granted, the review time is shortened from the standard 10 months to 6 months, beginning either at the 60 day filing date (in the case of NME NDA submissions) or the date of receipt (in the case of non-NME original NDA submissions).

Breakthrough therapy designation applies to a drug that is intended to treat a serious condition and for which preliminary clinical evidence indicates that the drug may demonstrate substantial improvement on a clinically significant endpoint(s) over available therapies. It can be requested with the IND submission and ideally no later than the end-of-phase 2 meeting. The FDA must respond within 60 days of receipt of the request. If granted, the applicant receives intensive guidance on efficient drug development, intensive involvement of senior managers and experienced review and regulatory health project management staff in a proactive, collaborative, cross-disciplinary review, rolling review, and other actions to expedite review. Designation may be rescinded if the product no longer meets the criteria for breakthrough therapy designation. ALIS has been designated as a breakthrough therapy.

Drugs that are designated as QIDPs are eligible for priority review and fast track designation, and well as market exclusivity. A product is eligible if it is an antibacterial or anti-fungal drug for human use that is intended to treat serious or life-threatening infections, including: those caused by an anti-bacterial or anti-fungal resistant pathogen, including novel or emerging infectious pathogens; or caused by qualifying pathogens listed by the FDA. A drug sponsor may request that the FDA designate its product as a QIDP at any time prior to NDA submission. The FDA must make a QIDP determination within 60 days of receiving the designation request. ALIS has been designated as a QIDP for NTM lung disease.

Exclusivities

After NDA approval, owners of relevant drug patents may apply for up to a five-year patent extension on a single patent. The allowable patent term extension is calculated as half of the drug's testing phase (the time between IND application and NDA submission) and all of the review phase (the time between NDA submission and approval) up to a maximum of five years. The time can be shortened if the FDA determines that the applicant did not pursue approval with due diligence. The total patent term after the extension may not exceed 14 years. For patents that might expire during the application phase, the patent owner may request an interim patent extension. An interim patent extension increases the patent term by one year and may be renewed up to four times. For each interim patent extension granted, the post-approval patent extension is reduced by one year. The director of the United States Patent and Trademark Office must determine that approval of the drug covered by the patent

for which a patent extension is being sought is likely. Interim patent extensions are not available for a drug for which an NDA has not been submitted.

A variety of non-patent exclusivity periods are available under the FDCA that can delay the submission or approval of certain applications for competing products.

A five-year period of non-patent exclusivity within the US is granted to the first applicant to gain approval of an NDA for a new chemical entity (NCE). An NCE is a drug that contains no active moiety (the molecule or ion responsible for the action of the drug substance) that has been approved by the FDA in any other application submitted under section 505(b) of the Act. During the exclusivity period for a NCE, the FDA may not accept for review an abbreviated new drug application, or ANDA, or a 505(b)(2) NDA submitted by another company that references (i.e., relies on FDA prior approval of) the NCE drug. However, an ANDA or 505(b)(2) NDA may be submitted after four years if it contains a certification of patent invalidity or non-infringement with respect to a patent listed with the FDA for the reference NDA.

A three-year period of non-patent exclusivity is granted for a drug product that contains an active moiety that has been previously approved, when the application contains reports of new clinical investigations (other than bioavailability studies) conducted or sponsored by the sponsor that were essential to approval of the application, for example, for new indications, dosages, strengths or dosage forms of an existing drug. This three-year exclusivity covers only the conditions of use associated with the new clinical investigations, which means that the FDA may approve applications for other versions of the original, unmodified drug product. Where this form of exclusivity applies, it prevents FDA approval of an ANDA or 505(b)(2) NDA subject to the exclusivity for the three-year period; however, the FDA may accept and review ANDAs or 505(b)(2) NDAs during the three-year period.

These exclusivities also do not preclude FDA approval of a 505(b)(1) application for a duplicate version of the drug during the period of exclusivity, provided that the applicant conducts or obtains a right of reference to all of the preclinical studies and adequate and well-controlled clinical trials necessary to demonstrate safety and effectiveness.

Products with QIDP designation may receive a five-year extension of other non-patent exclusivities for which the drug is also eligible. The exclusivity does not prevent the FDA from approving a subsequent application for a change to the QIDP-designated drug that results in a new indication, route of administration, dosing, schedule, dosage form, delivery system, delivery device or strength. For example, a drug that has been designated as both an orphan drug and a QIDP for the same indication, like ALIS, could be eligible for a combined 12 years of exclusivity for that indication.

Medical Device Regulation

Medical devices, such as the eFlow Nebulizer System, may receive marketing authorization from the FDA as stand-alone devices, or in some cases, may receive marketing authorization as part of a combination product. In either case, the ultimate product will need to satisfy FDA requirements. The primary pathways for marketing authorization for devices in the US are 510(k) clearance or premarket approval (PMA).

Medical devices are also subject to certain post-clearance, post-approval requirements. Those requirements include continuing Quality System Regulation compliance, Medical Device Reporting, Correction and Removal, and requirements governing labeling and promotional advertising.

The FDCA permits medical devices intended for investigational use to be shipped to clinical sites if such devices comply with prescribed procedures and conditions. Devices intended for investigational use may be exempted from premarket notification and premarket approval requirements when shipped for use in clinical trials, but they must bear a label indicating that they are for investigational use. This labeling may not represent that the device is safe or effective for the purposes for which it is being investigated.

Combination Products

A combination product is a product comprising two or more regulated components (e.g., a drug and device) that are combined into a single product, co-packaged, or sold separately but intended for co-administration, as evidenced by the labeling for the products. A drug that is administered using a nebulizer, such as ALIS or INS1009, is an example of a combination drug/device product.

The FDA is divided into various Centers, which each have authority over a specific type of product. NDAs are reviewed by personnel within the Center for Drug Evaluation and Research, while device applications and premarket notifications are reviewed by the Center for Devices and Radiological Health. Combination products, such as drug/device combinations, generally will be reviewed by the Center that regulates the product's primary mode of action (PMOA), which is the single mode of a combination product that provides the most important therapeutic action of the combination product. If the PMOA is unclear or in dispute, a sponsor may file a Request for Designation with FDA’s Office of Combination Products (OCP), which will render a determination and assign a lead Center. OCP generally assigns jurisdiction based on PMOA. If there are two independent modes of action, neither of which is subordinate to the other, the FDA makes a determination as to

which Center to assign the product based on consistency with other combination products raising similar types of safety and effectiveness questions or to the Center with the most expertise in evaluating the most significant safety and effectiveness questions raised by the combination product.

When evaluating an application for a combination product, a lead Center may consult other Centers and apply the standards that would be applicable but still retain reviewing authority, or it may assign review of a specific section of the application to another Center, delegating its review authority for that section. Depending on the type of combination product, approval or clearance could be obtained through submission of a single marketing application or through separate applications for the individual constituent parts (e.g., an NDA for the drug and a premarket notification for the device). The FDCA directs the FDA to conduct a review of a combination product under a single marketing application whenever appropriate. The agency has the discretion to require separate applications to more than one Center, and applicants may choose to submit separate applications for constituent parts of a combination (unless the FDA determines one application is necessary). One reason to submit multiple applications is if the applicant wishes to receive some benefit that accrues only from approval under a particular type of application, like new drug product exclusivity. If multiple applications are submitted, each application is generally reviewed by the Center with authority over each application type. For combination products that contain an approved constituent part (such as a drug-device combination product in which the device has previously received clearance), the FDA may require that the application(s) include only such information as is necessary to meet the standard for clearance or approval, taking into account any prior finding of safety or effectiveness for the approved constituent part.

Like their constituent products—e.g., drugs and devices—combination products are highly regulated and subject to a broad range of post marketing requirements including cGMPs, adverse event reporting, periodic reports, labeling and advertising and promotion requirements and restrictions.

Disclosure of Clinical Trial Information

Under US and certain foreign laws intended to improve clinical trial transparency, sponsors of clinical trials may be required to register and disclose certain information about their clinical trials. This can include information related to the investigational drug, patient population, phase of investigation, study sites and investigators, and other aspects of the clinical trial. This information is then made publicly available. Under a recently revised regulation in the US, sponsors are obligated to disclose the results of these trials after completion (prior to the new rulemaking, disclosure of results was only required if the product or new indication was approved by the FDA). In the US, disclosure of the results of these trials can be delayed for up to two years if the sponsor is seeking approval of the product or a new indication. Competitors may use this publicly-available information to gain knowledge regarding the progress of development programs.

Other Post-approval Regulatory Requirements

Once an NDA is approved, a product will be subject to certain post-approval requirements, including those relating to advertising, promotion, adverse event reporting, recordkeeping, and cGMP, as well as registration, listing, and inspection. There also are continuing, annual user fee requirements, as well as new application fees for supplemental applications with clinical data.

The FDA regulates the content and format of prescription drug labeling, advertising, and promotion, including direct-to-consumer advertising and promotional Internet communications. FDA also establishes parameters for permissible non-promotional communications between industry and the medical community, including industry-supported scientific and educational activities. The FDA and other agencies actively enforce the laws and regulations prohibiting the promotion for uses not consistent with the approved labeling, and a company that is found to have improperly promoted off-label uses or otherwise not to have met applicable promotion rules may be subject to significant liability under both the FDCA and other statutes, including the False Claims Act.

Manufacturers are subject to requirements for adverse event reporting and submission of periodic reports following FDA approval of an NDA.

All aspects of pharmaceutical manufacture must conform to cGMPs after approval. Drug manufacturers and certain of their subcontractors are required to register their establishments with the FDA and certain state agencies, and are subject to periodic unannounced inspections by the FDA during which the FDA inspects manufacturing facilities to assess compliance with cGMPs. Changes to the manufacturing process are strictly regulated and often require prior FDA approval before being implemented. FDA regulations also require investigation and correction of any deviations from cGMP and impose reporting and documentation requirements upon the sponsor and any third-party manufacturers that the sponsor may decide to use. Accordingly, manufacturers must continue to expend time, money and effort in the areas of production and quality control to maintain compliance with cGMPs.

Drugs may be marketed only for the approved indications and in accordance with the provisions of the approved labeling. Changes to some of the conditions established in an approved application, including changes in indications, labeling, product formulation, or manufacturing processes or facilities, require submission and FDA approval of a new NDA or NDA

supplement, in some cases before the change may be implemented. An NDA supplement for a new indication typically requires clinical data similar to that in the original application, and the FDA uses the same procedures and actions in reviewing NDA supplements as it does in reviewing NDAs.

As previously mentioned, the FDA also may require phase 4 studies and may require a REMS, which could restrict the distribution or use of the product.

In addition, the distribution of prescription pharmaceutical products is subject to the Prescription Drug Marketing Act (PDMA), which regulates the distribution of drugs and drug samples at the federal level, and sets minimum standards for the registration and regulation of drug distributors by the states. Both the PDMA and state laws limit the distribution of prescription pharmaceutical product samples and impose requirements to ensure accountability in distribution.

Japan

Under the Japanese regulatory system administered by the MHLW and the PMDA (which is responsible for product review and evaluations under the supervision of the MHLW), pre-marketing approval and clinical studies are required for all pharmaceutical products. The Law on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices (Act No. 145 of 1960) requires a license for marketing authorization when importing to Japan and selling pharmaceutical products manufactured in other countries. It also requires a foreign manufacturer to get each of its manufacturing sites certified as a manufacturing site of pharmaceutical products to be marketed in Japan. To receive a license for marketing authorization, the manufacturer or seller must, at the very least, employ certain manufacturing marketing, quality and safety personnel. A license for marketing authorization may not be granted if the quality management methods and post marketing safety management methods applied with respect to the pharmaceutical product fail to conform to the standards stipulated in the ordinances promulgated by the MHLW. To obtain manufacturing/marketing approval for a new product, a Company must submit an application for approval to the MHLW with results of nonclinical and clinical studies to show the quality, efficacy and safety of the product candidate. A data compliance review, on-site inspection for good clinical practice, audit and detailed data review for compliance with current good manufacturing practices are undertaken by the PMDA. The application is then discussed by the committees of the Pharmaceutical Affairs and Food Sanitation Council. Based on the results of these reviews, the final decision on approval is made by the MHLW. The time required for the approval process varies depending on the product, but it can take years. The product also needs approval for pricing to be applied for redemption of health insurance. The medical products which once are approved and marketed are also subject to regular post-marketing vigilance of safety and quality under the standards of Good Manufacturing Practice. In Japan, the National Health Insurance system maintains a Drug Price List specifying which pharmaceutical products are eligible for reimbursement, and the MHLW sets the prices of the products on this list. After receipt of marketing approval, negotiations regarding the reimbursement price with the MHLW would begin. Price would be determined within 60 to 90 days unless the applicant disagrees, which may result in extended pricing negotiations. The government generally introduces price cut rounds every other year and also mandates price decreases for specific products. New products judged innovative or useful, that are indicated for pediatric use, or that target orphan or small population diseases, however, may be eligible for a pricing premium. The government has also promoted the use of generics, where available.

European Union

Marketing Authorization Application

To obtain approval of a drug under the EU regulatory system, an application for a marketing authorization may be submitted under a centralized, a decentralized or a national procedure. The centralized procedure, which is compulsory for medicines produced by certain biotechnological processes or for orphan drugs, provides for the grant of a single marketing authorization that is valid for all EU member states, which grants the same rights and obligations in each member state as a national marketing authorization. As a general rule, only one marketing authorization may be granted for drugs approved through the centralized procedure and the marketing authorization is also relevant for the EEA countries.

Under the centralized procedure, the Committee for Medicinal Products for Human Use (CHMP) is required to adopt an opinion on a valid application within 210 days, excluding clock stops when additional information is to be provided by the applicant in response to questions. More specifically, on day 120 of the procedure, once the CHMP has received the preliminary assessment reports and opinions from the Rapporteur and Co-Rapporteur designated by the CHMP, it adopts a list of questions, which are sent to the applicant together with the CHMP's overall conclusions. Applicants then have three months to respond to the CHMP (and can request a three-month extension). The Rapporteur and Co-Rapporteur assess the applicant's replies, revise the assessment report as necessary and may prepare a list of outstanding issues. The revised assessment report and list of outstanding issues are sent to the applicant together with the CHMP's recommendation by day 180 of the procedure. Applicants then have one month to respond to the CHMP (and can request a one or two-month extension). The Rapporteur and Co-Rapporteur assess the applicant's replies, submit them for discussion to the CHMP and prepare a final assessment report.

Once its scientific evaluation is completed, the CHMP gives a favorable or unfavorable opinion as to whether to grant the marketing authorization. After the adoption of the CHMP opinion, a decision must be adopted by the European Commission, after consulting the Standing Committee of the Member States. The European Commission prepares a draft decision and circulates it to the member states; if the draft decision differs from the CHMP opinion, the Commission must provide detailed explanations. The European Commission adopts a decision within 15 days of the end of the consultation procedure.

Accelerated Procedure, Conditional Approval and Approval Under Exceptional Circumstances

Various programs, including accelerated procedure, conditional approval and approval under exceptional circumstances, are intended to expedite or simplify the approval of drugs that meet certain qualifications. The purpose of these programs is to provide important new drugs to patients earlier than under standard approval procedures.

For drugs which are of major interest from the point of view of public health, in particular from the viewpoint of therapeutic innovation, applicants may submit a substantiated request for accelerated assessment. If the CHMP accepts the request, the review time is reduced from 210 to 150 days.

Furthermore, for certain categories of medicinal products, marketing authorizations may be granted on the basis of less complete data than is normally required in order to meet unmet medical needs of patients or in the interest of public health. In such cases, the company may request, or the CHMP may recommend, the granting of a marketing authorization, subject to certain specific obligations; such marketing authorization may be conditional or under exceptional circumstances. The timelines for the centralized procedure described above also apply with respect to applications for a conditional marketing authorization or marketing authorization under exceptional circumstances.

Conditional marketing authorizations may be granted for products designated as orphan medicinal products, if all of the following conditions are met: (1) the risk-benefit balance of the product is positive, (2) the applicant will likely be in a position to provide the required comprehensive clinical trial data, (3) the product fulfills unmet medical needs, and (4) the benefit to public health of the immediate availability on the market of the medicinal product concerned outweighs the risk inherent in the fact that additional data are still required.

Conditional marketing authorizations are valid for one year, on a renewable basis until the holder provides a comprehensive data package. The granting of conditional marketing authorization depends on the applicant's ability to fulfill the conditions imposed within the agreed upon deadline. They are subject to "conditions", i.e. the holder is required to complete ongoing studies or to conduct new studies with a view to confirming that the benefit-risk balance is positive or to fulfill specific obligations in relation to pharmacovigilance. Once the holder has provided a comprehensive data package, the conditional marketing authorization is replaced by a 'regular' marketing authorization.

Marketing authorizations under exceptional circumstances may be granted where the applicant demonstrates that, for objective and verifiable reasons, they are unable to provide comprehensive data on the efficacy and safety of the drug under normal conditions of use. Such marketing authorizations are subject to certain conditions, in particular relating to safety of the drug, notification of incidents relating to its use or actions to be taken. They are valid for an indefinite period of time, but the conditions upon which they are based are subject to an annual reassessment in order to ensure that the risk-benefit balance remains positive.

Exclusivities

If an approved drug contains a new active substance, it is protected by data exclusivity for eight years from the notification of the Commission decision granting the marketing authorization and then by marketing protection for an additional two or three years. Overall, the drug is protected for ten or eleven years against generic competition, and no additional exclusivity protection is granted for any new development of the active substance it contains.

During the eight-year period of data exclusivity, competitors may not refer to the marketing authorization dossier of the approved drug for regulatory purposes. During the period of marketing protection, competitors may not market their generic drugs. The period of marketing protection is normally two years but may become three years if, during the eight-year data exclusivity period, a new therapeutic indication is approved that is considered as bringing a significant clinical benefit over existing therapies.

Medical Devices Regulations

In the EU, the marketing of medical devices is not subject to a prior approval by a health authority, but, depending on the class of device, may require prior review by a Notified Body. Notified Bodies are technical review bodies that are accredited and supervised by national health authorities. They conduct conformity assessment procedures of, among others, medical devices.

Medical devices are generally governed by Directive 93/42/EEC on Medical Devices that harmonizes the conditions for placing medical devices on the European market. This Directive however does not regulate certain important marketing aspects, such as advertising or pricing and reimbursement, which remain governed by national law.

Directive 93/42 requires medical devices to meet the essential requirements which are enumerated in the annexes to the Directive. Compliance with those requirements is demonstrated by the CE mark as the manufacturer may only affix the CE mark if it may declare conformity with the essential requirement for each medical device that is marketed. Directive 93/42 provides recourse to harmonized European standards in order to facilitate compliance with the essential requirements. Harmonized standards provide a presumption of conformity with the essential requirements.

Directive 93/42 institutes several conformity assessment procedures. The relevant conformity assessment procedure depends on the type of medical device and the risks involved. Devices are divided in four groups: Class I, Class IIa, Class IIb, and Class III. Class I devices present the lowest level of risk so that, for most of these devices the manufacturer can self-certify the product and need not rely on certification by a Notified Body. For the other classes, a Notified Body must review the manufacturer's procedures and/or the product. Every device is initially classified by the manufacturer. However, the Notified Body may dispute the classification and assert that the device should be included in a class requiring stricter conformity assessment procedures. Specific rules apply to custom-made medical devices, medical devices that are used in clinical trials, and medical devices that incorporate a medicinal ingredient.

For classes of devices other than Class I, a manufacturer must have a Notified Body test and certify conformity of its design and production procedures or its products with the essential requirements of Directive 93/42. Certification takes the form of a certificate of conformity issued by the Notified Body, which is valid throughout the European Union. Upon certification by the Notified Body, the manufacturer affixes the CE mark to the medical device, which allows the product to move freely within the EU and thus prevents EU Member States from restricting sales and marketing of the devices, unless such measure is justified on the basis of evidence of non-compliance. Ultimately, the manufacturer is responsible for the conformity of the device with the essential requirements and for the affixing of the CE mark. The eFlow Nebulizer System is CE marked by PARI in the EU.

Manufacturers of medical devices are subject to materiovigilance obligations that require reporting of incidents or near incidents related to the use of a medical device, which incidents may demonstrate the need for corrective action by the manufacturer. In addition, Notified Bodies regularly re-assess the conformity of a medical device to the essential requirements of Directive 93/42 and may from time to time audit the manufacturer and may, where needed, suspend or withdraw the manufacturer's certificate of conformity.

Pediatric Information

United States

Under the Pediatric Research Equity Act of 2003 (PREA), NDAs and NDA supplements must contain data that are adequate to assess the safety and effectiveness of the drug for the claimed indications in all relevant pediatric subpopulations and to support dosing and administration for each pediatric subpopulation for which the drug is safe and effective. The FDA may, on its own initiative or at the request of an applicant, grant deferrals for submission of data or full or partial waivers. Unless otherwise required by regulation, PREA does not apply to any drug for an indication for which orphan designation has been granted. Under the Best Pharmaceuticals for Children Act (BPCA), pediatric research is incentivized by the possibility of six additional months of pediatric exclusivity, which if granted, is added to existing exclusivity periods and patent terms listed for the applicable drug in the FDA's Orange Book at the time the sponsor satisfies the FDA's "written request" for pediatric research. Sponsors may seek to negotiate the terms of a written request during drug development. While the sponsor of an orphan designated drug may not be required to perform pediatric studies under PREA, they are eligible to participate in the incentives under the BPCA.

Japan

In Japan, there is no statutory rule which imposes any obligation on pharmaceutical manufacturers engaging in pediatric drug development. However, the guidelines of the MHLW (Handling of Pharmaceuticals during the Reexamination Interval Period (Issue No. 107, February 1, 1999 and No. 1324, December 27, 2000)) state as follows: (i) since information on pediatric patients obtained in clinical trials may be limited, the MHLW recommends that pharmaceutical manufacturers conduct adequate post-marketing surveillance during the reexamination interval period and collect as much information as possible for proper use of drugs for pediatric patients; and (ii) if a pharmaceutical manufacturer plans to conduct a clinical trial to set the dose of a pediatric drug to prepare application for manufacturing/marketing approval or after receiving the same approval, the reexamination interval period may be extended up to 10 years. In addition, since 2010 the MHLW has been promoting the development of children’s drugs that have been approved for use in Europe and the US but are not yet approved in Japan, so that they can be used as early as possible in Japan as well.

European Union

In the EU, new drugs (i.e. drugs containing a new active substance) for adults, must also be tested in children. This mandatory pediatric testing is carried out through the implementation of a pediatric investigation plan, or PIP, which is proposed by the applicant and approved by the EMA. A PIP contains all the studies to be conducted and measures to be taken in order to support the approval of the new drug, including pediatric pharmaceutical forms, in all subsets of the pediatric population. Validation of the marketing authorization application for adults is subject to the implementation of the PIP, subject to one or more waivers or deferrals. On the one hand, the PIP may allow a deferral for one or more of the studies or measures included therein in order not to delay the approval of the drug in adults, and, on another hand, the EMA may grant either a product-specific waiver for the (adult) disease/condition or one or more pediatric subsets or a class waiver for the disease/condition. PIPs are subject to modifications from time to time, when they no longer are workable. Prior to obtaining the validation of a marketing authorization application for adults, the applicant has to demonstrate compliance with the PIP at the time of submission of the application. In the case of orphan medicinal products, completion of an approved PIP can result in an extension of the market exclusivity period from ten to twelve years.

Regulation Outside the US, Japan and Europe

In addition to regulations in the US, Japan and Europe, we will be subject to a variety of regulations in other jurisdictions governing clinical studies of our candidate products, including medical devices. Regardless of whether we obtain FDA approval for a product candidate, we must obtain approval of the product candidate (including a medical device) by the comparable regulatory authorities of countries outside the US before we can commence clinical studies or marketing of the product candidate in those countries. The requirements for approval and the approval process vary from country to country, and the time may be longer or shorter than that required for FDA approval. Under certain harmonized medical device approval/clearance regulations outside the US, reference to US clearance permits fast-tracking of market clearance. Other regions are harmonized with EU standards, and therefore recognize the CE mark as a declaration of conformity to applicable standards. Furthermore, we must obtain any required pricing approvals in addition to regulatory approval prior to launching a product candidate in the approving country.

Health Canada

Health Canada (HC) is the government agency that provides regulatory and marketing approval for drugs and therapeutic products in Canada. The ongoing Legislative and Regulatory Modernization (LRM) is the most significant drug regulatory system reform in Canada in more than 50 years and is expected to overhaul Canada's Food and Drugs Act and Regulations. The LRM supports a 'lifecycle' regulatory approach and is focused on strengthening evidence-based decision making, good regulatory planning, licensing, post-licensing, accountability, authority and enforcement. Through this framework, HC intends to improve the market authorization process and implement necessary regulatory frameworks. In October 2010, HC accelerated its modernization efforts. This included the proposed regulatory pathways for orphan drugs (harmonized with US/EU regulations).

Australia

The Therapeutic Goods Administration (TGA) is the regulatory body, under the Australian Department of Health, responsible for conducting assessment and monitoring activities of therapeutic goods in Australia. Products under the jurisdiction of the TGA include prescription medicines, medical devices (simple and complex), diagnostic products, vaccines, and biologics. Activities of the TGA include classifying the product based on risk to the person, implementing appropriate regulatory controls for the manufacturing processes, and monitoring approved products with a comprehensive adverse event reporting program. The TGA requires that a marketing authorization be submitted and reviewed for safety and efficacy, and approved before a medication can be marketed and provided to patients commercially. A separate regulatory pathway is utilized to conduct clinical trials in Australia. Australia has also an Orphan drug designation.

Early Access Programs in the European Union

Under EU law, member states are authorized to adopt national legal regimes for the supply or use of non-authorized drugs in case of therapeutic needs. The most common national legal regimes are compassionate use programs and named patient sales, but other national regimes for early access may be available, depending on the member state. For drugs that must be approved through the centralized procedure, such as orphan drugs, compassionate use programs are also regulated at the European level. ALIS is available in certain European countries under early access programs.

Special programs can be set up to make available to patients with an unmet medical need a promising drug which has not yet been authorized for their condition (compassionate use). As a general rule, compassionate use programs can only be put in place for drugs or biologics that are expected to help patients with life-threatening, long-lasting or seriously disabling illnesses who currently cannot be treated satisfactorily with authorized medicines, or who have a disease for which no medicine has yet been authorized. The compassionate use route may be a way for patients who cannot enroll in an ongoing clinical trial to obtain treatment with a potentially life-saving medicine. Compassionate use programs are coordinated and implemented by the EU member states, which decide independently how and when to open such programs according to national rules and

legislation. Generally, doctors who wish to obtain a promising drug for their seriously ill patients will need to contact the relevant national authority in their respective country and follow the procedure that has been set up. Typically, the national authority keeps a register of the patients treated with the drug within the compassionate use program, and a system is in place to record any side effects reported by the patients or their doctors. Orphan drugs very often are subject to compassionate use programs due to their very nature (rare diseases are life-threatening, long-lasting or seriously disabling diseases) and the long time required for both their approval and effective marketing.

Doctors can also obtain certain drugs for their patients by requesting a supply of a drug from the manufacturer or a pharmacist located in another country, to be used for an individual patient under their direct responsibility. This is often called treatment on a 'named-patient basis' and is distinct from compassionate use programs. In this case, the doctor responsible for the treatment will either contact the manufacturer directly or issue a prescription to be fulfilled by a pharmacist. While manufacturers or pharmacists do record what they supply, there is no central register of the patients that are being treated in this way.

Reimbursement of Pharmaceutical Products

In the US, many independent third-party payers, as well as the Medicare and state Medicaid programs, reimburse buyers of pharmaceutical products. Medicare is the federal program that provides health care benefits to senior citizens and certain disabled and chronically ill persons. Medicaid is the need-based federal and state program administered by the states to provide health care benefits to certain persons.

As one of the conditions for obtaining Medicaid and Medicare Part B coverage for our marketed pharmaceutical products, we will need to agree to pay a rebate to state Medicaid agencies that provide reimbursement for those products. We will also have to agree to sell our commercial products under contracts with the Department of Veterans Affairs, Department of Defense, Public Health Service, and numerous other federal agencies as well as certain hospitals that are designated by federal statutes to receive drugs at prices that are significantly below the price we charge to commercial pharmaceutical distributors. These programs and contracts are highly regulated and will impose restrictions on our business. Failure to comply with these regulations and restrictions could result in a loss of our ability to continue receiving reimbursement for our drugs once approved.

Private healthcare payers also attempt to control costs and influence drug pricing through a variety of mechanisms, including through negotiating discounts with the manufacturers and through the use of tiered formularies and other mechanisms that provide preferential access to certain drugs over others within a therapeutic class. Payers also set other criteria to govern the uses of a drug that will be deemed medically appropriate and therefore reimbursed or otherwise covered. The US President has indicated an interest in having the federal government negotiate drug prices with pharmaceutical manufacturers.

Different pricing and reimbursement schemes exist in other countries. In Japan, drugs can be sold on the market if they undergo the PMDA’s review of safety, effectiveness and quality and receive manufacturing/marketing approval. However, in order for drugs to be covered by the National Health Insurance, they must be included in a Drug Price List. The "Drug Pricing Organization," which is a division of the Central Social Insurance Medical Council (CSIMC), calculates the price of drugs, the general meeting of the CSIMC approves the calculated price, and the MHLW includes the drugs and the calculated price in the Drug Price List. After receiving manufacturing/marketing approval, drugs are included in the Drug Price List within 60 to 90 days unless the applicant disagrees, which may result in extended pricing negotiations. The MHLW updates the Drug Price List biennially after taking into account the survey result of the actual sales price of drugs and hearing the opinion of the CSIMC.

In the EU, governments influence the price of drugs through their pricing and reimbursement rules and control of national health care systems that fund a large part of the cost of those products to patients. Some jurisdictions operate positive and negative list systems under which drugs may only be marketed once a reimbursement price has been agreed. To obtain reimbursement or pricing approval, some of these countries may require the completion of clinical trials that compare the cost-effectiveness of a particular drug candidate to currently available therapies. Other member states allow companies to fix their own prices for drugs, but monitor and control company profits. The downward pressure on health care costs in general, particularly prescription drugs, has become very intense. As a result, increasingly high barriers are being erected to the entry of new drugs. In addition, in some countries, cross-border imports from low-priced markets exert a commercial pressure on pricing within a country. There can be no assurance that any country that has price controls or reimbursement limitations for drugs will allow favorable reimbursement and pricing arrangements for any of our products.

Fraud and Abuse and Other Laws

Physicians and other healthcare providers and third-party payers (government or private) often play a primary role in the recommendation and prescription of health care products. In the US and most other jurisdictions, numerous detailed requirements apply to government and private health care programs, and a broad range of fraud and abuse laws, transparency

laws, and other laws are relevant to pharmaceutical companies. US federal and state healthcare laws and regulations in these areas include the following:

- The federal anti-kickback statute;
- The federal civil False Claims Act;
- The federal Health Insurance Portability and Accountability Act of 1996 (HIPAA), as amended by the Health Information Technology for Economic and Clinical Health Act (HITECH);
- The federal criminal false statements statute;
- The price reporting requirements under the Medicaid Drug Rebate Program and the Veterans Health Care Act of 1992;
- The federal Physician Payment Sunshine Act, being implemented as the Open Payments Program; and
- Analogous and similar state laws and regulations.

Similar restrictions apply in Japan and the member states of the EU, which have been set out by laws or industry codes of conduct.

Employees

As of December 31, 2017, we had a total of 214 employees, including 98 in research, clinical, regulatory, medical affairs and quality assurance; 20 in technical operations, manufacturing and quality control; 42 in general and administrative functions; and 54 in pre-commercial activities. We had 190 employees in the US and 24 employees in Europe. We anticipate increasing our headcount in 2018.

None of our employees are represented by a labor union and we believe that our relations with our employees are generally good. Generally, our employees are at-will employees; however, we have entered into employment agreements with certain of our executive officers.

Available Information

We file electronically with the SEC 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 Securities Exchange Act of 1934 (Exchange Act). We make available on our website at http://www.insmed.com, free of charge, copies of these reports as soon as reasonably practicable after filing, or furnishing them to, the SEC. The public can also obtain materials that we file with the SEC through the SEC's website at http://www.sec.gov or at the SEC's Public Reference Room at 100 F Street, NE, Washington, DC 20549. Information on the operation of the Public Reference Room is available by calling the SEC at 1-800-SEC-0330.

Also available through our website's "Investor Relations Corporate Governance" page are charters for the Audit, Compensation and Nominations and Governance committees of our board of directors, our Corporate Governance Guidelines, and our Code of Business Conduct and Ethics.

The references to our website and the SEC's website are intended to be inactive textual references only. Neither the information in or that can be accessed through our website, nor the contents of the SEC's website, are incorporated by reference in this Annual Report on Form 10-K.

Financial Information

The financial information required under this Item 1 is incorporated herein by reference to Item 8 of this Annual Report on Form 10-K.

ITEM 1A. RISK FACTORS

Our business is subject to substantial risks and uncertainties. Any of the risks and uncertainties described below, either alone or taken together, could materially and adversely affect our business, financial condition, results of operations, prospects for growth, and the value of an investment in our common stock. In addition, these risks and uncertainties could cause actual results to differ materially from those expressed or implied by forward-looking statements contained in this Form 10-K (please read the Cautionary Note Regarding Forward-Looking Statements appearing at the beginning of this Form 10-K). The risks and uncertainties described below are not the only ones we face. Additional risks and uncertainties not currently known to us or that we currently deem to be immaterial may also materially and adversely affect our business, financial condition, results of operations, prospects and the value of an investment in our common stock and could cause actual results, performance or achievements to differ materially from those expressed or implied by forward-looking statements.

Risks Related to Development, Regulatory Approval and Commercialization of our Product Candidates

The currently reported results of the CONVERT study and the 312 study are based on top-line and interim data for the studies and may differ from complete study results once additional data are received and evaluated.

The reported results of our CONVERT study consist of only top-line data from the first six months of the study and interim data regarding durability of culture conversion in patients off of all therapy for three months. Top-line data are based on a preliminary analysis of currently available efficacy and safety data, and therefore these results are subject to change following a comprehensive review of the more extensive data we expect to receive when the full set of six-month data becomes available. Top-line data are based on important assumptions, estimations, calculations and information currently available to us, and we have not received or had an opportunity to evaluate all of the six-month data from the CONVERT study. As a result, the top-line six-month results may differ from the full six-month data, or different conclusions or considerations may qualify such top-line results, once the complete six-month data have been received and fully evaluated. Similarly, the durability data we have reported from the CONVERT study consist only of interim data for evaluable study participants who have completed treatment and continued in the study off all therapy for three months. The CONVERT study is ongoing, and subsequent data from the treatment and off-treatment phases of the study may differ from the reported top-line and interim results.

The reported results of our 312 study, which are discussed herein, consist only of interim data for evaluable study participants who have completed six months of treatment under the 312 study as of December 2017. The currently reported results are subject to change following a comprehensive review of the more extensive data we expect to receive when this study is completed. The 312 study is a twelve-month study and remains ongoing, and subsequent data from the study may differ from the reported interim results.

If these top-line and interim data differ from the results of the full six-month data or subsequent data from patients during the remainder of the treatment phase or the off-treatment phase of the CONVERT study, or the full twelve-month data from the 312 study, our ability to obtain or maintain approval for, and commercialize, ALIS may be harmed, which could materially adversely affect our business, financial condition, results of operations and prospects and the value of our common stock.

Our prospects are highly dependent on the success of our most advanced product candidate, ALIS. If we are unable to successfully complete the development of, obtain or subsequently maintain regulatory approval for, and successfully commercialize ALIS, our business, financial condition, results of operations and prospects and the value of our common stock will be materially adversely affected.

We are investing significant efforts and financial resources in the development of ALIS, our most advanced product candidate. Our ability to generate product revenue from ALIS will depend heavily on the successful completion of development of, receipt of regulatory approval for, and commercialization of, ALIS.

Positive results from preclinical studies of a product candidate may not be predictive of similar results in human clinical trials, and promising results from earlier clinical trials of a product candidate may not be replicated in later clinical trials. Many companies in the pharmaceutical and biotechnology industries have suffered significant setbacks in late-stage clinical trials even after achieving promising results in earlier stages of development. Accordingly, even if the full six-month data for the primary endpoint of the CONVERT study, the interim durability data from the CONVERT study and the interim efficacy data from the 312 study are all positive, such data may not be predictive of the results from the remainder of either the CONVERT study or the 312 study, or future trials related to ALIS.

In addition, even if we believe our clinical trials for ALIS demonstrate promising results, regulators may decline to grant regulatory approval. Regulators may disagree with our interpretation of data or the study design or execution from our clinical trials and may refuse to accept our application for review or decline to grant approval based on effectiveness and/or safety concerns. For instance, in the fourth quarter of 2014, we filed a MAA with the EMA for ALIS as a treatment for, among other things, NTM lung disease in adult patients. The filing was based in part on data from our phase 2 study in patients with NTM lung disease. We subsequently withdrew our MAA after the CHMP concluded that the data submitted did not provide enough evidence to support an approval. We currently expect to submit an NDA to the FDA pursuant to Subpart H for ALIS based on the efficacy data from the CONVERT study through Month 6. Although we view the top-line six-month results and the interim durability data from the CONVERT study as promising, the FDA may not agree that the six-month data are sufficient to support submission, or that the six-month data and the available interim durability data are sufficient to support approval, of our NDA under Subpart H.

Further, even if we obtain approval for ALIS from a regulator, including from the FDA pursuant to Subpart H, confirmatory clinical studies will be required and could fail to demonstrate sufficient safety and efficacy to support continued approval. For instance, if we obtain approval from the FDA based on the NDA filing described above, the FDA may nonetheless conclude that the data generated from the remainder of the CONVERT study or the 312 study is not sufficient to support continued approval for ALIS in its approved indication, and the approval may be withdrawn.

We do not expect ALIS to be commercially available in any market until we receive requisite approval from the FDA, MHLW, EMA or an equivalent regulatory agency. The failure to obtain or subsequently maintain such approvals will materially adversely affect our business, financial condition, results of operations and prospects and the value of our common stock.

We may not be able to obtain regulatory approvals for ALIS or any other products we develop in the US, Japan, Europe or other markets. If we fail to obtain such approvals, we will not be able to commercialize our products.

We are required to obtain various regulatory approvals prior to studying our products in humans and then again before we market and distribute our products, and the failure to do so will prevent us from commercializing our products, which would materially adversely affect our business, financial condition, results of operations and prospects and the value of our common stock. The regulatory review and approval processes in the US, Japan and Europe require evaluation of preclinical studies and clinical studies, as well as the evaluation of our manufacturing processes and quality systems. Securing regulatory approval to market our products requires the submission of much more extensive preclinical and clinical data, manufacturing and quality information regarding the process and facility, scientific data characterizing our product and other supporting data to the regulatory authorities in order to establish its safety and effectiveness. These processes are complex, lengthy, expensive, resource intensive and uncertain. We have limited experience in submitting and pursuing applications necessary to gain these regulatory approvals. In addition, the FDA will conduct a rigorous review of any trade name we intend to use for our product candidates. Even after the FDA approves a trade name, the FDA may request that we adopt an alternative name for the product if adverse event reports indicate a potential for confusion with other trade names and medication error. If we are required to adopt an alternative name, the commercialization of ALIS could be delayed or interrupted, which would limit our ability to commercialize ALIS and generate revenues.

As described above, data submitted to regulators are subject to varying interpretations that could delay, limit or prevent regulatory agency approval. For example, based on our communications with FDA to date, we need to demonstrate to FDA that our proposed in vitro release test (IVRT) is sufficient to ensure that amikacin is consistently released from batch to batch of ALIS and is discriminating of acceptable and unacceptable batches. Although we believe that our proposed testing methodology adequately characterizes the release of amikacin from the liposomal suspension, if FDA does not accept our proposed IVRT, the approval of ALIS could be prevented or delayed.

We may also encounter delays or rejections based on changes in regulatory agency policies during the period in which we develop a product and the period required for review of any application for regulatory agency approval of a particular product. For example, the FDA has designated ALIS for fast track, breakthrough therapy and QIDP status, all programs intended to expedite or streamline the development and regulatory review of the drug. If we were to lose the current designation under one or more of those programs, we could face various consequences, including delays in the FDA review and approval process. In addition, the FDA review and approval process could be delayed in the event of a federal government shutdown. Resolving such delays could force us or third parties to incur significant costs, could limit our allowed activities or the allowed activities of third parties, could diminish any competitive advantages that we or our third parties may attain or could adversely affect our ability to receive royalties, any of which could materially adversely affect our business, financial condition, results of operations and prospects and the value of our common stock. Even with these designations, there is no guarantee we will receive approval for ALIS on a timely basis, or at all.

Similarly, we are currently assessing regulatory strategies which could expedite the development and regulatory review of INS1007 in the US and the EU, but we may be unsuccessful in pursuing such strategies. The FDA recently denied our request for orphan drug designation for INS1007 in non-CF bronchiectasis. In addition, although we believe that INS1009 could be eligible for approval under Section 505(b)(2), and thus could rely at least in part on studies not conducted by or for us and for which we do not have a right of reference, we may not obtain approval from the FDA to use this pathway.

Approval by the FDA does not ensure approval by the regulatory authorities of other countries. To market our products outside of the US, we, and potentially our third-party providers, must comply with numerous and varying regulatory requirements of other countries. The approval procedures vary among countries and can involve additional product testing and administrative review periods. The time required to obtain approval in these other territories might differ from that required to obtain FDA approval. In addition, we may be subject to fines, suspension or withdrawal of regulatory approvals, product recalls, seizure of products, operating restrictions (including with respect to our target market) and criminal prosecution if we fail to comply with applicable US or foreign regulatory requirements.

We have not completed the research and development stage of ALIS or any other product candidates. If we are unable to successfully develop and commercialize ALIS or any other products, it will materially adversely affect our business, financial condition, results of operations and prospects and the value of our common stock.

Our long-term viability and growth depend on the successful commercialization of ALIS and potentially other product candidates. Pharmaceutical product development is an expensive, high risk, lengthy, complicated, resource intensive process. In order to conduct the development programs for our products, we must, among other things, be able to successfully:

- Identify potential product candidates;
- Design and conduct appropriate laboratory, preclinical and other research;
- Submit for and receive regulatory approval to perform clinical studies;
- Design and conduct appropriate preclinical and clinical studies according to good laboratory practices and good clinical practices and disease-specific expectations of the FDA and other regulatory bodies;
- Select and recruit clinical investigators and subjects for our studies;
- Collect, analyze and correctly interpret the data from our studies;
- Obtain data establishing adequate safety of our product candidates and demonstrating with statistical significance that our product candidates are effective for their proposed indications, as indicated by satisfaction of pre-established endpoints;
- Submit for and receive regulatory approvals for marketing;
- Submit for and receive reimbursement approvals for market access; and
- Manufacture the product candidates and device components according to current good manufacturing practices (cGMP) and other applicable standards and regulations.

The development program with respect to any given product will take many years and thus delay our ability to generate profits associated with that product. In addition, potential products that appear promising at early stages of development may fail for a number of reasons, including the possibility that the products may require significant additional testing or turn out to be unsafe, ineffective, too difficult or expensive to develop or manufacture, too difficult to administer or unstable, or regulators may require additional testing to substantiate our claims. For instance, as described above, although we view the top-line six-month results from the CONVERT study and the interim data we have reported from the CONVERT study and 312 study as promising, our clinical studies of ALIS for refractory NTM lung disease caused by MAC are ongoing, and outcomes from those studies cannot be predicted. If we do not proceed with the development of our ALIS program in the NTM lung disease or CF indications, certain of our contract counterparties may elect to proceed with the development of these indications. Even if we are successful in obtaining regulatory approval for our product candidates, including ALIS, we may not obtain labeling that permits us to market them with commercially viable claims because the final wording of the approved indication may be restrictive, or the available clinical data may not provide adequate comparative data with other products.

Failure to successfully commercialize our products will materially adversely affect our business, financial condition, results of operations and prospects and the value of our common stock.

If our clinical studies do not produce positive results or our clinical trials are delayed, or if serious side effects are identified during drug development, we may experience delays, incur additional costs and ultimately be unable to commercialize our product candidates in the US, Japan, Europe or other markets.

Before obtaining regulatory approval for the sale of our product candidates, we must conduct, at our own expense, extensive preclinical tests to demonstrate the safety of our product candidates in animals, and clinical trials to demonstrate the safety and efficacy of our product candidates in humans. Preclinical and clinical testing is expensive, difficult to design and implement and can take many years to complete. Special challenges can arise in conducting trials in diseases or conditions with small populations, such as difficulties enrolling adequate numbers of patients. Our product development costs have and may continue to increase if we experience further delays in testing or approvals. A failure of one or more of our preclinical studies or clinical trials can occur at any stage of testing. We may experience numerous unforeseen events during, or as a result of, preclinical testing and the clinical trial process that could delay or prevent our ability to obtain regulatory approval or commercialize our product candidates, including:

- Our preclinical tests or clinical trials may produce negative or inconclusive results, and we may decide, or regulators may require us, to conduct additional preclinical testing or clinical trials or we may abandon projects that we expect to be promising;
- Regulators, ethics committees or institutional review boards (IRBs) may prevent us from commencing a clinical trial or conducting a clinical trial at a prospective trial site;
- Enrollment in the clinical trials may take longer than expected or the clinical trials as designed may not allow for sufficient patient accrual to complete enrollment of the trial;
- We may experience difficulties or delays due to the number of clinical sites involved in our clinical trials;
- We may decide to limit or abandon our commercial development programs;
- Conditions imposed on us by the FDA or any non-US regulatory authority regarding the scope or design of our clinical trials may require us to collect and submit information to regulatory authorities, ethics committees, IRBs or others for review and approval;
- The number of patients required for our clinical trials may be larger than we anticipate or participants may drop out of our clinical trials at a higher rate than we anticipate;
- Our third-party contractors, contract research organizations (CROs), clinical investigators, clinical laboratories, product suppliers or nebulizer supplier may fail to comply with regulatory requirements or fail to meet their contractual obligations to us in a timely manner;
- We may have to suspend or terminate one or more of our clinical trials if we, regulators, ethics committees or the IRBs determine that the participants are being exposed to unacceptable health risks or for other reasons;
- We may not be able to claim that a product candidate provides an advantage over current standard of care or future competitive therapies in development because our clinical studies may not have been designed to support such claims;
- Regulators, ethics committees or IRBs may require that we hold, suspend or terminate clinical research for various reasons, including potential safety concerns or noncompliance with regulatory requirements;
- The cost of our clinical trials may be greater than we anticipate;
- The supply or quality of product used in clinical trials or other materials necessary to conduct our clinical trials may be insufficient or inadequate or we may not be able to reach agreements on acceptable terms with prospective contract manufacturers or CROs;

- The effects of our product candidates may not be the desired effects or may include undesirable side effects or the product candidates may have other unexpected characteristics; and

- Our competitors may be able to bring products to market before we do.

If we are required to conduct additional clinical trials or other testing of our product candidates beyond those that we currently contemplate, if we are unable to successfully complete our clinical trials or other testing, if the results of these trials or tests are not positive or are only modestly positive or if there are safety concerns, we may:

- Experience increased product development costs, as we have in the past;

- Be delayed in obtaining, or be unable to obtain, regulatory approval for one or more of our product candidates;

- Obtain approval for indications that are not as broad as intended or entirely different than those indications for which we sought approval or labeling with black box or other warnings or contraindications;

- Have the product removed from the market after obtaining regulatory approval; or

- Face a shortened patent protection period during which we may have the exclusive right to commercialize our product candidates.

We have limited experience in conducting and managing the preclinical development activities and clinical trials necessary to obtain regulatory approvals, including approval by the FDA, MHLW, PMDA, EMA and other regulatory agencies.

We have limited experience in conducting and managing the preclinical development activities and clinical trials necessary to obtain regulatory approvals, including approval by the FDA, MHLW, PMDA and EMA, which might prevent us from successfully designing, implementing, or completing the clinical trials required to support regulatory approval of our product candidates. Since our merger with Transave, we have not completed a regulatory filing and review process for, obtained regulatory approval of or commercialized any of our product candidates. The application processes for the FDA, MHLW, PMDA, EMA and other regulatory agencies are complex and difficult and vary by regulatory agency, and we have limited experience in conducting and managing the application processes necessary to obtain regulatory approvals in these various jurisdictions and might not be able to demonstrate that our product candidates meet the appropriate standards for regulatory approval. If we are not successful in conducting and managing our preclinical development activities or clinical trials or obtaining regulatory approvals, we might not be able to commercialize ALIS or other product candidates, or might be significantly delayed in doing so, which may materially adversely affect our business, financial condition, results of operations and prospects and the value of our common stock.

There is little or no precedent for clinical development and regulatory expectations for agents to treat NTM lung disease; as a result, we may encounter challenges developing clinical endpoints that will ultimately be satisfactory to regulators, which could cause our product candidates not to be approved by regulators, delay commercialization of our product candidates or subject us to the risk of having any approval withdrawn.

Based on the top-line six-month data from the CONVERT study, we expect to submit an NDA under Subpart H to request accelerated approval for ALIS. The FDA may base accelerated approval for drugs intended to treat serious or life-threatening illnesses on whether the drug has an effect on a surrogate endpoint or an intermediate clinical endpoint (other than survival or irreversible morbidity). We are using culture conversion as the surrogate endpoint in our CONVERT study. While we have discussed our protocol for potential accelerated approval under Subpart H with the FDA, the FDA has not indicated its agreement or disagreement with the protocol. In addition, the FDA has indicated that the results of the six-minute walk test, a secondary endpoint in the CONVERT study, will be important in assessing the clinical benefit of ALIS in this patient population. Developing clinical endpoints that are unsatisfactory to regulators could delay clinical trials and the FDA approval process, which could materially adversely affect our business, financial condition, results of operations and prospects and the value of our common stock.

Additionally, if ALIS or any of our other product candidates is approved based on a surrogate endpoint or an intermediate clinical endpoint under the accelerated approval program, the approval will be subject to the requirement that we study the product candidate further to verify and describe its clinical benefit. Thus, even if we are successful in obtaining accelerated approval in the US or under comparable pathways in other jurisdictions, we may face requirements and limitations that will adversely affect our prospects. For example, we may be approved only for a very limited indication, we may not

successfully complete required post-approval trials, or such trials may not confirm the clinical benefit of our drug, and approval of the drug may be withdrawn.

For ALIS to be successfully developed and commercialized in a given market, in addition to regulatory approvals required for ALIS, the eFlow Nebulizer System must satisfy certain regulatory requirements and its use as a delivery system for ALIS must be approved or cleared by regulators.

ALIS is administered using the eFlow Nebulizer System. As such, the eFlow Nebulizer System must receive regulatory approval or clearance on its own or in conjunction with ALIS as a combination product in order for us to develop and commercialize ALIS. Although the eFlow Nebulizer System is CE marked by PARI in the EU, outside the EU, it is labeled as investigational for use in our clinical trials, including in the US, Japan, Canada and Australia. The eFlow Nebulizer System is not approved for commercial use in the US, Japan, Canada or certain other markets in which we may seek to commercialize ALIS.

In the US, we plan to seek approval of the eFlow Nebulizer System in conjunction with ALIS as a combination product through a single NDA submission, and the increased complexity of the review process in this circumstance may delay approval. Additionally, while we continue to work closely with PARI to coordinate efforts regarding regulatory requirements, we will be responsible for this NDA submission, and we, in consultation and collaboration with PARI, may not be successful in meeting the regulatory requirements for the eFlow Nebulizer System, which would prevent or delay our ability to bring ALIS to market or to market it successfully. Failure of PARI to successfully supply, or to maintain regulatory approval or clearance, of the eFlow Nebulizer System could result in increased development costs, delays in or failure to obtain regulatory approval, and associated delays in ALIS reaching the market. Further, based on our discussions to date with the FDA, we conducted a human factors study for the eFlow Nebulizer System in preparation for submission of our NDA for ALIS. If the FDA does not find the results of that study to be acceptable, that might delay or prevent the approval of ALIS.

We may not be able to enroll enough patients to complete our clinical trials or retain a sufficient number of patients in our clinical trials to generate the data necessary for regulatory approval of our product candidates.

The completion rate of our clinical studies is dependent on, among other factors, the patient enrollment rate. Patient enrollment is a function of many factors, including:

- Investigator identification and recruitment;
- Regulatory approvals to initiate study sites;
- Patient population size;
- The nature of the protocol to be used in the trial;
- Patient proximity to clinical sites;
- Eligibility criteria for the study;
- The patients' willingness to participate in the study;
- Discontinuation rates; and
- Competition from other companies' potential clinical studies for the same patient population.

Delays in patient enrollment for our clinical trials, including in the WILLOW study, our global phase 2 study of INS1007 in non-CF bronchiectasis that currently is enrolling patients, such as those we encountered in enrolling the CONVERT study, could increase costs and delay ultimate commercialization and sales, if any, of our products. Once enrolled, patients may elect to discontinue participation in a clinical trial at any time. If patients elect to discontinue participation in our clinical trials at a higher rate than expected, we may be unable to generate the data required by regulators for approval of our product candidates.

Even if we obtain regulatory approval for ALIS or any of our other product candidates, we will continue to face extensive regulatory requirements and our products may face future development and regulatory difficulties.

Even if regulatory approval in the US is obtained, the FDA may still impose significant restrictions on a product's indicated uses or marketing, including risk evaluation and mitigation strategies (REMS), or may impose ongoing requirements on us or our contract partners, including with respect to:

- Labeling, such as a boxed warning or other warnings or contraindications;
- Post-market surveillance, post-market studies or post-market clinical trials;
- Packaging, storage, distribution, safety surveillance, advertising, promotion, recordkeeping and reporting of safety and other postmarket information;
- Monitoring and reporting complaints, adverse events and instances of the failure of a product to meet specifications;
- Compliance with cGMPs and certain quality systems requirements for device components;
- Changes to the approved product, product labeling or manufacturing process;
- Advertising and other promotional material; and
- Disclosure of clinical trial results on publicly available databases.

In addition, the distribution, sale and marketing of our products are subject to a number of additional requirements, including:

- State wholesale drug distribution laws and the distribution of our product samples to physicians must comply with the requirements of the Prescription Drug Marketing Act of 1987;
- Sales, marketing and promotion, scientific exchange, speaker programs, charitable donations and educational grant programs must comply with federal and state laws; and
- Pricing and rebate arrangements must comply with reporting and payment obligations under the Medicaid drug rebate program, and additional laws and regulations apply to making products available to authorized users of the Federal Supply Schedule of the General Services Administration.

All of these activities also may be subject to federal and state consumer protection and unfair competition laws.

If we fail to comply with applicable regulatory requirements, a regulatory agency may:

- Issue warning letters or untitled letters asserting that we are in violation of the law;
- Seek an injunction or impose civil monetary penalties or pursue civil or criminal prosecutions and fines against our company or responsible officers;
- Suspend or withdraw regulatory approval;
- Suspend or terminate any ongoing clinical trials;
- Refuse to approve pending applications or supplements to applications submitted by us;
- Suspend or impose restrictions on operations, including costly new manufacturing requirements;
- Seize or detain products, refuse to permit the import or export of products, or require us to initiate a product recall; and/or
- Refuse to allow us to enter into supply contracts, including government contracts.

Any government investigation of alleged violations of law could require us to expend significant time and resources in response, and could generate negative publicity. The occurrence of any event or penalty described above may inhibit our ability to commercialize our product candidates and generate revenues.

The commercial success of ALIS or any other product candidates that we may develop will depend upon many factors, including the degree of market acceptance by physicians, patients, third-party payers and others in the medical community.

Even if we are able to successfully complete development of, obtain regulatory approval for, and bring to market our product candidates, they may not gain market acceptance by physicians, patients, third-party payers and others in the medical community. If ALIS, or any other product candidate we bring to market, does not achieve an adequate level of acceptance, we may not generate significant product revenue and we may not become profitable. The degree of market acceptance of ALIS and any other product candidates, if approved for commercial sale, will depend on a number of factors, including:

- The prevalence and severity of any side effects, including any limitations or warnings contained in a product's approved labeling;
- The efficacy and potential advantages over alternative treatments;
- The pricing of our products;
- Relative convenience and ease of administration;
- The willingness of the target patient population to try new therapies and of physicians to prescribe these therapies;
- The strength of marketing and distribution support and timing of market introduction of competitive products;
- Publicity concerning our products or competing products and treatments, including competing products becoming subject to generic pricing; and
- Sufficient third-party insurance coverage and reimbursement.

Even if a potential product displays a favorable efficacy and safety profile in preclinical and clinical trials, market acceptance of the product will not be known until after it is launched. For example, if a clinical trial is not designed to demonstrate advantages over alternative treatments, we may be prohibited from promoting our product candidates on any such advantages. Our efforts to educate the medical community and third-party payers on the benefits of our product candidates may require significant resources and may never be successful. Such efforts to educate the marketplace may require more resources than are required to commercialize more established technologies marketed by our competitors.

We currently are building our marketing and sales organization, and we have limited experience as a company in marketing drug products. If we are unable to successfully market and sell our products after they are approved, our ability to generate product revenues will be adversely affected.

We are building our commercial organization for the marketing, market access, sales and distribution of our products. In order to commercialize ALIS or any other product candidates, we must develop these capabilities on our own or make arrangements with third parties for the marketing, sales and distribution of our products. The establishment and development of our own sales force is and will continue to be expensive and time consuming and could delay any product launch, and we may be unable to successfully develop this capability. As a result, we may seek one or more partners to handle some or all of the sales and marketing of ALIS in certain markets. However, we may not be able to enter into arrangements with third parties to sell ALIS on favorable terms or at all. In the event we are unable to develop our own marketing, market access, and sales force or collaborate with a third-party marketing, market access, and sales organization, we may not be able to successfully commercialize ALIS or any other product candidates that we develop, which would adversely affect our ability to generate product revenues. Further, whether we commercialize products on our own or rely on a third party to do so, our ability to generate revenue will be dependent on the effectiveness of the sales force.

If estimates of the size of the potential markets for our product candidates, including ALIS, are overstated or regulators limit the proposed treatment population for our product candidates, our ability to commercialize such product candidates successfully or achieve sufficient revenue to support our business could be materially adversely affected.

We have relied on currently available information from external sources, including market research funded by us and third parties, and internal analyses and calculations to estimate the potential market opportunities for NTM lung disease in 2018 in the US, Japan and the EU5. The externally sourced information used to develop these estimates has been obtained from sources we believe to be reliable, but we have not verified the data from such sources, and their accuracy and completeness cannot be assured. Similarly, our internal analyses and calculations are based upon management's understanding and assessment of numerous inputs and market conditions, including, but not limited to, the projected increase in prevalence of NTM lung disease, Medicare patient population growth and ongoing population shifts to geographies with increased rates of NTM lung disease. These understandings and assessments necessarily require assumptions subject to significant judgment and may prove to be inaccurate. As a result, our estimates of the size of these potential markets for ALIS could prove to be overstated, perhaps materially. In addition, while we believe we have identified the physicians who treat the majority of the NTM lung disease patients in the US, we are relying on third party data to identify those physicians and to determine how to deploy our resources to market to those physicians. We cannot ensure that we are marketing our products to all appropriate physicians and we may therefore be limiting our market opportunity. We also cannot ensure that physicians will prescribe our products to the appropriate patients.

We may develop estimates with respect to market opportunities for other product candidates in the future, and such estimates would be subject to similar risks. In addition, a potential market opportunity could be reduced if a regulator limits the proposed treatment population for one of our product candidates. In either circumstance, even if we obtain regulatory approval for a product candidate, we may be unable to commercialize it on a scale sufficient to generate material revenues, which could have a material adverse effect on our business, financial condition, results of operations and prospects and the value of our common stock.

Risks Related to Our Reliance on Third Parties

We rely on third parties including collaborators, CROs, clinical and analytical laboratories, CMOs and other providers for many services that are critical to our business. If we are unable to form and sustain these relationships, or if any third-party arrangements that we may enter into are unsuccessful, including due to non-compliance by such third parties with our agreements or applicable law, our ability to develop and commercialize our products may be materially adversely affected.

We currently rely, and expect that we will in the future continue to rely, on third parties for significant research, analytical services, preclinical development, clinical development and manufacturing of our product candidates. For example, almost all of our clinical trial work is done by CROs, such as SynteractHCR, Inc., our CRO for both the CONVERT and 312 studies, and clinical laboratories. Reliance on these third parties poses a number of risks, including the following:

- Significant competition in seeking appropriate partners;
- The complex and time-consuming nature of negotiation, documentation and implementation of agreements with third parties in the pharmaceutical industry;
- Our potential inability to establish and implement collaborations or other alternative arrangements that we might pursue on favorable terms;
- Our potential inability to control whether third parties devote sufficient resources to our programs or products, including with respect to meeting contractual deadlines;
- Our potential inability to control the regulatory and contractual compliance of third parties, including their quality systems, processes and procedures, systems utilized to collect and analyze data, and equipment used to test drug product and/or clinical supplies;
- Disagreements with third parties, including CROs, that result in a dispute over and loss of intellectual property rights, delay or termination of research, development, or commercialization of product candidates or litigation or arbitration;
- Contracts with our collaborators that fail to provide sufficient protection of our intellectual property; and

- Difficulty enforcing the contracts if one of these third parties fails to perform.

We also rely on third parties to select and enter into agreements with clinical investigators to conduct clinical trials to support approval of our product candidates, and the failure of these third parties to appropriately carry out such evaluation and selection can adversely affect the quality of the data from these studies and, potentially, the approval of our products. In particular, as part of future drug approval submissions to the FDA, we must disclose certain financial interests of investigators who participated in any of the clinical studies being submitted in support of approval, or must certify to the absence of such financial interests. The FDA evaluates the information contained in such disclosures to determine whether disclosed interests may have an impact on the reliability of a study. If the FDA determines that financial interests of any clinical investigator raise serious questions of data integrity, the FDA can institute a data audit, request that we submit further data analyses, conduct additional independent studies to confirm the results of the questioned study, or refuse to use the data from the questioned study as a basis for approval. A finding by the FDA that a financial relationship of an investigator raises serious questions of data integrity, could delay or otherwise adversely affect approval of our products.

Such risks could materially harm our business, financial condition, results of operations and prospects and the value of our common stock.

We may not have, or may be unable to obtain, sufficient quantities of our product candidates to meet our required supply for clinical studies or commercialization requirements, which would materially harm our business.

We do not have any in-house manufacturing capability other than for small-scale pre-clinical development programs and depend completely on a small number of third-party manufacturers and suppliers for the manufacture of our product candidates on a clinical or commercial scale. For instance, we are and expect to remain dependent upon Therapure, Althea and eventually Patheon and other suppliers being able to provide an adequate supply of ALIS both for our clinical trials and for commercial sale in the event ALIS receives regulatory approvals. Althea currently manufactures ALIS at a relatively small scale. In order to meet potential commercial demand, if ALIS is approved, we funded a manufacturing expansion at Therapure in Canada that operates at a larger scale than Althea and have entered into certain agreements with Patheon related to increasing our long-term production capacity for ALIS commercial inventory. The agreements provide for Patheon to manufacture and supply ALIS for our anticipated commercial needs. However, Patheon's supply obligations will commence only after certain technology transfer and construction services are completed. Any delay in Patheon's supply obligations commencing, whether due to delays in technology transfer and construction or from adding Patheon to our NDA as a contract manufacturer, would increase the risks associated with either Therapure or Althea being unable to provide us with an adequate supply of ALIS.

We are also dependent upon PARI being able to provide an adequate supply of nebulizers both for our clinical trials and for commercial sale in the event ALIS receives regulatory approval, as PARI is the sole manufacturer of the eFlow Nebulizer System. We have no alternative supplier for the nebulizer, and we do not intend to seek an alternative or secondary supplier. Significant effort and time were expended in the optimization of the nebulizer for use with ALIS. In the event PARI cannot provide us with sufficient quantities of the nebulizer, replication of the optimized device by another party may require considerable time and additional regulatory approval. In the case of certain defined supply failures, we will have the right under our Commercialization Agreement with PARI to make the nebulizer and have it made by certain third parties, but not those deemed under the Commercialization Agreement to compete with PARI.

We do not have long-term commercial agreements with all of our suppliers and if any of our suppliers are unable or unwilling to perform for any reason, we may not be able to locate suppliers or enter into favorable agreements with them. In such circumstances, an inadequate supply of ALIS or the nebulizer could delay, impair or prevent clinical trials, the development and commercialization of ALIS and adversely affect our business, financial condition, results of operations and prospects and the value of our common stock.

Risks Related to Our Financial Condition and Future Capital Requirements

We have a history of operating losses, and we currently have no material source of revenue. We expect to incur operating losses for the foreseeable future and may never achieve or maintain profitability.

We have incurred losses each previous year of our operation, except in 2009, when we sold our manufacturing facility and certain other assets to Merck, and we did not generate material revenue during the years ended December 31, 2017, 2016, 2015 or 2014. We expect to continue incurring operating losses for the foreseeable future. The process of developing and commercializing our products requires significant pre-clinical and clinical testing as well as regulatory approvals for commercialization and marketing before we are allowed to begin product sales. In addition, we are significantly expanding our sales and marketing organization and establishing contractual relationships to enable product manufacturing and other related

activities to support commercialization of ALIS and our other product candidates, if approved. We expect that our activities, together with our general and administrative expenses, will continue to result in substantial operating losses for the foreseeable future. As of December 31, 2017, our accumulated deficit was $957.9 million. For the years ended December 31, 2017 and 2016, our consolidated net loss was $192.6 million and $176.3 million, respectively. To achieve and maintain profitability, we need to generate significant revenues from future product sales. The process of developing and commercializing our products will require significant expenditures for pre-clinical and clinical testing, regulatory approvals for commercialization and marketing, development of an internal or external sales and marketing organization and other related activities. Because of the numerous risks and uncertainties associated with drug development and commercialization, we are unable to predict the extent of any future losses, and we may never generate significant future revenues or achieve and sustain profitability.

We may need additional funds in the future to continue our operations, but we face uncertainties with respect to our ability to access capital.

Our operations have consumed substantial amounts of cash since our inception. We expect to continue to incur substantial research and development expenses, and we expect to expend substantial financial resources to complete development of, seek regulatory approval for, and prepare for commercialization of ALIS. In addition, if we obtain regulatory approval for ALIS or any of our other product candidates, we expect to incur significant commercialization expenses related to product sales, marketing, manufacturing and distribution. We may need additional capital to fund these expenses and our other research and development activities, including due to changes in our product development plans or misjudgment of expected costs, fund corporate development, maintain our intellectual property portfolio or resolve litigation. As of December 31, 2017, we had $381.2 million of cash and cash equivalents on hand. In January 2018, we completed a public offering of $450.0 million of convertible debt which resulted in net proceeds of approximately $435.8 million after underwriting fees and expenses. We expect our operating expenses, capital expenditures and long-term investments will be significantly higher in 2018 than in 2017, reflecting our investment in the build-out of our commercial organization to support global expansion activities for ALIS, including the potential launch of ALIS in the US in late 2018; the build-up of third-party manufacturing capacity and preparation of commercial inventory, which includes capital and long term investments; and continued investment in research and development (primarily associated with our ongoing and future clinical trials and clinical studies for ALIS and ongoing phase 2 program for INS 1007, along with advancement of other pipeline programs, including INS 1009) as well as general and administrative expenses. We do not know whether additional financing will be available when needed, or, if available, that the terms will be favorable. If adequate funds are not available to us when needed, we will be forced to delay, restrict or eliminate all or a portion of our development programs or commercialization efforts.

Our loan agreement with Hercules contains covenants and other provisions that impose restrictions on our operations, which may adversely affect our ability to optimally operate our business or to maximize shareholder value.

Our loan agreement with Hercules, under which we had outstanding indebtedness of $55.6 million as of December 31, 2017, contains various restrictive covenants, including restrictions on our ability to incur additional debt, transfer or place a lien or security interest on our assets, including our intellectual property, merge with or acquire other companies, redeem or repurchase any shares of our capital stock or pay cash dividends to our shareholders. The loan agreement also contains certain other covenants (including limitations on other indebtedness, liens, acquisitions, investments and dividends). Upon the occurrence of an event of default, a default interest rate of an additional 5% may be applied to the outstanding loan balances, and Hercules may terminate its lending commitment, declare all outstanding obligations immediately due and payable, and take such other actions as set forth in the loan agreement. The interest-only period under the loan agreement extends through May 1, 2019. The maturity date of the loan facility is October 1, 2020. In February 2018, we notified Hercules that we will repay the A&R Loan Agreement in full on February 28, 2018. The total aggregate cash payable to Hercules for the early prepayment of debt, inclusive of accrued interest, the backend fee and an early payment penalty will be approximately $58.0 million.

Our borrowings under the loan agreement are secured by a lien on our assets, excluding our intellectual property, and in the event of a default on the loan, Hercules may have the right to seize the assets securing our obligations under the loan agreement. The terms and restrictions provided in the loan agreement may inhibit our ability to conduct our business and to maximize shareholder value. Future debt securities or other financing arrangements could contain negative covenants similar to, or even more restrictive than, the Hercules loan agreement.

We have indebtedness in the form of convertible senior notes which could adversely affect our financial position, prevent us from implementing our strategy, and dilute the ownership interest of our existing shareholders.

In January 2018, we completed an underwritten public offering of 1.75% convertible senior notes due 2025 (the Convertible Notes). The Convertible Notes may be convertible into common stock at an initial conversion rate of 25.5384 shares of common stock per $1,000 principal amount of Convertible Notes. We sold $450.0 million aggregate principal amount

of the Convertible Notes, including the exercise in full of the underwriters' option to purchase additional Convertible Notes. Our net proceeds from the offering, after deducting underwriting discounts and commissions and other offering expenses of $14.2 million were approximately $435.8 million. Holders of the Convertible Notes may convert their Convertible Notes at their option at any time prior to the close of business on the business day immediately preceding October 15, 2024 only under certain circumstances. On or after October 15, 2024 until the close of business on the second scheduled trading day immediately preceding the maturity date, holders may convert their Convertible Notes at any time. Upon conversion of the Convertible Notes, we will deliver cash, shares of our common stock or a combination of cash and shares of our common stock, at our election. The degree to which we are leveraged could have negative consequences such as the following:

- we may be more vulnerable to economic downturns, less able to withstand competitive pressures, and less flexible in responding to changing economic conditions;
- our ability to obtain financing in the future may be limited;
- a substantial portion of our cash flows from operations in the future may be required for the payment of the principal amount of our existing indebtedness when it becomes due;
- we may elect to make cash payments upon conversion, which would reduce our available cash.

Our ability to pay principal or interest on or to refinance our indebtedness, including the indebtedness incurred as a result of the issuance of the Convertible Notes, depends on our future performance, which is subject to economic, financial, competitive and other factors, some of which are beyond our control. Our business may not generate cash flow from operations in the future sufficient to satisfy any obligations under the Convertible Notes to make cash payments to noteholders or our obligations under any future indebtedness we may incur. If we are unable to generate such cash flow, we may be required to adopt one or more alternatives, such as reducing or delaying investments or capital expenditures, selling assets, refinancing or obtaining additional equity capital on terms that may be onerous or highly dilutive. Our ability to refinance the Convertible Notes or future indebtedness will depend on the capital markets. If we do not meet our debt obligations, it could materially adversely affect our results of operations, financial condition and the value of our common stock.

The conversion of some or all of the Convertible Notes will dilute the ownership interests of existing shareholders to the extent we deliver shares upon conversion of any of the Convertible Notes. Any sales in the public market of the common stock issuable upon such conversion could adversely affect prevailing market prices of our common stock. In addition, the existence of the Convertible Notes may encourage short selling by market participants because the conversion of the Convertible Notes could be used to satisfy short positions, or anticipated conversion of the notes into shares of our common stock could depress the price of our common stock.

The accounting method for convertible debt securities that may be settled in cash, such as the Convertible Notes, may have a material effect on our reported financial results.

Under Accounting Standards Codification 470-20, Debt with Conversion and Other Options, which we refer to as ASC 470-20, an entity must separately account for the liability and equity components of the convertible debt instruments (such as the Convertible Notes) that may be settled entirely or partially in cash upon conversion in a manner that reflects the issuer's economic interest cost. The effect of ASC 470-20 on the accounting for the Convertible Notes is that the equity component is required to be included in the additional paid-in capital section of shareholders' equity on our consolidated balance sheet, and the value of the equity component would be treated as original issue discount for purposes of accounting for the debt component of the Convertible Notes. As a result, we may be required to record a greater amount of non-cash interest expense in current periods presented as a result of the amortization of the discounted carrying value of the Convertible Notes to their face amount over the term of the Convertible Notes. We may report lower net income (or greater net loss) in our financial results because ASC 470-20 requires interest to include both the current period's amortization of the debt discount and the instrument's coupon interest, which could adversely affect our reported or future financial results, the market price of our common stock and the trading price of the Convertible Notes.

Holders may convert their Convertible Notes at their option at any time prior to the close of business on the business day immediately preceding October 15, 2024 only under certain circumstances. For example, holders may convert their Convertible Notes at their option during any quarter commencing after the quarter ending March 31, 2018 (and only during such quarter) if the last reported sale price of our common stock for at least 20 trading days (whether or not consecutive) during a period of 30 consecutive trading days ending on the last trading day of the immediately preceding quarter is greater than or equal to 130% of the conversion price on each applicable trading day. If the Convertible Notes become convertible prior to October 15, 2024, we would be required to reclassify our Convertible Notes and the related debt issuance costs as current liabilities and certain portions of our equity outside of equity to mezzanine equity, which would have an adverse impact on our reported financial results for such quarter, and could have an adverse impact on the market price of our common stock and the trading price of the Convertible Notes.

In addition, convertible debt instruments (such as the Convertible Notes) that may be settled entirely or partly in cash are currently accounted for utilizing the treasury stock method if we have the ability and intent to settle in cash, the effect of which is that the shares issuable upon conversion of the Convertible Notes are not included in the calculation of diluted earnings per share except to the extent that the conversion value of the Convertible Notes exceeds their principal amount. Under the treasury stock method, for diluted earnings per share purposes, the transaction is accounted for as if the number of shares of common stock that would be necessary to settle such excess, if we elected to settle such excess in shares, are issued. We cannot be sure that we will be able to continue to demonstrate the ability or intent to settle in cash or that the accounting standards in the future will continue to permit the use of the treasury stock method. If we are unable to use the treasury stock method in accounting for the shares issuable upon conversion of the Convertible Notes, then our diluted earnings per share would be adversely affected.

In-process research and development (IPRD) comprised approximately 13% of our total assets as of December 31, 2017. A reduction in the value of our IPRD could have a material adverse effect on our results of operations, financial condition and the value of our common stock.

As a result of the merger with Transave, Inc. in 2010, we recorded an intangible IPRD asset of $77.9 million and goodwill of $6.3 million on our balance sheet. As a result of the clinical hold on ALIS announced in late 2011, we recorded a charge of $26.0 million in the fourth quarter of 2011 that reduced the value of IPRD to $58.2 million and reduced goodwill to zero. Potential future activities or results could result in additional writedowns of IPRD, which could materially adversely affect our results of operations, financial condition and the value of our common stock.

We may be unable to use certain of our net operating losses and other tax assets.

We have substantial tax loss carry forwards for US federal income tax and state income tax purposes, and beginning in 2015, we had tax loss carry forwards in Ireland as well. In general, our net operating losses and tax credits have been fully offset by a valuation allowance due to uncertainties surrounding our ability to realize these tax benefits. In particular, our ability to fully use certain US tax loss carry forwards and general business tax credit carry forwards recorded prior to December 2010 to offset future income or tax liability is limited under section 382 of the Internal Revenue Code of 1986, as amended (the Code). Changes in the ownership of our stock, including those resulting from the issuance of shares of our common stock offerings or upon exercise of outstanding options, may limit or eliminate our ability to use certain net operating losses and tax credit carry forwards in the future.

Comprehensive tax reform legislation could adversely affect our business and financial condition.

On December 22, 2017, the US government signed into law comprehensive tax legislation, referred to as the Tax Cuts and Jobs Act (the Tax Act). The Tax Act introduced significant changes to the US tax laws.

The Tax Act, among other things, contains significant changes to corporate taxation, including reduction of the corporate tax rate from a top marginal rate of 35% to a flat rate of 21%, limitation of the tax deduction for interest expense to 30% of adjusted earnings (except for certain small businesses), limitation of the deduction for net operating losses to 80% of current year taxable income in respect of losses arising in taxable years beginning after 2017 and elimination of net operating loss carrybacks, one time taxation of offshore earnings at reduced rates regardless of whether they are repatriated, immediate deductions for certain new investments instead of deductions for depreciation expense over time, and modifying or repealing many business deductions and credits (including reducing the business tax credit for certain clinical testing expenses incurred in the testing of certain drugs for rare diseases or conditions generally referred to as “orphan drugs”). Our federal net operating loss carryovers for taxable years beginning after 2017 will be carried forward indefinitely pursuant to the Tax Act.

The Tax Act did not have a material impact on our financial statements because our deferred temporary differences are fully offset by a valuation allowance and we do not have any significant offshore earnings from which to record the mandatory transition tax. However, given the significant complexity of the Tax Act, anticipated guidance from the US Treasury about implementing the Tax Act, and the potential for additional guidance from the SEC or the FASB related to the Tax Act, these estimates may be adjusted during the measurement period. We continue to examine the impact the Tax Act may have on our business. Notwithstanding the reduction in the federal corporate income tax rate, the overall impact of the Tax Act is uncertain and our business and financial condition could be adversely affected.

Any acquisitions we make, or collaborative relationships we enter into, may require a significant amount of our available cash and may not be clinically or commercially successful.

As part of our business strategy, we may effect acquisitions to obtain additional businesses, products, technologies, capabilities and personnel, but we cannot assure you that we will identify suitable products or enter into such acquisitions on acceptable terms.

Acquisitions involve a number of operational risks, including:

- Failure to achieve expected synergies;
- Difficulty and expense of assimilating the operations, technology and personnel of the acquired business;
- Our inability to retain the management, key personnel and other employees of the acquired business;
- Our inability to maintain the acquired company's relationship with key third parties, such as alliance partners;
- Exposure to legal claims for activities of the acquired business prior to the acquisition;
- The diversion of our management's attention from our core business; and
- The potential impairment of goodwill and write-off of IPRD costs, adversely affecting our reported results of operations and financial condition.

We also may enter into collaborative relationships that would involve our collaborators conducting proprietary development programs. Any conflict with our collaborators could limit our ability to obtain future collaboration agreements and negatively influence our relationship with existing collaborators. Disagreements with collaborators may also develop over the rights to our intellectual property.

If we make one or more significant acquisitions or enter into a significant collaboration in which the consideration includes cash, we may be required to use a substantial portion of our available cash and/or need to raise additional capital. For instance, in September and October of 2016 we borrowed $30.0 million under our loan agreement with Hercules to fund the payment due under the license agreement with AstraZeneca and this investment, as with any acquisition or collaboration, may not be successful.

Risks Related to Regulatory Matters

The manufacturing facilities of our third-party manufacturers are subject to significant government regulations and approvals, which are often costly and could result in adverse consequences to our business if we and our manufacturing partners fail to comply with the regulations or maintain the approvals.

Manufacturers of our product candidates are subject to cGMP and similar standards, and while we have policies and procedures in place to select manufacturers that adhere, and monitor their adherence to, such standards, they may nonetheless fail to do so. If one of them fails to obtain or maintain compliance or experiences problems in the scale-up of commercial production, the production of our product candidates could be interrupted, resulting in delays, additional costs or restrictions on the marketing or sale of our products. These manufacturers and their facilities will be subject to pre-approval cGMP inspection by the FDA and other regulatory authorities, and the findings of the cGMP inspection could result in a failure to obtain, or a delay in obtaining, regulatory approval. In addition, these manufacturers and their facilities will be subject to continual review and periodic inspections by the FDA and other regulatory authorities following regulatory approval, if any, of our product candidates. For instance, to monitor compliance with applicable regulations, the FDA routinely conducts inspections of facilities and may identify potential deficiencies. The FDA issues what are referred to as "FDA Form 483s" that set forth observations and concerns that are identified during its inspections. Failure to satisfactorily address the concerns or potential deficiencies identified in a Form 483 could result in the issuance of a warning letter, which is a notice of the issues that the FDA believes to be significant regulatory violations requiring prompt corrective actions. Failure to respond adequately to a warning letter, or to otherwise fail to comply with applicable regulatory requirements could result in enforcement, remedial and/or punitive actions by the FDA or other regulatory authorities.

Even if we obtain regulatory approval for ALIS or any of our other product candidates, adverse effects discovered after approval could limit the commercial profile of any approved product.

If we obtain regulatory approval for ALIS or any other product candidate that we develop, such products will be used by a larger number of patients and for longer periods of time than they were used in clinical trials. For these or other reasons, we or others may later discover that our products have adverse event profiles that limit their usefulness or require their withdrawal. This discovery could have a number of potentially significant negative consequences, including:

- Regulatory authorities may withdraw their approval or clearance of the product and may require recall of product in distribution;
- Regulatory authorities may require the addition of labeling statements, such as black box or other warnings or contraindications, or the issuance of "Dear Doctor Letters" or similar communications to healthcare professionals;
- Regulatory authorities may impose additional restrictions on marketing and distribution of the products, or other risk management measures, such as a REMS;
- We may be required to change the way the product is administered, conduct additional clinical studies or restrict the distribution of the product;
- We could be sued and held liable for harm caused to subjects; and
- We could be subject to negative publicity, including communications issued by regulatory authorities.

Any of these events could prevent us from maintaining market acceptance of the affected product, cause substantial reduction in sales or substantially increase the costs of commercializing our product candidates, cause significant financial losses or result in significant reputational damage.

If we are unable to obtain adequate reimbursement from governments or third-party payers for ALIS or any other products that we may develop or if we are unable to obtain acceptable prices for those products, our prospects for generating revenue and achieving profitability may be materially adversely affected.

Our prospects for generating revenue and achieving profitability depend heavily upon the availability of adequate reimbursement for the use of our approved products from governmental and other third-party payers, both in the US and in other markets. We expect a substantial majority of potential future ALIS revenues would come from Medicare reimbursement. Reimbursement by a third-party payer may depend upon a number of factors, including the third-party payer's determination that use of a product is:

- A covered benefit under its health plan;
- Safe, effective and medically necessary;
- Appropriate for the specific patient;
- Cost-effective; and
- Neither experimental nor investigational.

Obtaining a determination of coverage and reimbursement for a product from each government or other third-party payer is a time consuming and costly process that could require us to provide supporting scientific, clinical and cost effectiveness data for the use of our products to each payer. We may not be able to provide data sufficient to gain a positive coverage and reimbursement determination or we might need to conduct post-marketing studies in order to demonstrate the cost-effectiveness of any future products to such payers' satisfaction. Such studies might require us to commit a significant amount of management time and financial and other resources. Even when a payer determines that a product is eligible for reimbursement, the payer may impose coverage limitations that preclude payment for some uses that are approved by the FDA or non-US regulatory authorities. Moreover, eligibility for coverage does not imply that any product will be reimbursed in all cases or at a rate that allows us to make a profit or even cover our costs. Interim payments for new products, if applicable, also may not be sufficient to cover our costs and may not be made permanent. Subsequent approvals of competitive products could result in a detrimental change to the reimbursement of our products.

There is a significant focus in the US healthcare industry and elsewhere on cost containment and value. We expect changes in the Medicare program and state Medicaid programs, as well as managed care organizations and other third-party payers, to continue to put pressure on pharmaceutical product pricing. For instance, the Medicare Prescription Drug, Improvement, and Modernization Act of 2003 (MMA) expanded Medicare outpatient prescription drug coverage for the elderly through Part D prescription drug plans sponsored by private entities and authorized such plans to use formularies where they can limit the number of drugs that will be covered in any therapeutic class. The plans generally negotiate significant price concessions as a condition of formulary placement. The MMA also introduced a new reimbursement methodology based on average sales prices for physician-administered drugs, which is generally believed to have resulted in lower Medicare reimbursement for physician-administered drugs. These cost reduction initiatives and other provisions of this legislation provide additional pressure to contain and reduce drug prices and could decrease the coverage and price that we receive for any approved products and could seriously harm our business. Although the MMA applies only to drug benefits for Medicare beneficiaries, private payers often follow Medicare coverage policy and payment limitations when setting their own reimbursement rates, and any reimbursement reduction resulting from the MMA may result in a similar reduction in payments from private payers. Additionally, the Patient Protection and Affordable Care Act (ACA) revised the definition of "average manufacturer price" for reporting purposes and increased the minimum percentage for Medicaid drug rebates to states, and has imposed a significant annual fee on companies that manufacture or import branded prescription drug products. We believe it is likely that the ACA, or any legislation enacted to amend or replace it, will continue the pressure on pharmaceutical pricing, especially under the Medicare program, and also may increase our regulatory burdens and operating costs. If one or more of our product candidates reaches commercialization, such changes may have a significant impact on our ability to set a price we believe is fair for our products and may adversely affect our ability to generate revenue and achieve or maintain profitability. We expect further federal and state proposals and health care reforms to continue to be proposed by legislators and/or the US President, which could limit the prices that can be charged for the products we develop and may limit our commercial opportunity. In addition, any reduction of assistance from independent charitable organizations that provide co-pay assistance to Medicare patients could limit the ability of the primarily elderly NTM lung disease patient population to afford ALIS.

Moreover, in markets outside the US, including Japan, Canada and the countries in the EU, pricing of pharmaceutical products is subject to governmental control. Evaluation criteria used by many EU government agencies for the purposes of pricing and reimbursement typically focus on a product's degree of innovation and its ability to meet a clinical need unfulfilled by currently available therapies. The ACA created a similar entity, the Patient-Centered Outcomes Research Institute (PCORI) designed to review the effectiveness of treatments and medications in federally-funded health care programs. The PCORI began its first research initiatives recently, and an adverse result may result in a treatment or product being removed from Medicare or Medicare coverage. The decisions of such governmental agencies could affect our ability to sell our products profitably.

Government health care reform could increase our costs, and could materially adversely affect our business, financial condition, results of operations and prospects and the value of our common stock.

Our industry is highly regulated and changes in or revisions to laws and regulations that make gaining regulatory approval, reimbursement and pricing more difficult or subject to different criteria and standards may adversely impact our business, operations or financial results. For example, under the ACA, drug manufacturers are required to report information on payments or transfers of value to US physicians and teaching hospitals as well as investment interests held by physicians and their immediate family members. Failure to submit required information may result in civil monetary penalties. The reported data are posted in searchable form on a public website.

The Administration and the majority party in both Houses of Congress have indicated their ongoing desire to repeal the ACA. It is unclear whether, when and how that repeal may be effectuated and what the effect on the healthcare sector will be. The US President has indicated an interest in having the federal government negotiate drug prices with pharmaceutical manufacturers. Changes to the ACA, to the Medicare or Medicaid programs, or to the ability of the federal government to negotiate drug prices, or other federal legislation regarding healthcare access, financing or legislation in individual states, could affect our business, financial condition, results of operations and prospects and the value of our common stock.

If we are found in violation of federal or state "fraud and abuse" laws, we may be required to pay a penalty or may be suspended from participation in federal or state health care programs, which may adversely affect our business, financial condition, results of operations and prospects and the value of our common stock.

In the US, we are subject to various federal and state health care "fraud and abuse" laws, including anti-kickback laws, false claims laws and other laws intended to reduce fraud and abuse in federal and state health care programs. Although we seek to structure our business arrangements in compliance with all applicable requirements, these laws are broadly written, and it is often difficult to determine precisely how the law will be applied in specific circumstances. Accordingly, it is possible that our practices may be challenged under these laws. Violations of fraud and abuse laws may be punishable by criminal and/

or civil sanctions, including fines or exclusion or suspension from federal and state health care programs such as Medicare and Medicaid and debarment from contracting with the US government, and our business, financial condition, results of operations and prospects and the value of our common stock may be adversely affected. Our reputation could also suffer. In addition, private individuals have the ability to bring actions on behalf of the government under the federal False Claims Act as well as under the false claims laws of several states.

Several states also impose other marketing restrictions or require pharmaceutical companies to make marketing or price disclosures to the state. Some states, as well as other countries, including France, require the disclosure of certain payments to health care professionals. Health record privacy laws may limit access to information identifying those individuals who may be prospective users. There are ambiguities as to what is required to comply with these state requirements, and we could be subject to penalties if a state determines that we have failed to comply with an applicable state law requirement.

Risks Related to Our Intellectual Property

If we are unable to protect our intellectual property rights adequately, the value of our product candidates could be diminished.

The patent position of biotechnology and pharmaceutical companies generally is highly uncertain and involves complex legal, technical, scientific and factual questions, and our success depends in large part on our ability to protect our proprietary technology and to obtain patent protection for our products, prevent third parties from infringing on our patents, both domestically and internationally. We have sought to protect our proprietary position by filing patent applications in the US and abroad related to our novel technologies and products that are important to our business. This process is expensive and time-consuming, and we may not be able to file and prosecute all necessary or desirable patent applications at a reasonable cost or in a timely manner. It is also possible that we will fail to identify patentable aspects of our research and development output before it is too late to obtain patent protection. Our existing patents and any future patents we obtain may not be sufficiently broad to prevent others from using our technologies or from developing competing products and technologies.

Even if our owned and licensed patent applications issue as patents, they may not issue in a form that will provide us with any meaningful protection, prevent competitors from competing with us or otherwise provide us with any competitive advantage. Any conclusions we may reach regarding non-infringement, inapplicability or invalidity of a third party's intellectual property vis-à-vis our proprietary rights, or those of a licensor, are based in significant part on a review of publicly available databases and other information. There may be information not available to us or otherwise not reviewed by us that could render these conclusions inaccurate. Our competitors may also be able to circumvent our owned or licensed patents by developing similar or alternative technologies or products in a non-infringing manner.

Additionally, patents issued to us or our licensors may be challenged, narrowed, invalidated, held to be unenforceable or circumvented through litigation, which could limit our ability to stop competitors from marketing similar products or reduce the term of patent protection we may have for our products. US patents and patent applications may also be subject to interference or derivation proceedings, and US patents may be subject to re-examination proceedings, reissue, post-grant review and/or *inter partes* review in the PTO. Foreign patents may be subject to opposition or comparable proceedings in the corresponding foreign patent office, which could result in either loss of the patent or denial of the patent application or loss or reduction in the scope of one or more of the claims of the patent or patent application. See *Intellectual Property - ALIS Patents and Trade Secrets* in Item 1 of Part I of this Annual Report on Form 10-K for the year ended December 31, 2017 (2017 Annual Report) for more information on our European patent that was previously opposed, the decision of which is now under appeal by Generics (UK) Ltd. Another of our European patents has been opposed by Generics (UK) Ltd., and was revoked in November 2017. We intend to appeal that decision, and the patent remains enforceable during the appeal. These European patents have statutory expiration dates in 2026 and 2023, respectively, not including additional term that might be added via a Supplementary Protection Certificate.

Changes in either patent laws or in interpretations of patent laws in the US and other countries may also diminish the value of our intellectual property or narrow the scope of our patent protection, including making it easier for competitors to challenge our patents. For example, the America Invents Act included a number of changes to established practices, including the transition to a first-inventor-to-file system and new procedures for challenging patents and implementation of different methods for invalidating patents.

If we are not able to adequately prevent disclosure of trade secrets and other proprietary information, the value of our product candidates could be significantly diminished.

We rely on trade secrets to protect our proprietary technologies, especially where we do not believe patent protection is appropriate or obtainable. However, trade secrets are difficult to protect. We rely in part on confidentiality agreements with our employees, consultants, advisors, collaborators, and other third parties and partners to protect our trade secrets and other proprietary information. These agreements may not effectively prevent disclosure of confidential information or may not provide an adequate remedy in the event of unauthorized disclosure of confidential information. In addition, third parties may independently develop or discover our trade secrets and proprietary information. Regulators also may disclose information we consider to be proprietary to third parties under certain circumstances, including in response to third-party requests for such disclosure under the Freedom of Information Act or comparable laws. Additionally, the FDA, as part of its Transparency Initiative, continues to consider whether to make additional information publicly available on a routine basis, including information that we may consider to be trade secrets or other proprietary information, and it is not clear at the present time whether and how the FDA's disclosure policies may change in the future.

We may not be able to enforce our intellectual property rights throughout the world.

The laws of some foreign countries do not protect intellectual property rights to the same extent as the laws of the US Many companies have encountered significant problems in protecting and defending intellectual property rights in certain foreign jurisdictions. The legal systems of some countries, particularly developing countries, do not favor the enforcement of patents and other intellectual property protection, especially those relating to life sciences. This could make it difficult for us to stop the infringement of our patents or in-licensed patents or the misappropriation of our other intellectual property rights. For example, many foreign countries have compulsory licensing laws under which a patent owner may be required to grant licenses to third parties. In addition, many countries limit the enforceability of patents against third parties, including government agencies or government contractors. In these countries, patents may provide limited or no benefit.

Proceedings to enforce our patent rights in foreign jurisdictions could result in substantial costs and divert our efforts and attention from other aspects of our business. Our efforts to protect our intellectual property rights in such countries may be inadequate. In addition, changes in the law and legal decisions by courts in the US and foreign countries may affect our ability to obtain adequate protection for our technology and to enforce intellectual property rights.

The drug research and development industry has a history of intellectual property litigation, and we may be involved in costly intellectual property disputes which may prevent or delay our product development efforts, prevent us from commercializing our products or increase the costs of commercializing our products.

Third parties may claim that we have infringed upon or misappropriated their proprietary rights. Any existing third-party patents, or patents that may later issue to third parties, could negatively affect our commercialization of ALIS, INS1007, INS1009 or any other product. For instance, PAH is a competitive indication with established products, including other formulations of treprostinil. Our supply of the active pharmaceutical ingredient for INS1009 is dependent upon a single supplier. The supplier owns patents on its manufacturing process, and we have filed patent applications for INS1009; however, a competitor in the PAH indication may claim that we or our supplier have infringed upon or misappropriated its proprietary rights. Moreover, in the event that we pursue approval of INS1009, or any other product candidate, via the 505(b)(2) regulatory pathway, we will be required to file a certification against any unexpired patents listed in the Orange Book for the third party drug we rely upon as part of our regulatory submission. This certification process may lead to litigation and could delay also launch of a product candidate.

In the event of a successful claim against us for infringement or misappropriation of a third party's proprietary rights, we may be required to take actions including but not limited to the following:

- Pay damages, including up to treble damages, royalties, and the other party's attorneys' fees, which may be substantial;
- Cease the development, manufacture, marketing and sale of products or use of processes that infringe the proprietary rights of others;
- Expend significant resources to redesign our products or our processes so that they do not infringe the proprietary rights of others, which may not be possible;

- Redesign our products or processes to avoid third-party proprietary rights, which means we may suffer significant regulatory delays associated with conducting additional clinical trials or other steps to obtain regulatory approval; and/or

- Obtain one or more licenses arising out of a settlement of litigation or otherwise from third parties which license(s) may not be available to us on acceptable terms or at all.

We may also have to undertake costly litigation or engage in other proceedings, such as interference or inter partes review, to enforce any patents issued or licensed to us, to confirm the scope and validity of our or a licensor's proprietary rights or to defend against allegations that we have infringed a third party's intellectual property rights. Such proceedings are likely to be time consuming and may divert management attention from operation of our business, and could have a material adverse effect on our business, financial condition, results of operations and prospects and the value of our common stock.

Certain of our existing license agreements include, and our future license agreements also may include, restrictions on our ability to freely develop or commercialize the product candidates that are subject to those agreements. If we fail to comply with our obligations under these agreements, or if these license agreements are terminated for other reasons, we could lose license rights that are important to our business.

We are a party to licensing agreements with PARI and AstraZeneca, which we view as material to our business. For additional information regarding the terms of these agreements, see *Business - License and Other Agreements* in Item 1 of Part I of this 2017 Annual Report. Under our license agreement with AstraZeneca, AstraZeneca retains a right of first negotiation pursuant to which it may exclusively negotiate with us before we can negotiate with a third party regarding any transaction to develop or commercialize INS1007, subject to certain exceptions. While this right of first negotiation is not triggered by a change of control, it may impede or delay our ability to consummate certain other transactions involving INS1007.

Additionally, if we fail to comply with our obligations under the agreements with PARI and AstraZeneca, our counterparty may have the right to take action against us, up to and including termination of the relevant license. For instance, under our licensing agreement with PARI, with respect to NTM, CF and bronchiectasis, we have specific obligations to use commercially reasonable efforts to achieve certain developmental and regulatory milestones by set deadlines. Additionally, for NTM, we are obligated to use commercially reasonable efforts to achieve certain commercial milestones in the US and Europe. The consequences of our failing to use commercially reasonable efforts to achieve certain commercial milestones are context-specific, but include ending PARI's non-compete obligation, making the license non-exclusive and terminating the license, in each case with respect to the applicable indication. Similarly, under our license agreement with AstraZeneca, AstraZeneca may terminate our license to INS1007 if we fail to use commercially reasonable efforts to develop and commercialize a product based on INS1007, or we are subject to a bankruptcy or insolvency. Reduction or elimination of our licensed rights may result in our having to negotiate new or reinstated licenses with less favorable terms and may materially harm our business.

Risks Related to Our Industry

We operate in a highly competitive and changing environment, and if we are unable to adapt to our environment, we may be unable to compete successfully.

Biotechnology and related pharmaceutical technology have undergone and are likely to continue to experience rapid and significant change. 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 and to obtain and maintain protection for our intellectual property. Any compounds, products or processes that we develop may become obsolete before we recover any expenses incurred in connection with their development. In each of our potential product areas, we face substantial competition from pharmaceutical, biotechnology and other companies, universities and research institutions. Relative to us, most of these entities have substantially greater capital resources, research and development staffs, facilities and experience in conducting clinical studies and obtaining regulatory approvals, as well as in manufacturing and marketing pharmaceutical products. Many of our competitors may achieve product commercialization or obtain patent protection earlier than us. Furthermore, we believe that our competitors have used, and may continue to use, litigation to gain a competitive advantage. Our competitors may also use different technologies or approaches to the development of products similar to the products we are seeking to develop.

We expect that competing successfully will depend, among other things, on product efficacy, safety, reliability, availability, timing and scope of regulatory approval and price. Specifically, we expect crucial factors will include the relative speed with which we can develop products, complete the clinical testing and regulatory approval processes and supply

commercial quantities of the product to the market. We expect competition to increase as technological advances are made and commercial applications broaden. There are potential competitive products, both approved and in development, which include oral, systemic, or inhaled antibiotic products to treat chronic respiratory infections. For instance, certain entities have expressed interest in studying their products for NTM lung disease and are seeking to advance studies in NTM lung disease caused by mycobacterial species other than MAC; however, we are not aware that any such entities are currently conducting clinical trials for the treatment of refractory NTM lung disease caused by MAC or of any approved inhaled therapies specifically indicated for NTM lung disease in North America, Japan or Europe. If any of our competitors develops a product that is more effective, safe, tolerable or, convenient or less expensive than ALIS or our other product candidates, it would likely materially adversely affect our ability to generate revenues. We also may face lower priced generic competitors if third-party payers encourage use of generic or lower-priced versions of our product or if competing products are imported into the US or other countries where we may sell ALIS.

In addition, there are other amikacin products that have been approved by the FDA, MHLW and other regulatory agencies for use in other indications, and physicians may elect to prescribe those products rather than ALIS to treat the indications for which ALIS may receive approval, which is commonly referred to as off-label use. Although regulations prohibit a drug company from promoting off-label use of its product, the FDA and other regulatory agencies do not regulate the practice of medicine and cannot direct physicians as to what product to prescribe to their patients. As a result, we would have limited ability to prevent any off-label use of a competitor's product to treat diseases for which we have received FDA or other regulatory agency approval, even if such use violates our patents or any statutory exclusivities that FDA may grant for the use of amikacin to treat such diseases. If we are unable to compete successfully, it will materially adversely affect our business, financial condition, results of operations and prospects and the value of our common stock.

If another party obtains orphan drug exclusivity for a product that is essentially the same as a product we are developing for a particular indication, we may be precluded or delayed from commercializing the product in that indication.

Under the Orphan Drug Act, the FDA may grant orphan drug designation to drugs intended to treat a rare disease or condition. The company that obtains the first regulatory approval from the FDA for a designated orphan drug for a rare disease generally receives marketing exclusivity for use of that drug for the designated condition for a period of seven years. Similar laws exist in the EU with a term of ten years. See *Business - Government Regulation - Orphan Drugs* in Item 1 of Part I of this 2017 Annual Report for additional information. If a competitor obtains approval of the same drug for the same indication or disease before us, and the FDA grants such orphan drug exclusivity, we would be prohibited from obtaining approval for our product for seven or more years, unless our product can be shown to be clinically superior. In addition, even if we obtain orphan exclusivity, the FDA may approve another product during our orphan exclusivity period for the same indication under certain circumstances.

Our research, development and manufacturing activities used in the production of ALIS involve the use of hazardous materials, which could expose us to damages, fines, penalties and sanctions and materially adversely affect our results of operations and financial condition.

We are subject to numerous environmental, health and safety laws and regulations, including those governing laboratory procedures and the handling, use, storage, treatment and disposal of hazardous materials and wastes. Our research and development program and manufacturing activities for ALIS and our other product candidates involve the controlled use of hazardous materials and chemicals. We generally contract with third parties for the disposal of these materials and wastes. Although we strive to comply with all pertinent regulations, we cannot eliminate the risk of environmental contamination, damage to facilities or injury to personnel from the accidental or improper use or control of these materials. In addition to any liability we could have for any misuse by us of hazardous materials and chemicals, we could also potentially be liable for activities of our CMOs or other third parties. Any such liability, or even allegations of such liability, could materially adversely affect our results of operations and financial condition. We also could incur significant costs associated with civil or criminal fines and penalties.

In addition, we may incur substantial costs in order to comply with current or future environmental, health and safety laws and regulations. These current or future laws and regulations may impair our research, development or production efforts. Failure to comply with these laws and regulations also may result in substantial fines, penalties or other sanctions.

We may be subject to product liability claims, and we have only limited product liability insurance.

The manufacture and sale of human therapeutic products involve an inherent risk of product liability claims, which can lead to significant adverse publicity and obligations to pay damages. We currently have only limited product liability insurance for our products. We do not know if we will be able to maintain existing, or obtain additional, product liability

insurance on acceptable terms or with adequate coverage against potential liabilities. This type of insurance is expensive and may not be available on acceptable terms. If we are unable to obtain or maintain sufficient insurance coverage on reasonable terms or to otherwise protect against potential product liability claims, we may be unable to commercialize our products. A successful product liability claim brought against us in excess of our insurance coverage, if any, may require us to pay substantial amounts and may materially adversely affect our business, financial condition, results of operations and prospects and the value of our common stock.

Risks Related to Employee Matters and Managing Growth

We are dependent upon retaining and attracting key personnel, the loss of whose services could materially adversely affect our business, financial condition, results of operations and prospects and the value of our common stock.

We depend heavily on our management team and our principal clinical and commercial personnel, the loss of whose services might significantly delay or prevent the achievement of our research, development or business objectives. Our success depends, in large part, on our ability to attract and retain qualified management, clinical and commercial personnel, and on our ability to develop and maintain important relationships with commercial partners, leading research institutions and key distributors. We plan to hire additional personnel in anticipation of seeking regulatory approval for and commercial launch of ALIS.

Competition for skilled personnel in our industry and market is very intense because of the numerous pharmaceutical and biotechnology companies that seek similar personnel. These companies may have greater financial and other resources, offer a greater opportunity for career advancement and have a longer history in the industry than we do. We also experience competition for the hiring of our clinical and commercial personnel from universities, research institutions, and other third parties. We cannot assure that we will attract and retain such persons or maintain such relationships. Our inability to retain and attract qualified employees would materially harm our business, financial condition, results of operations and prospects and the value of our common stock.

We expect to expand our development, manufacturing, regulatory and sales and marketing capabilities, and as a result, we may encounter difficulties in managing our growth, which could disrupt our operations.

We expect that our potential expansion into areas and activities requiring additional expertise, such as further clinical trials, governmental approvals, manufacturing, sales, marketing and distribution will place additional requirements on our management, operational and financial resources. Future growth would impose significant added responsibilities on members of management, including the need to identify, recruit, maintain, motivate and integrate additional employees. Also, our management may need to divert a disproportionate amount of its attention away from our day-to-day activities and devote a substantial amount of time to managing these growth activities. We may not be able to effectively manage the expansion of our operations, which may result in weaknesses in our infrastructure, give rise to operational mistakes, loss of business opportunities, loss of employees and reduced productivity among remaining employees.

The anticipated commercialization of ALIS and the development of additional product candidates will require significant expenditures by us and place a strain on our resources. If our management is unable to effectively manage our activities in anticipation of commercialization, as well as our development efforts, we may incur higher than expected expenditures or other expenses and our business may otherwise be adversely affected.

Risks Related to Our Common Stock and Listing on the Nasdaq Global Select Market

The market price of our stock has been and may continue to be highly volatile.

Our common stock is listed on the Nasdaq Global Select Market under the ticker symbol “INSM”. The market price of our stock has been and may continue to be highly volatile, and could be subject to wide fluctuations in price in response to various factors, including those discussed herein, many of which are beyond our control. In addition, the stock market has from time to time experienced extreme price and volume fluctuations, which have particularly affected the market prices for emerging biotechnology and pharmaceutical companies like us, and which have often been unrelated to their operating performance. These broad market fluctuations may adversely affect the market price of our common stock. Historically, when the market price of a stock has been volatile, shareholders are more likely to institute securities and derivative class action litigation against the issuer of such stock. As described below, a securities class action lawsuit was initiated against us during 2016 following a decline in our stock price.

We, certain of our executive officers and directors and the underwriters from a prior securities offering were subject to a recently dismissed securities class action lawsuit, which, if a second amended complaint is filed, may require significant management and board time and attention and significant expense to us and result in an unfavorable outcome, which could have a material adverse effect on our business, financial condition, results of operations and prospects and the value of our common stock.

We, certain of our executive officers and directors and the underwriters from a prior securities offering were named as defendants in a securities class action lawsuit initially filed on July 15, 2016. The amended complaint, filed December 15, 2016, alleged that we and certain of our executive officers and directors violated Sections 11 and 12(a)(2) of the Securities Act of 1933, as amended (the Securities Act), and that we, certain of our executive officers and the underwriters violated Section 10(b) of the Exchange Act and Rule 10b-5 promulgated thereunder of the Exchange Act, by making materially false and misleading statements and omissions relating to the development of ALIS and/or related requests for regulatory approval. It also alleged that the defendant officers and directors violated Section 15 of the Securities Act and that the defendant officers violated Section 20(a) of the Exchange Act. On February 15, 2018, the Court issued a decision granting our motion and dismissing the amended complaint without prejudice. The lead plaintiff has until March 19, 2018 to file a second amended complaint. For additional information, see Note 11, Commitments and Contingencies, in Item 1 of Part I of this 2017 Annual Report. While we believe that we have substantial legal and factual defenses to the claims that were asserted in the class action and intend to continue vigorously defend the case if a second amended complaint is filed, this lawsuit could divert our management's and board's attention from other business matters, the outcome of the litigation is difficult to predict and quantify, and the defense against the underlying claims will likely be costly. The ultimate resolution of this matter could result in payments of monetary damages or other costs, materially and adversely affect our business, financial condition and results of operations, and adversely affect our reputation and prospects, and consequently, could negatively impact the value of our common stock.

We have insurance policies related to some of the risks associated with our business, including directors' and officers' liability insurance policies. However, there is no assurance that our insurance coverage will be sufficient or that our insurance carriers will cover all claims in that litigation. If we are not successful in our defense of the claims asserted in the putative action and those claims are not covered by insurance or exceed our insurance coverage, we may have to pay damage awards, indemnify our executive officers and directors from damage awards that may be entered against them and pay the costs and expenses incurred in defense of, or in any settlement of, such claims. In addition, we are indemnifying the underwriters that are party to this action against the claims asserted against them, and these costs and expenses might not be covered by insurance.

In addition, there is the potential for additional shareholder litigation against us, and we could be materially and adversely affected by such matters.

Certain provisions of Virginia law, our articles of incorporation and amended and restated bylaws and arrangements between us and our employees could hamper a third party's acquisition of, or discourage a third party from attempting to acquire control of us.

Certain provisions of Virginia law, our articles of incorporation and amended and restated bylaws and arrangements with our employees could hamper a third party's acquisition of, or discourage a third party from attempting to acquire control of, us or limit the price that investors might be willing to pay for shares of our common stock. These provisions or arrangements include:

- The ability to issue preferred stock with rights senior to those of our common stock without any further vote or action by the holders of our common stock. The issuance of preferred stock could decrease the amount of earnings and assets available for distribution to the holders of our common stock or could adversely affect the rights and powers, including voting rights, of the holders of our common stock. In certain circumstances, such issuance could have the effect of decreasing the market price of our common stock.

- The existence of a staggered board of directors in which there are three classes of directors serving staggered three-year terms, thus expanding the time required to change the composition of a majority of directors.

- The requirement that shareholders provide advance notice when nominating director candidates to serve on our Board of Directors.

- The inability of shareholders to convene a shareholders' meeting without the chairman of the board, the president or a majority of the board of directors first calling the meeting.

- The prohibition against entering into a business combination with the beneficial owner of 10% or more of our outstanding voting stock for a period of three years after the 10% or greater owner first reached that level of stock ownership, unless certain criteria are met.

- In addition to severance agreements with our officers and provisions in our incentive plans that permit acceleration of equity awards upon a change in control, a severance plan for eligible full-time employees that provides such employees with severance equal to six months of their then-current base salaries in connection with a termination of employment without cause upon, or within 18 months following, a change in control.

We previously had a shareholder rights plan, or "poison pill", which expired in May 2011. Under Virginia law, our Board of Directors may implement a new shareholders' rights plan without shareholder approval. Our Board of Directors intends to regularly consider this matter, even in the absence of specific circumstances or takeover proposals, to facilitate its future ability to quickly and effectively protect shareholder value.

Other Risks Related to Our Business

We have limited experience operating internationally, are subject to a number of risks associated with our international activities and operations and may not be successful in our efforts to expand internationally.

We currently have limited operations outside of the US. As of December 31, 2017, we had 24 employees located in Europe, and we have suppliers located around the world. In order to meet our long-term goals, we will need to grow our international operations over the next several years, including in Japan, and continue to source material used in the manufacture of our product candidates from abroad. Consequently, we are and will continue to be subject to additional risks related to operating in foreign countries, including:

- Our limited experience operating our business internationally;

- An inability to achieve the optimal pricing and reimbursement for ALIS or subsequent changes in reimbursement, pricing and other regulatory requirements;

- Any implementation of, or changes to, tariffs, trade barriers and other import-export regulations in the US or other countries in which we, or our third-party partners, operate;

- Unexpected adverse events related to ALIS or our other product candidates occurring in foreign markets that we have not experienced in the US;

- Economic and political conditions, including geopolitical events, such as war and terrorism, foreign currency fluctuations and inflation, which could result in increased or unpredictable operating expenses and reduced revenues and other obligations incident to doing business in, or with a company located in, another country;

- Changes resulting from (i) the uncertainty and instability in economic and market conditions caused by the UK's vote to exit the European Union; and (ii) the uncertainty regarding how the UK's access to the EU Single Market and the wider trading, legal, regulatory and labor environments will be impacted by the UK's vote to exit the European Union, including the resulting impact on our business; and

- Compliance with foreign or US laws, rules and regulations, including data privacy requirements, labor relations laws, tax laws, anti-competition regulations, import, export and trade restrictions, anti-bribery/anti-corruption laws, regulations or rules, which could lead to actions by us or our licensees, distributors, manufacturers, other third parties who act on our behalf or with whom we do business in foreign countries or our employees who are working abroad that could subject us to investigation or prosecution under such foreign or US laws.

These and other risks associated with our international operations may materially adversely affect our business, financial condition, results of operations and prospects and the value of our common stock.

Our internal computer systems, or those of our CROs or other contractors or consultants, may fail or suffer security breaches, which could result in a material disruption of our business operations, including our drug development programs.

Despite the implementation of security measures, our internal computer systems and those of our CROs and other contractors and consultants are vulnerable to damage from computer viruses, unauthorized access, natural disasters, terrorism,

war and telecommunication and electrical failures. If such an event were to occur and cause interruptions in our operations, it could result in a material adverse effect on our business operations, including a material disruption of our drug development programs. Unauthorized disclosure of sensitive or confidential client or employee data, whether through breach of computer systems, systems failure, employee negligence, fraud or misappropriation, or otherwise, could damage our reputation. Similarly, unauthorized access to or through our information systems and networks, whether by our employees or third parties, could result in negative publicity, legal liability and damage to our reputation. For example, the loss of clinical trial data from completed or ongoing clinical trials for any of our product candidates could result in delays in our regulatory approval efforts and significantly increase our costs to recover or reproduce the data. To the extent that any disruption or security breach was to result in a loss of or damage to our data or applications, or inappropriate disclosure of confidential or proprietary information, we could incur liability and the further development of our product candidates could be delayed.

Although we have general liability insurance coverage, including coverage for errors and omissions, our insurance may not cover all claims, continue to be available on reasonable terms or be sufficient in amount to cover one or more large claims; additionally, the insurer may disclaim coverage as to any future claim. The successful assertion of one or more large claims against us that exceed or are not covered by our insurance coverage or changes in our insurance policies, including premium increases or the imposition of large deductible or co-insurance requirements, could have a material adverse effect on our business, financial condition, results of operations and prospects and the value of our common stock.

We are subject to the US Foreign Corrupt Practices Act, the UK Bribery Act and other anti-corruption laws and trade control laws, as well as other laws governing our operations. If we fail to comply with these laws, we could be subject to negative publicity, civil or criminal penalties, other remedial measures, and legal expenses, which could adversely affect our business, financial condition, results of operations and prospects and the value of our common stock.

Our operations are subject to anti-corruption laws, including the US Foreign Corrupt Practices Act (FCPA), the UK Bribery Act and other anti-corruption laws that apply in countries where we do business. The FCPA, UK Bribery Act and these other laws generally prohibit us, our employees and our intermediaries from making prohibited payments to government officials or other persons to obtain or retain business or gain some other business advantage. The CONVERT study includes more than 125 sites in 18 countries, and we are conducting the 312 study and plan to conduct the WILLOW study, our global phase 2 study of INS1007 in non-CF bronchiectasis, at a broad range of trial sites around the world. Certain of these jurisdictions pose a risk of potential FCPA violations, and we have relationships with third parties whose actions could potentially subject us to liability under the FCPA or local anti-corruption laws. In addition, we cannot predict the nature, scope or effect of future regulatory requirements to which our international operations might be subject or the manner in which existing laws might be administered or interpreted.

We are also subject to other laws and regulations governing our international operations, including regulations administered by the US Department of Commerce's Bureau of Industry and Security, the US Department of Treasury's Office of Foreign Assets Control, and various non-US government entities, including applicable export control regulations, economic sanctions on countries and persons, customs requirements, currency exchange regulations and transfer pricing regulations (collectively, Trade Control laws).

We may not be effective in ensuring our compliance with all applicable anti-corruption laws, including the FCPA or other legal requirements, including Trade Control laws. If we are not in compliance with the FCPA and other anti-corruption laws or Trade Control laws, we may be subject to criminal and civil penalties, disgorgement and other sanctions and remedial measures, and legal expenses, which could have an adverse impact on our business, financial condition, results of operations and prospects and the value of our common stock. Likewise, even an investigation by US or foreign authorities of potential violations of the FCPA other anti-corruption laws or Trade Control laws could have an adverse impact on our reputation, business, financial condition, results of operations and prospects and the value of our common stock.

ITEM 1B. UNRESOLVED STAFF COMMENTS

None.

ITEM 2. PROPERTIES

We currently lease 56,617 square feet of laboratory and office space in Bridgewater, New Jersey. The initial term of the lease will expire in November 2019, and we have the option to extend the lease for two additional five year periods beyond the initial term. We also lease 14,311 square feet of additional laboratory space located in Bridgewater, NJ for which the initial lease term expires in September 2021. In addition, we lease office space in Ireland, the Netherlands and Japan.

ITEM 3. LEGAL PROCEEDINGS

On July 15, 2016, a lawsuit captioned Hoey v. Insmed Incorporated, et al, No. 3:16-cv-04323-FLW-TJB (D.N.J. July 15, 2016) was filed in the US District Court for the District of New Jersey on behalf of a putative class of investors who purchased our common stock from March 18, 2013 through June 8, 2016. The complaint alleged that we and certain of our executives violated Sections 10(b) and 20(a) of the Exchange Act by misrepresenting and/or omitting the likelihood of the EMA approving our European MAA for use of ALIS in the treatment of NTM lung disease and the likelihood of commercialization of ALIS in Europe.

On October 25, 2016, the Court issued an order appointing Bucks County Employees Retirement Fund as lead plaintiff for the putative class. On December 15, 2016, the lead plaintiff filed an amended complaint that shortens the putative class period for the Exchange Act claims to March 26, 2014 through June 8, 2016 and adds claims under Sections 11, 12, and 15 of the Securities Act on behalf of a putative class of investors who purchased common stock in or traceable to our March 31, 2015 public offering. The amended complaint names as defendants in the Securities Act claims the Company, certain directors and officers, and the investment banks who served as underwriters in connection with the secondary offering. The amended complaint alleges defendants violated the Securities Act by using a purportedly misleading definition of "culture conversion" and supposedly failing to disclose in the offering materials purported flaws in its Phase 2 study that made the secondary offering risky or speculative. The amended complaint seeks damages in an unspecified amount. We moved to dismiss the amended complaint on March 1, 2017. The lead plaintiff opposed the motion on May 17, 2017 and we provided our reply brief on July 11, 2017. On July 20, 2017, the plaintiff asked for leave to file a sur-reply in further opposition to our motion to dismiss the amended complaint, which we had opposed.

On February 15, 2018, the Court issued a decision granting our motion and dismissing the amended complaint without prejudice. The lead plaintiff has until March 19, 2018 to file a second amended complaint. If a second amended complaint is filed, we intend to continue to defend the lawsuit vigorously; however, there can be no assurance regarding the ultimate outcome of the lawsuit.

From time to time, we are a party to various other lawsuits, claims and other legal proceedings that arise in the ordinary course of business. While the outcomes of these matters are uncertain, management does not expect that the ultimate costs to resolve these matters will have a material adverse effect on our consolidated financial position, results of operations or cash flows.

ITEM 4. MINE SAFETY DISCLOSURES

Not applicable.

PART II

ITEM 5. MARKET FOR REGISTRANT'S COMMON EQUITY, RELATED STOCKHOLDER MATTERS AND ISSUER PURCHASES OF EQUITY SECURITIES

Our trading symbol is "INSM." Our common stock currently trades on the Nasdaq Global Select Market. Until February 3, 2014, our common stock traded on the Nasdaq Capital Market. The following table lists the high and low sale prices per share for our common stock on a quarterly basis for both 2017 and 2016.

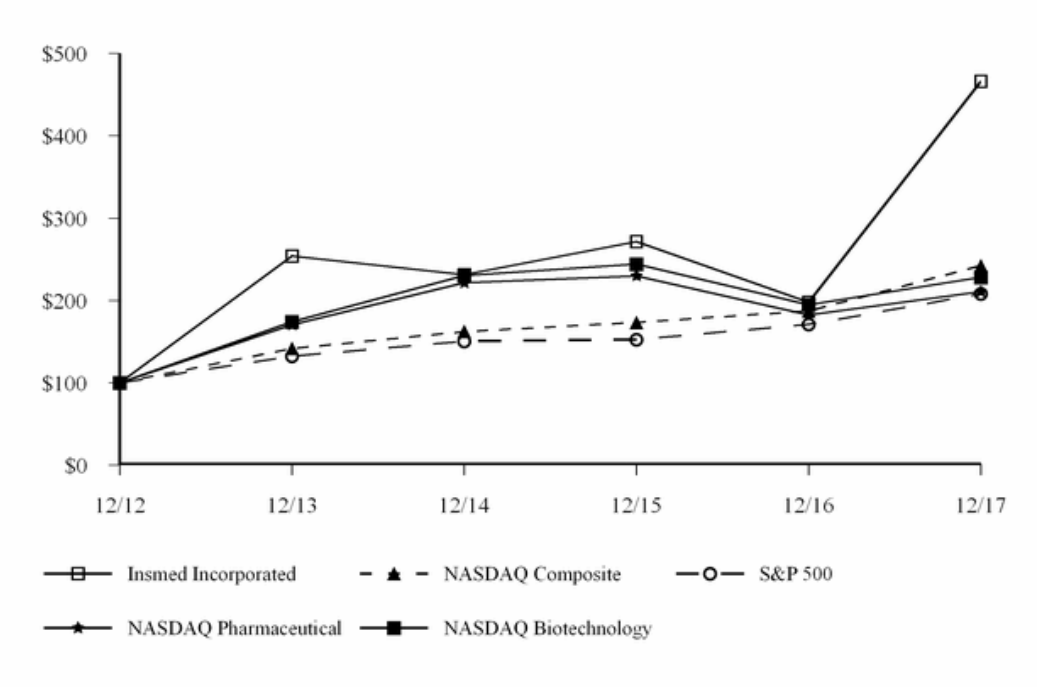
Fiscal Year 2017	**High**	**Low**
Fourth Quarter	$ 32.94	$ 25.81
Third Quarter	$ 31.39	$ 11.49
Second Quarter	$ 19.35	$ 14.61
First Quarter	$ 17.51	$ 12.74

Fiscal Year 2016	**High**	**Low**
Fourth Quarter	$ 15.49	$ 10.21
Third Quarter	$ 15.35	$ 9.75
Second Quarter	$ 14.53	$ 9.02
First Quarter	$ 18.60	$ 10.53

On February 1, 2018, the last reported sale price for our common stock on the Nasdaq Global Select Market was $26.37 per share. As of February 1, 2018, there were 138 holders of record of our common stock.

We have never declared or paid cash dividends on our common stock. We anticipate that we will retain all earnings, if any, to support operations and to finance the growth and development of our business for the foreseeable future. Under the terms of our loan agreement with Hercules, we are prohibited from declaring or paying any cash dividend or making a cash distribution on any class of our stock or on other equity interest, except that our subsidiaries (defined in the loan agreement as a corporate entity in which we control more than 50% of the voting securities) may pay dividends or make distributions to their equity owners. Any future determination as to the payment of dividends will be dependent upon these and any contractual or other restrictions to which we may be subject and, to the extent permissible thereunder, will be at the sole discretion of our board of directors and will depend on our financial condition, results of operations, capital requirements and other factors our board of directors deems relevant at that time.

COMPARISON OF 5 YEAR CUMULATIVE TOTAL RETURN*
Among Insmed Incorporated, the NASDAQ Composite Index,
the S&P 500 Index, the NASDAQ Pharmaceutical Index and the NASDAQ Biotechnology Index



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* $100 invested on 12/31/12 in stock or index, including reinvestment of dividends.
Fiscal year ending December 31.

ITEM 6. SELECTED FINANCIAL DATA

The following selected financial data reflects our consolidated statements of operations and consolidated balance sheets as of and for the years ended December 31, 2017, 2016, 2015, 2014 and 2013. The data below should be read in conjunction with, and is qualified by reference to, *Management's Discussion and Analysis of Financial Condition and Results of Operations* and our consolidated financial statements and notes thereto contained elsewhere in this Annual Report on Form 10-K.

	Year Ended December 31,				
	2017	2016	2015	2014	2013
	(in thousands, except per share data)				
Historical Statement of Operations Data:					
Revenues	$ —	$ —	$ —	$ —	$ 11,500
Operating expenses:					
Research and development	109,749	122,721	74,277	56,292	44,279
General and administrative	79,171	50,679	43,216	31,073	22,236
Total operating expenses	188,920	173,400	117,493	87,365	66,515
Operating loss	(188,920)	(173,400)	(117,493)	(87,365)	(55,015)
Investment income	1,624	604	261	58	166
Interest expense	(5,925)	(3,498)	(2,889)	(2,415)	(2,412)
Other income (expense), net	300	119	(33)	141	(33)
Loss before income taxes	(192,921)	(176,175)	(120,154)	(89,581)	(57,294)
Income tax (benefit) provision	(272)	98	(1,971)	(10,422)	(1,221)
Net loss	$ (192,649)	$ (176,273)	$ (118,183)	$ (79,159)	$ (56,073)
Basic and diluted net loss per share	$ (2.89)	$ (2.85)	$ (2.02)	$ (1.84)	$ (1.60)
Weighted average basic and diluted common shares outstanding	66,576	61,892	58,633	43,095	34,980
Historical Balance Sheet Data:					
Cash, cash equivalents and short-term investments	$ 381,165	$ 162,591	$ 282,876	$ 159,226	$ 113,894
Total assets	$ 462,047	$ 237,956	$ 356,556	$ 230,864	$ 176,498
Current portion of long-term debt	$ —	$ —	$ 3,113	$ —	$ 3,283
Debt, long-term	$ 55,567	$ 54,791	$ 22,027	$ 24,856	$ 16,338
Total shareholders' equity	$ 361,059	$ 154,483	$ 311,698	$ 186,237	$ 143,324

ITEM 7. MANAGEMENT'S DISCUSSION AND ANALYSIS OF FINANCIAL CONDITION AND RESULTS OF OPERATIONS

The following discussion also should be read in conjunction with our consolidated financial statements and the notes thereto contained elsewhere in this Annual Report on Form 10-K. This discussion contains forward-looking statements that involve risks and uncertainties. As a result of many factors, such as those set forth under the section entitled Risk Factors, Cautionary Note Regarding Forward-Looking Statements and elsewhere herein, our actual results may differ materially from those anticipated in these forward-looking statements.

EXECUTIVE OVERVIEW

Insmed is a global biopharmaceutical company focused on the unmet needs of patients with rare diseases. Our operations are based on the technology and products historically developed by Transave. We have legal entities in the US, Ireland, Germany, France, the United Kingdom (UK), the Netherlands and Japan.

We have not generated material revenue to date, except for in 2013, and through December 31, 2017, we had an accumulated deficit of $957.9 million. We have financed our operations primarily through the public offerings of our equity securities and debt financings. Although it is difficult to predict our future funding requirements, based upon our current operating plan, we anticipate that our cash and cash equivalents as of December 31, 2017 will enable us to fund our operations for at least the next 12 months.

We expect that over the next few years we will continue to incur losses from operations as we increase our expenditures in research and development in connection with our ongoing and future clinical trials, and for expenses related to the preparation for the commercial launch of ALIS globally, if approved.

PIPELINE PROGRESS

ALIS for Patients with NTM Lung Disease

Our lead product candidate is ALIS, a novel, once-daily liposomal formulation of amikacin that is in late-stage clinical development for adult patients with treatment refractory NTM lung disease caused by MAC, a rare and often chronic infection that can cause irreversible lung damage and can be fatal. Amikacin solution for parenteral administration is an established drug that has activity against a variety of NTM; however, its use is limited by the need to administer it intravenously and by toxicity to hearing, balance, and kidney function (Peloquin et al., 2004). Unlike amikacin solution for intravenous administration, our advanced liposome technology uses charge-neutral liposomes to deliver amikacin directly to the lung where it is taken up by the lung macrophages where the NTM infection resides. This technology prolongs the release of amikacin in the lungs, while minimizing systemic exposure thereby, offering the potential for decreased systemic toxicities. ALIS's ability to deliver high levels of amikacin directly to the lung distinguishes it from intravenous amikacin. ALIS is administered once-daily, using a portable aerosol delivery system, via an optimized, investigational eFlow® Nebulizer System manufactured by PARI.

The FDA has designated ALIS as an orphan drug, a breakthrough therapy, and a QIDP for NTM lung disease. Orphan designation features seven years of post-approval marketing exclusivity in the approved indication, and QIDP features an additional five years of post-approval exclusivity in the approved indication. As a result, ALIS could have 12 years of post-approval marketing exclusivity in the US, if approved. A QIDP-designated product is eligible for fast track status and is often granted priority review status. A priority review designation for a drug which is not a NME means the FDA's goal is to take action on the NDA within six months following the receipt of the NDA.

The CONVERT Study and 312 Study

CONVERT Top-Line Efficacy Data

We announced top-line data for the CONVERT study on September 5, 2017. The CONVERT study enrolled 336 adult patients with NTM lung disease caused by MAC who were refractory to at least six months of treatment on current GBT of a multi-drug regimen. After a screening period of up to 10 weeks, eligible patients were randomized 2:1 to once-daily ALIS plus GBT or GBT only. The primary endpoint of the study was the proportion of patients achieving culture conversion, which we defined as three consecutive monthly negative sputum cultures, by month six. Based on top-line results, the CONVERT study met its primary endpoint, with 29% of patients in the ALIS plus GBT arm achieving culture conversion, compared to 9% of patients in the GBT-only arm ($p<0.0001$).

We also reported top-line data for certain secondary and exploratory endpoints for the first six months of the study. Top-line data for the six-minute walk test indicated no statistically significant difference between patients in the two arms of the study. However, an analysis of these data (per a pre-specified exploratory endpoint) showed that patients who achieved culture conversion in either arm demonstrated an improvement in six-minute walk distance when compared to patients who did not culture convert (p=0.0108). Top-line data for the secondary endpoint of time to conversion demonstrated that patients in the GBT-only arm took approximately 30% longer to convert when compared to patients on ALIS plus GBT (p<0.0001). We are continuing our analysis of the impact of conversion on a variety of other clinical measures.

The protocol for the CONVERT study incorporates feedback from the FDA and the EMA via its scientific advice working party process, as well as local health authorities in other countries, including Japan's PMDA. Because the CONVERT study met the primary endpoint of culture conversion at month six based on the top-line results, we plan to submit an NDA for ALIS to the FDA by the end of March 2018 pursuant to Subpart H, which permits the FDA to approve a product candidate based on a surrogate or intermediate endpoint subject to the requirement that we conduct post-approval studies to verify and describe the clinical benefit of the product. We expect to receive a six-month priority review from the FDA. We believe that efficacy data from the CONVERT study at month six will be sufficient to support the accelerated approval of ALIS. We expect that full approval would be contingent on FDA review of, among other things, the final analyses of durability of culture conversion for converters.

CONVERT Top-Line Safety and Tolerability Data

Approximately 98% of patients in the ALIS plus GBT arm of the CONVERT study experienced at least one treatment-emergent adverse event (TEAE), compared to 91% of patients in the GBT-only arm, with most events being mild or moderate in severity. A greater percentage of patients in the ALIS plus GBT arm than in the GBT-only arm experienced TEAEs involving dysphonia, cough, haemoptysis, dyspnoea, oropharyngeal pain, diarrhea, nausea, and fatigue. Based on our review of the top-line study safety data, the incidence of dysphonia, cough and dyspnoea among patients in the ALIS plus GBT arm generally decreased after the second study month. Approximately 20% and 18% of patients in the ALIS plus GBT arm and GBT-only arm of the study, respectively, experienced at least one serious treatment emergent adverse event (STEAE). The table below provides additional information regarding certain STEAEs experienced by patients in the CONVERT study.

		2:1 Randomization	
Patients Reporting STEAEs >3% in Either Arm		**ALIS + GBT (n=223)**	**GBT (n=112)**
Patients Reporting At Least One STEAE		20.2% (45)	17.9% (20)
System Organ Class	**Preferred Term**		
Respiratory, Thoracic, Mediastinal Disorders		11.7% (26)	9.8% (11)
	Hemoptysis	2.7% (6)	4.5% (5)
	COPD (exacerbation)	3.1% (7)	0.9% (1)
Infections and Infestations		9.0% (20)	5.4% (6)
	Pneumonia	3.6% (8)	1.8% (2)
Cardiac Disorders		0.4% (1)	4.5% (5)
Patient Deaths		2.7% (6)	4.5% (5)

There were no distinctions between treatment arms for adverse events of hearing loss or renal impairment, side effects commonly associated with the intravenous use of amikacin. As of September 2017, the overall dropout rate in the CONVERT study was 16.1%, with an 8.9% dropout rate in the GBT-only arm and a 19.6% dropout rate in the ALIS plus GBT arm. As of December 2017, the overall dropout rate in the CONVERT study was 18% (n=60/336).

CONVERT Long-Term Durability Data

We also recently announced interim data on the durability of culture conversion, as defined by patients that have completed treatment and continued in the CONVERT study off all therapy for three months, which we expect will be the endpoint necessary to support full regulatory approval in the US. The following data are interim results observed through December 2017, and have not been further analyzed. As of December 2017, of the 75 patients achieving culture conversion in the CONVERT study, 53 of these patients were evaluable for durability of culture conversion three months after the completion of treatment. Interim data for durability of culture conversion as of December 2017 on these 53 patients are detailed below:

	Evaluable Number of Patients as of December 2017 (At Least Three Months Post Treatment) *	Percent with Durable Culture Conversion Three Months After Completion of All Treatment
Converters in the ALIS + GBT arm (n=65)	46	60.9% (28/46)
Converters in the GBT-only arm (n=10)	7	0.0% (0/7)

* Evaluable number of patients includes all patients who reached three months post-treatment and all patients who discontinued prior to three months post-treatment.

312 Study

All non-converters in the CONVERT study, as determined at the month eight visit, may be eligible to enter the 312 study, which is a separate 12-month, single-arm, open-label study. The purpose of the 312 study is to evaluate the safety and tolerability of longer-term treatment with ALIS added to GBT. The secondary endpoints of the 312 study include evaluating the proportion of patients achieving culture conversion (three consecutive monthly negative sputum cultures) by month six and the proportion of patients achieving culture conversion by month 12 (end of treatment).

312 Study Interim Efficacy Data

We recently announced interim data for the 312 study, which enrolled 163 adult patients with NTM lung disease caused by MAC who completed six months of treatment in the CONVERT study, but did not demonstrate culture conversion by Month 6. The following data are interim results observed through December 2017, and have not been further analyzed. Patients in the ALIS plus GBT arm of the CONVERT study and patients in the GBT-only arm of the CONVERT study who did not achieve culture conversion by Month 6 had the option to enroll in the 312 study at Month 8. Under the study protocol, patients from both arms of the CONVERT study will receive 12 months of ALIS plus GBT in the 312 study. We will also use the data from this trial to further assess the impact of the addition of ALIS to background GBT on sputum culture conversion, by Month 6.

As of December 2017, of the 163 patients enrolled in the 312 study, 124 patients were evaluable for culture conversion. Descriptive interim culture conversion data as of December 2017 for these 124 patients are detailed below. The interim culture conversion data has not been statistically analyzed.

	Number of Patients Completing Six Months of Treatment in the 312 study as of December 2017 **	Percent Achieving Sputum Culture Conversion by Month 6 in the 312 study
Patients who received GBT only in the 212 study and crossed over to receive six months of treatment with ALIS + GBT (n=90)	67	28.4% (19/67)
Patients who received ALIS + GBT in the 212 study and crossed over to continue treatment in the 312 study, to receive a combined total of 14 months of ALIS + GBT treatment in both studies (n=73)	57	12.3% (7/57)

** Includes all patients completing six months of treatment, all patients who discontinued prior to six months and for all ongoing patients prior to six months who completed two months of treatment.

312 Study Interim Safety and Tolerability Data

We have not yet performed a final analysis of any safety data for the 312 study. However, based on an interim review of data available from the 312 study, we believe that STEAEs were similar to the STEAEs we reported in September 2017 as part of our top-line data results for the 212 study. As of December 2017, the overall dropout rate in the 312 study was 24% (n=39/163).

Further Research and Lifecycle Management for ALIS

We are currently exploring and supporting research and lifecycle management programs for ALIS beyond refractory NTM lung infections caused by MAC. Specifically, we are evaluating future study designs focusing on the MAC disease treatment pathway, including front-line treatment and monotherapy maintenance to prevent recurrence (defined as true relapse or reinfection) of NTM lung disease. In addition, we are evaluating non-MAC NTM species, such as *M. abscessus*. If the data from the CONVERT study are sufficient to support our MAAs and regulatory bodies approve ALIS, such lifecycle management studies could enable us to reach more potential patients. These initiatives may include new clinical studies sponsored by us or investigator-initiated studies, which are clinical studies initiated and sponsored by physicians or research institutions with funding from us.

INS1007

INS1007 is a small molecule, oral, reversible inhibitor of DPP1, which we in-licensed from AstraZeneca in October 2016. DPP1 is an enzyme responsible for activating neutrophil serine proteases in neutrophils when they are formed in the bone marrow. Neutrophils are the most common type of white blood cell and play an essential role in pathogen destruction and inflammatory mediation. Neutrophils contain the neutrophil serine proteases, neutrophil elastase, proteinase 3, and cathepsin G, that have been implicated in a variety of inflammatory diseases. In chronic inflammatory lung diseases, neutrophils accumulate in the airways and release active neutrophil serine proteases in excess that cause lung destruction and inflammation. INS1007 may decrease the damaging effects of inflammatory diseases, such as non-CF bronchiectasis, by inhibiting DPP1 and its activation of neutrophil serine proteases. Non-CF bronchiectasis is a progressive pulmonary disorder in which the bronchi become permanently dilated due to chronic inflammation and infection. Currently, there is no cure, and we are not aware of any FDA-approved therapies specifically indicated for non-CF bronchiectasis.

The WILLOW Study

The WILLOW study, a global phase 2, randomized, double-blind, placebo-controlled, parallel group, multi-center clinical study to assess the efficacy, safety and tolerability, and pharmacokinetics of INS1007 administered once daily for 24 weeks in subjects with non-CF bronchiectasis. We commenced enrollment in the WILLOW study in December 2017. In addition, we are exploring the potential of INS1007 in various neutrophil-driven inflammatory conditions.

INS1009

INS1009 is an investigational sustained-release inhaled treprostinil prodrug nanoparticle formulation that has the potential to address certain of the current limitations of existing prostanoid therapies. We believe that INS1009 prolongs duration of effect and may provide PAH patients with greater consistency in pulmonary arterial pressure reduction over time. Current inhaled prostanoid therapies must be dosed four to nine times per day for the treatment of PAH. Reducing dose frequency has the potential to ease patient burden and improve compliance. Additionally, we believe that INS1009 may be associated with fewer side effects, including elevated heart rate, low blood pressure, and severity and/or frequency of cough, associated with high initial drug levels and local upper airway exposure when using current inhaled prostanoid therapies. We believe INS1009 may offer a differentiated product profile for rare pulmonary disorders, including PAH, and we are currently evaluating our options to advance its development, including exploring its use as an inhaled dry powder formulation.

Other Development Activities

Our earlier-stage pipeline includes preclinical compounds that we are evaluating in multiple rare diseases of unmet medical need, including methicillin-resistant staph aureus (MRSA) and NTM. To complement our internal research and development, we actively evaluate in-licensing and acquisition opportunities for a broad range of rare diseases.

KEY COMPONENTS OF OUR RESULTS OF OPERATIONS

Research and Development (R&D) Expenses

R&D expenses consist of salaries, benefits and other related costs, including stock-based compensation, for personnel serving in our research and development functions, including medical affairs. Expenses also include other internal operating expenses, the cost of manufacturing our drug candidate(s) for clinical study, the cost of conducting clinical studies, and the cost of conducting preclinical and research activities. In addition, our R&D expenses include payments to third parties for the license rights to products in development (prior to marketing approval), such as for INS1007. Our expenses related to

manufacturing our drug candidate(s) for clinical study are primarily related to activities at CMOs that manufacture our product candidates for our use, including purchases of active pharmaceutical ingredients. Our expenses related to clinical trials are primarily related to activities at contract research organizations that conduct and manage clinical trials on our behalf.

Since 2011, we have focused our development activities principally on our proprietary, advanced liposomal technology designed specifically for inhalation lung delivery. In 2015, we commenced the CONVERT study for ALIS for adult patients with treatment refractory NTM lung disease. In 2015, we also completed an open-label extension study in which CF patients that completed our phase 3 trial received ALIS for a period of two years. The majority of our research and development expenses have been for our ALIS development programs. Our development efforts in 2017 and 2016 principally related to the development of ALIS in the NTM lung disease indication described above.

General and Administrative Expenses

General and administrative expenses consist primarily of salaries, benefits and other related costs, including stock-based compensation, for our non-employee directors and personnel serving in our executive, finance and accounting, legal, pre-commercial, corporate development, information technology, program management and human resource functions. General and administrative expenses also include professional fees for legal services, including fees incurred in connection with the securities litigation filed against us and patent-related expenses, consulting services including for pre-commercial planning activities such as non-branded disease awareness, insurance, board of director fees, tax and accounting services.

Investment Income and Interest Expense

Investment income consists of interest and dividend income earned on our cash and cash equivalents. Interest expense consists primarily of interest costs and amortization of debt issuance costs related to our debt obligations. Debt issuance costs are amortized to interest expense using the effective interest rate method over the term of the debt. Our balance sheet reflects debt, net of debt issuance costs paid to the lender and other third party costs. Unamortized debt issuance costs associated with extinguished debt are expensed in the period of the extinguishment.

RESULTS OF OPERATIONS

Comparison of the Years Ended December 31, 2017 and 2016

Net Loss

Net loss for the year ended December 31, 2017 was $192.6 million, or $2.89 per common share—basic and diluted, compared with a net loss of $176.3 million, or $2.85 per common share—basic and diluted, for the year ended December 31, 2016. The $16.4 million increase in our net loss for the year ended December 31, 2017 as compared to the same period in 2016 was due to:

- Decreased R&D expenses of $13.0 million primarily resulting from the $30.0 million upfront payment for the license agreement entered into with AstraZeneca for exclusive global rights to INS1007 in October 2016, offset in part by, an increase in expenses related to the WILLOW study and higher compensation and related expenses due to an increase in headcount; and
- Increased general and administrative expenses of $28.5 million resulting from an increase in pre-commercial planning activities, including external consulting expenses, and higher compensation and related expenses due to an increase in headcount.

In addition, there was a $2.4 million increase in interest expense resulting from the increase in our debt in the second half of 2016.

R&D Expenses

R&D expenses for the years ended December 31, 2017 and 2016 were comprised of the following (in thousands):

	Years Ended December 31,		Increase (decrease)	
	2017	2016	$	%
External Expenses				
Clinical development and research	$ 40,511	$ 35,890	$ 4,621	12.9%
INS1007 license payment	—	30,000	(30,000)	(100.0)%
Manufacturing	19,808	17,313	2,495	14.4%
Regulatory, quality assurance, and medical affairs	7,308	4,064	3,244	79.8%
Subtotal—external expenses	$ 67,627	$ 87,267	$ (19,640)	(22.5)%
Internal Expenses				
Compensation and related expenses	$ 34,180	$ 28,513	$ 5,667	19.9%
Other internal operating expenses	7,942	6,941	1,001	14.4%
Subtotal—internal expenses	$ 42,122	$ 35,454	$ 6,668	18.8%
Total	$ 109,749	$ 122,721	$ (12,972)	(10.6)%

R&D expenses decreased to $109.7 million during the year ended December 31, 2017 from $122.7 million in the same period in 2016. The $13.0 million decrease was due to a $30.0 million upfront payment under the AZ License Agreement related to INS1007 in October 2016 and a $3.7 million decrease in expenses relating to INS1009. These decreases were partially offset by a $10.2 million increase in raw materials purchases and expenses related to the WILLOW trial for INS1007 and a $5.7 million increase in compensation and related expenses, including stock-based compensation, due to an increase in headcount. There was also an increase of $3.2 million due to increased regulatory, quality assurance and medical affairs consulting expenses and medical grants.

General and Administrative Expenses

General and administrative expenses for the year ended December 31, 2017 and 2016 were comprised of the following (in thousands):

	Years Ended December 31,		Increase (decrease)	
	2017	2016	$	%
General & administrative	$ 46,249	$ 35,291	$ 10,958	31.1%
Pre-commercial expenses	32,922	15,388	17,534	113.9%
Total general & administrative expenses	$ 79,171	$ 50,679	$ 28,492	56.2%

General and administrative expenses increased to $79.2 million during the year ended December 31, 2017 from $50.7 million in the same period in 2016. The $28.5 million increase was primarily due to an increase of $12.8 million in consulting fees relating to pre-commercial planning activities, an increase of $7.7 million due to higher compensation costs related to an increase in headcount, and a one-time payment in October 2017 related to the buy-down of future royalties payable to PARI on the global net sales of ALIS, if approved.

Interest Expense

Interest expense was $5.9 million during the year ended December 31, 2017 as compared to $3.5 million in the same period in 2016. The $2.4 million increase in interest expense in 2017 relates primarily to an increase in our borrowings from Hercules in September and October of 2016. We entered into an Amended and Restated Loan Agreement (A&R Loan Agreement) with Hercules which increased our borrowing capacity by an additional $30.0 million to an aggregate total of $55.0 million. The increase in borrowings under the A&R Loan Agreement was used to fund the upfront payment owed under the AZ License Agreement for the exclusive global rights to INS1007.

Income tax (benefit) provision

The income tax (benefit) provision was $(0.3) million and $0.1 million for the years ended December 31, 2017 and 2016, respectively. The income tax (benefit) for the year ended December 31, 2017 reflects the reversal of the valuation allowance related to alternative minimum tax (AMT) that we paid in 2009. As a result of the Tax Act, we recorded a noncurrent receivable to reflect the tax amount due to us in future periods relating to a refund due for the prior AMT paid. In addition, the income tax (benefit) provision for the years ended December 31, 2017 and 2016 reflects current income tax expense recorded as a result of taxable income in certain of our subsidiaries in Europe.

On December 22, 2017 the Tax Act was signed into law. The Tax Act introduced significant changes to the Code. The Tax Act, among other things, contains significant changes to corporate taxation, including reduction of the corporate tax rate from a top marginal rate of 35% to a flat rate of 21%, limitation of the tax deduction for interest expense to 30% of adjusted earnings (except for certain small businesses), limitation of the deduction for net operating losses to 80% of current year taxable income in respect of losses arising in taxable years beginning after 2017 and elimination of net operating loss carrybacks, one time taxation of offshore earnings at reduced rates regardless of whether they are repatriated, immediate deductions for certain new investments instead of deductions for depreciation expense over time, and modifying or repealing many business deductions and credits (including reducing the business tax credit for certain clinical testing expenses incurred in the testing of certain drugs for rare diseases or conditions generally referred to as "orphan drugs"). Our federal net operating loss carryovers for taxable years beginning after 2017 will be carried forward indefinitely pursuant to the Tax Act. Notwithstanding the reduction in the federal corporate income tax rate, the overall impact of the Tax Act is uncertain and our business and financial condition could be adversely affected. The Tax Act did not have a material impact on our financial statements because our deferred temporary differences are fully offset by a valuation allowance and we do not have any significant offshore earnings from which to record the mandatory transition tax. However, given the significant complexity of the Tax Act, anticipated guidance from the US Treasury about implementing the Tax Act, and the potential for additional guidance from the SEC or the FASB related to the Tax Act, these estimates may be adjusted during the measurement period. We continue to examine the impact the Tax Act may have on our business.

Comparison of the Years Ended December 31, 2016 and 2015

Net Loss

Net loss for the year ended December 31, 2016 was $176.3 million, or $2.85 per common share—basic and diluted, compared with a net loss of $118.2 million, or $2.02 per common share—basic and diluted, for the year ended December 31, 2015. The $58.1 million increase in our net loss for the year ended December 31, 2016 as compared to the same period in 2015 was due to:

- Increased R&D expenses of $48.4 million primarily resulting from a $30.0 million upfront payment for the license agreement entered into with AstraZeneca for exclusive global rights to INS1007 in October 2016 (AZ License Agreement), an increase in clinical trial expenses related to the CONVERT study and higher compensation and related expenses due to an increase in headcount; and
- Increased general and administrative expenses of $7.5 million resulting from an increase in pre-commercial planning activities, legal and consulting expenses and higher compensation and related expenses, including an increase in noncash stock-based compensation, related to an increase in headcount.

In addition, there was a $2.1 million decrease in the income tax benefit resulting from the sale of a portion of our New Jersey State net operating losses (NOLs) under the State of New Jersey's Technology Business Tax Certificate Transfer Program (the Program) for cash of $2.0 million in 2015.

R&D Expenses

R&D expenses for the years ended December 31, 2016 and 2015 were comprised of the following:

	Years Ended December 31,		Increase (decrease)	
	2016	2015	$	%
External Expenses				
Clinical development and research	$ 35,890	$ 24,972	$ 10,918	43.7 %
INS1007 license payment	30,000	—	30,000	nm
Manufacturing	17,313	22,121	(4,808)	(21.7)%
Regulatory, quality assurance, and medical affairs	4,064	4,173	(109)	(2.6)%
Subtotal—external expenses	$ 87,267	$ 51,266	$ 36,001	70.2 %
Internal Expenses				
Compensation and related expenses	$ 28,513	$ 18,666	$ 9,847	52.8 %
Other internal operating expenses	6,941	4,345	2,596	59.7 %
Subtotal—internal expenses	$ 35,454	$ 23,011	$ 12,443	54.1 %
Total	$ 122,721	$ 74,277	$ 48,444	65.2 %

R&D expenses increased to $122.7 million during the year ended December 31, 2016 from $74.3 million in the same period in 2015. The $48.4 million increase was due to a $30.0 million upfront payment under the AZ License Agreement related to INS1007 in October 2016, a $10.9 million increase in external clinical development expenses primarily related to the CONVERT study and a $9.8 million increase in compensation and related expenses, including stock-based compensation, due to an increase in headcount. These increases were partially offset by a $4.8 million decrease in manufacturing expenses primarily due to the completion of the build-out of our production area at Therapure's facility in 2015.

General and Administrative Expenses

General and administrative expenses for the year ended December 31, 2016 and 2015 were comprised of the following (in thousands):

	Years Ended December 31,		Increase (decrease)	
	2016	2015	$	%
General & administrative	$ 35,291	$ 30,614	$ 4,677	15.3%
Pre-commercial expenses	15,388	12,602	2,786	22.1%
Total general & administrative expenses	$ 50,679	$ 43,216	$ 7,463	17.3%

General and administrative expenses increased to $50.7 million during the year ended December 31, 2016 from $43.2 million in the same period in 2015. The $7.5 million increase was primarily due to an increase of $3.7 million in consulting fees relating to pre-commercial planning activities, legal and consulting expenses and an increase of $3.7 million due to higher compensation costs, including stock-based compensation, related to an increase in headcount.

Interest Expense

Interest expense was $3.5 million during the year ended December 31, 2016 as compared to $2.9 million in the same period in 2015. The $0.6 million increase in interest expense in 2016 relates primarily to an increase in our borrowings from Hercules in September and October of 2016. We entered into an Amended and Restated Loan Agreement (A&R Loan Agreement) with Hercules which increased our borrowing capacity by an additional $30.0 million to an aggregate total of $55.0 million. The increase in borrowings under the A&R Loan Agreement was used to fund the upfront payment owed under the AZ License Agreement for the exclusive global rights to INS1007.

Income tax (benefit) provision

The income tax (benefit) provision was $0.1 million and $(2.0) million for the years ended December 31, 2016 and 2015, respectively. The income tax provision for the year ended December 31, 2016 reflects current income tax expense recorded as a result of taxable income in certain our subsidiaries in Europe. The income tax benefit recorded for the year ended December 31, 2015 primarily reflects the reversal of a valuation allowance previously recorded against our New Jersey State NOLs that resulted from the sale of a portion of our New Jersey State NOLs under the Program for cash of $2.0 million, net of commissions. The Program allows qualified technology and biotechnology businesses in New Jersey to sell unused amounts of NOLs and defined research and development tax credits for cash. In 2015, we reached the lifetime maximum cap of NOLs that can be sold to the State of New Jersey. Therefore, we received no cash proceeds from the Program in 2016 and will not receive cash proceeds from the Program in the future.

LIQUIDITY AND CAPITAL RESOURCES

Overview

There is considerable time and cost associated with developing a potential drug or pharmaceutical product to the point of regulatory approval and commercialization. In recent years, we have funded our operations through public offerings of equity securities and debt financings. We expect to continue to incur losses both in our US and certain international entities, as we plan to fund research and development activities and commercial launch activities.

We may need to raise additional capital to fund our operations, to develop and commercialize ALIS if approved, to develop INS1007 and INS1009, and to develop, acquire, in-license or co-promote other products that address orphan or rare diseases. We believe we currently have sufficient funds to meet our financial needs for at least the next 12 months. We may opportunistically raise additional capital and may do so through equity or debt financing(s), strategic transactions or otherwise. We expect such additional funding, if any, would be used to continue to develop our potential product candidates, to pursue the

license or purchase of other technologies, to commercialize our product candidates or to purchase other products. During 2018, we plan to continue to fund further clinical development of ALIS and INS1007, support efforts to obtain regulatory approvals, and prepare for commercialization of ALIS. Our cash requirements in 2018 will be impacted by a number of factors, the most significant of which are expenses related to the CONVERT and 312 studies and pre-commercialization efforts for ALIS, and to a lesser extent, expenses related to INS1007 and future ALIS clinical trials. We expect our operating expenses in 2018 to increase significantly as compared to 2017.

In January 2018, we completed an underwritten public offering of 1.75% convertible senior notes due 2025. We sold $450.0 million aggregate principal amount of the Convertible Notes, including the exercise in full of the underwriter's option to purchase additional Convertible Notes. Our net proceeds from the offering, after deducting underwriting discounts and commissions and other offering expenses of $14.2 million, were $435.8 million.

In September 2017, we completed an underwritten public offering of 14,123,150 shares of our common stock, which included the underwriter's exercise in full of its over-allotment option of 1,842,150 shares, at a price to the public of $28.50 per share. Our net proceeds from the sale of the shares, after deducting underwriting discounts and offering expenses of $24.8 million, were $377.7 million.

In April 2015, we completed an underwritten public offering of 11,500,000 shares of our common stock, which included the underwriter's exercise in full of its over-allotment option of 1,500,000 shares, at a price to the public of $20.65 per share. Our net proceeds from the sale of the shares, after deducting underwriting discounts and offering expenses of $14.5 million, were $222.9 million.

Cash Flows

As of December 31, 2017, we had total cash and cash equivalents of $381.2 million, as compared with $162.6 million as of December 31, 2016. The $218.6 million increase was due to the cash provided by financing activities in excess of our operating activities. Our working capital was $344.8 million as of December 31, 2017 as compared with $140.4 million as of December 31, 2016.

Net cash used in operating activities was $159.6 million and $146.7 million for the years ended December 31, 2017 and 2016, respectively. The net cash used in operating activities during 2017 and 2016 was primarily for the clinical, regulatory, manufacturing and pre-commercial activities related to ALIS, including in 2017 the exercise of an option to buy-down the future royalties payable to PARI. In 2017, there were increases in raw materials purchases and expenses related to the WILLOW study for INS1007. In addition, in the fourth quarter of 2016, we made a payment of $30.0 million to AstraZeneca under the AZ License Agreement for INS1007.

Net cash used in investing activities was $3.0 million and $4.2 million for the years ended December 31, 2017 and 2016, respectively. The net cash used in investing activities during 2017 was primarily related to the investment in our long-term production capacity build-out at Patheon and for the build out of our lab facility in Bridgewater, New Jersey. Net cash used in investing activities during 2016 was primarily related to payments for the build out of our headquarters and lab facility in Bridgewater, New Jersey.

Net cash provided by financing activities was $381.1 million and $30.7 million for the years ended December 31, 2017 and 2016, respectively. Net cash provided by financing activities during 2017 included net cash proceeds of $377.7 million from our issuance of 14.1 million shares of common stock in September 2017 and cash proceeds received from stock option exercises. Net cash provided by financing activities for the year ended December 31, 2016 was primarily net cash proceeds from the issuance of debt.

Contractual Obligations

On June 29, 2012, we and our domestic subsidiaries, as co-borrowers, entered into a Loan and Security Agreement with Hercules Technology Growth Capital, Inc. (as subsequently amended, the Prior Loan Agreement) under which we borrowed an aggregate of $25.0 million at an interest rate of 9.25%. We paid an "end of term" charge of $390,000 in January 2016, which was charged to interest expense (and accreted to the debt) using the effective interest method over the life of the Prior Loan Agreement.

On September 30, 2016, we and our domestic subsidiaries, as co-borrowers, entered into the A&R Loan Agreement with Hercules. The A&R Loan Agreement included a total commitment from Hercules of up to $55.0 million, of which $25.0 million was previously outstanding. The amount of borrowings was initially increased by $10.0 million to an aggregate total of $35.0 million on September 30, 2016. An additional $20.0 million was available at our option through June 30, 2017 subject to certain conditions, including the payment of a facility fee of 0.375%. We exercised this option in early October 2016 and borrowed an additional $20.0 million in connection with the upfront payment obligation under the AZ License Agreement.

The interest rate for the term is floating and is defined as the greater of (i) 9.25% or (ii) 9.25% plus the sum of the US prime rate minus 4.50%, along with a backend fee of 4.15% of the aggregate principal amount outstanding and an aggregate facility fee of $337,500. The interest-only period extends through November 1, 2018, but can be extended up to six months under certain conditions. The maturity date of the loan facility was also extended to October 1, 2020. In connection with the Company generating and announcing top-line data from the CONVERT study on September 5, 2017 that supports the filing of an NDA, along with the completion of the equity financing, the interest-only period was automatically extended through May 1, 2019 and the requirement to have a consolidated minimum cash liquidity in an amount no less than $25.0 million was eliminated.

In connection with the A&R Loan Agreement, we granted Hercules a first position lien on all of our assets, excluding intellectual property. Prepayment of the loans made pursuant to the A&R Loan Agreement is subject to penalty. The backend fee of 4.15% on the aggregate outstanding principal balance will be charged to interest expense (and accreted to the debt) using the effective interest method over the original life of the A&R Loan Agreement. Debt issuance fees paid to the lender were recorded as a discount on the debt and are being amortized to interest expense using the effective interest method over the life of the A&R Loan Agreement. In February 2018, we notified Hercules that we will repay the A&R Loan Agreement in full on February 28, 2018. The total aggregate cash payable to Hercules for the early prepayment of debt, inclusive of accrued interest, the backend fee and an early payment penalty will be approximately $58.0 million.

We have an operating lease for office and laboratory space located in Bridgewater, NJ, our corporate headquarters, for which the initial lease term expires in November 2019. Future minimum rental payments under this lease total approximately $2.0 million. In July 2016, we signed an operating lease for additional laboratory space located in Bridgewater, NJ for which the initial lease term expires in September 2021. Future minimum rental payments under this lease are $1.9 million.

In September 2015, we entered into a Commercial Fill/Finish Services Agreement (the Fill/Finish Agreement) with Althea, for Althea to produce, on a non-exclusive basis, ALIS in finished dosage form at a 50 kg scale. Under the Fill/Finish Agreement, we are obligated to pay a minimum of $2.7 million for the batches of ALIS produced each calendar year during the term of the Fill/Finish Agreement. The Fill/Finish Agreement was effective as of January 1, 2015, and had an initial term that was to end on December 31, 2017. In 2016, we signed an extension of the agreement through December 31, 2019 and it may be extended for additional two-year periods upon mutual written agreement of the Company and Althea at least one year prior to the expiration of its then-current term.

As of December 31, 2017, future payments under our long-term debt agreements, minimum future payments under non-cancellable operating leases and minimum future payment obligations are as follows:

	As of December 31, 2017 Payments Due By Period				
	Total	Less than 1 year	1 - 3 Years	3 - 5 Years	More than 5 Years
	(in thousands)				
Debt obligations					
Debt maturities	$ 55,000	$ —	$ 55,000	$ —	$ —
Contractual interest	14,871	5,158	9,713	—	—
Operating leases	3,917	1,521	1,898	498	—
Purchase obligations	5,400	2,700	2,700	—	—
Total contractual obligations	$ 79,188	$ 9,379	$ 69,311	$ 498	$ —

This table does not include: (a) any milestone payments which may become payable to third parties under our license and collaboration agreements as the timing and likelihood of such payments are not known; (b) any royalty payments to third parties as the amounts of such payments, timing and/or the likelihood of such payments are not known; (c) contracts that are entered into in the ordinary course of business which are not material in the aggregate in any period presented above; (d) the January 2018 underwritten public offering of 1.75% convertible senior notes due 2025 in the aggregate principal amount of $450.0 million; or (e) any payments related to the agreements mentioned below.

We currently have a licensing agreement with PARI for the use of the optimized eFlow Nebulizer System for delivery of ALIS in treating patients with NTM lung infections, CF and bronchiectasis. Under the licensing agreement, we have rights under several US and foreign issued patents, and patent applications involving improvements to the optimized eFlow Nebulizer System, to exploit such system with ALIS for the treatment of such indications, but we cannot manufacture such

nebulizers except as permitted under our Commercialization Agreement with PARI. Under the licensing agreement, we paid PARI an upfront license fee and PARI is entitled to receive milestone payments up to an aggregate of €4.3 million either in cash, qualified stock or a combination of both, at PARI's discretion, based on achievement of certain future milestone events including, first acceptance of MAA submission (or equivalent) in the US of ALIS and the device, first receipt of marketing approval in the US for ALIS and the device, and first receipt of marketing approval in a major EU country for ALIS and the device. In addition, PARI is entitled to receive royalty payments in the mid-single digits on the annual global net sales of ALIS pursuant to the licensing agreement, subject to certain specified annual minimum royalties. In October 2017, we exercised an option to buy-down the future royalties that will be payable to PARI. The payment to PARI was included as a component of general and administrative expenses in the fourth quarter of 2017.

In July 2014, we entered into a Commercialization Agreement with PARI for the manufacture and supply of eFlow nebulizer systems and related accessories (the Device) as optimized for use with ALIS. Under the Commercialization Agreement, PARI manufactures the Device except in the case of certain defined supply failures, when the Company will have the right to make the Device and have it made by third parties (but not certain third parties deemed under the Commercialization Agreement to compete with PARI). The Commercialization Agreement has an initial term of 15 years from the first commercial sale of ALIS pursuant to the licensing agreement (the Initial Term). The term of the Commercialization Agreement may be extended by us for an additional five years by providing written notice to PARI at least one year prior to the expiration of the Initial Term.

In October 2017, we entered into certain agreements with Patheon related to increasing our long-term production capacity for ALIS commercial inventory. The agreements provide for Patheon to manufacture and supply ALIS for our anticipated commercial needs. Under these agreements, we are required to deliver to Patheon the required raw materials, including active pharmaceutical ingredients, and certain fixed assets needed to manufacture ALIS. Patheon's supply obligations will commence once certain technology transfer and construction services are completed. Our manufacturing and supply agreement with Patheon will remain in effect for a fixed initial term, after which it will continue for successive renewal terms unless either we or Patheon have given written notice of termination. The technology transfer agreement will expire when the parties agree that the technology transfer services have been completed. The agreements may also be terminated under certain other circumstances, including by either party due to a material uncured breach of the other party or the other party’s insolvency. These early termination clauses may reduce the amounts due to the relevant parties. The investment in our long-term production capacity build-out, including under the Patheon agreements and related agreements or purchase orders with third parties for raw materials and fixed assets, is estimated to be approximately $60.0 million and will be incurred over the next three to four years.

In October 2016, we entered into the AZ License Agreement, pursuant to which AstraZeneca granted us exclusive global rights for the purpose of developing and commercializing AZD7986 (which we renamed INS1007). In consideration of the licenses and other rights granted by AstraZeneca, we made an upfront payment of $30.0 million, which was included as research and development expense in the fourth quarter of 2016. We are obligated to make a series of contingent milestone payments to AstraZeneca totaling up to an additional $85.0 million upon the achievement of clinical development and regulatory filing milestones. If we elect to develop INS1007 for a second indication, we will be obligated to make an additional series of contingent milestone payments totaling up to $42.5 million. We are not obligated to make any additional milestone payments for any additional indications. In addition, we have agreed to pay AstraZeneca tiered royalties ranging from a high single-digit to mid-teen on net sales of any approved product based on INS1007 and one additional payment of $35.0 million upon the first achievement of $1 billion in annual net sales. The AZ License Agreement provides AstraZeneca with the option to negotiate a future agreement with us for commercialization of INS1007 in chronic obstructive pulmonary disease or asthma.

In December 2014, we entered into a services agreement with SynteractHCR, Inc. (Synteract) pursuant to which we retained Synteract to perform implementation and management services in connection with the 212 study. We anticipate that aggregate costs relating to all work orders for the 212 study will be approximately $45 million over the period of the study. In April 2015, we entered into a work order with Synteract to perform implementation and management services for the 312 study. We anticipate that aggregate costs relating to all work orders for the 312 study will be approximately $25 million over the period of the study.

In February 2014, we entered into a contract manufacturing agreement with Therapure for the manufacture of ALIS at a 200 kg scale. Pursuant to the agreement, we collaborated with Therapure to construct a production area for the manufacture of ALIS in Therapure's existing manufacturing facility in Canada. Therapure manufactures ALIS for us on a non-exclusive basis. The agreement has an initial term of five years from the first date on which Therapure delivers ALIS to us after we obtain permits related to the manufacture of ALIS, and will renew automatically for successive periods of two years each, unless terminated by either party by providing the required two years' prior written notice to the other party. Under the agreement, we are obligated to pay certain minimum amounts for the batches of ALIS produced each calendar year.

In 2004 and 2009, we entered into research funding agreements with Cystic Fibrosis Foundation Therapeutics, Inc. (CFFT) whereby we received $1.7 million and $2.2 million for each respective agreement in research funding for the development of ALIS. If ALIS becomes an approved product for patients with CF in the US, we will owe a payment to CFFT of up to $13.4 million that is payable over a three-year period after approval as a commercialized drug in the US. Furthermore, if certain global sales milestones are met within five years of the drug's commercialization, we would owe an additional payment of $3.9 million. Since there is significant development and regulatory risk associated with ALIS, including with respect to the CF indication, we have not accrued these obligations.

Future Funding Requirements

To date, we have not generated material revenue from ALIS, and we do not know when, or if, we will generate such revenue. We do not expect to generate such revenue unless or until we obtain marketing approval of, secure reimbursement for, and commercialize, ALIS. We may need to raise additional capital to fund our operations, to develop and commercialize ALIS, to develop INS1007 and INS1009, and to develop, acquire, in-license or co-promote other products that address orphan or rare diseases. Our future capital requirements may be substantial and will depend on many factors, including:

- the timing and cost of our anticipated clinical trials of ALIS for the treatment of patients with NTM lung infections;
- the decisions of the FDA, MHLW, PMDA and EMA with respect to our applications for marketing approval of ALIS in the US, Japan and Europe; the costs of activities related to the regulatory approval process; and the timing of approvals, if received;
- the cost of putting in place the sales and marketing capabilities necessary to be prepared for a potential commercial launch of ALIS, if approved;
- the cost of filing, prosecuting, defending, and enforcing patent claims;
- the timing and cost of our anticipated clinical trials, including INS1007 and the related milestone payments due to AstraZeneca;
- the costs of our manufacturing-related activities;
- the costs associated with commercializing ALIS, if we receive marketing approval; and
- subject to receipt of marketing approval, the levels, timing and collection of revenue received from sales of approved products, if any, in the future.

In April 2015, we generated net proceeds of $222.9 million from the issuance of 11.5 million shares of common stock. In September 2017, we completed an underwritten public offering of 14,123,150 shares of our common stock, which included the underwriter’s exercise in full of its over-allotment option of 1,842,150 shares, at a price to the public of $28.50 per share. Our net proceeds from the sale of the shares, after deducting the underwriter’s discount and offering expenses of $24.8 million, were $377.7 million. In January 2018, we completed an underwritten public offering of 1.75% convertible senior notes due 2025. We sold $450.0 million aggregate principal amount of the Convertible Notes, including the exercise in full of the underwriters' option to purchase additional Convertible Notes. Our net proceeds from the offering, after deducting underwriting discounts and commissions and other offering expenses of $14.2 million, were approximately $435.8 million. The Convertible Notes bear interest payable semiannually in arrears on January 15 and July 15 of each year, beginning on July 15, 2018. We believe that we have sufficient capital resources to support scheduled interest payments on this debt. On September 30, 2016, the total committed amount under the A&R Loan Agreement with Hercules was increased to $55.0 million, $25.0 million of which was previously outstanding. During the fourth quarter of 2016, we drew down the remaining commitment. In February 2018, we notified Hercules that we will repay the A&R Loan Agreement in full on February 28, 2018. We believe we currently have sufficient funds to meet our financial needs for at least the next 12 months. However, our business strategy may require us to raise additional capital at any time through equity or debt financing(s), strategic transactions or otherwise.

Off-Balance Sheet Arrangements

We do not have any off-balance sheet arrangements, other than operating leases, that have or are reasonably likely to have a current or future material effect on our financial condition, revenues or expenses, results of operations, liquidity, capital expenditures or capital resources. We do not have any interest in special purpose entities, structured finance entities or other variable interest entities.

CRITICAL ACCOUNTING POLICIES

Preparation of financial statements in accordance with generally accepted accounting principles in the US requires us to make estimates and assumptions affecting the reported amounts of assets, liabilities, revenues and expenses and the disclosures of contingent assets and liabilities. We use our historical experience and other relevant factors when developing our estimates and assumptions. We continually evaluate these estimates and assumptions. The amounts of assets and liabilities reported in our consolidated balance sheets and the amounts of revenue reported in our consolidated statements of

comprehensive loss are affected by estimates and assumptions, which are used for, but not limited to, the accounting for research and development, stock-based compensation, identifiable intangible assets, and accrued expenses. The accounting policies discussed below are considered critical to an understanding of our consolidated financial statements because their application places the most significant demands on our judgment. Actual results could differ from our estimates. For additional accounting policies, see Note 2 to our Consolidated Financial Statements—*Summary of Significant Accounting Policies.*

Research and Development

Research and development expenses consist primarily of salaries, benefits and other related costs, including stock-based compensation, for personnel serving our research and development functions, and other internal operating expenses, the cost of manufacturing our drug candidate for clinical study, including the medical devices for drug delivery, the cost of conducting clinical studies, and the cost of conducting preclinical and research activities. In addition, research and development expenses include payments to third parties for the license rights to products in development (prior to marketing approval). Our expenses related to manufacturing our drug candidate and medical devices for clinical study are primarily related to activities at CMOs that manufacture ALIS, and to a lesser extent, our other clinical product requirements. Our expenses related to clinical trials are primarily related to activities at CROs that conduct and manage clinical trials on our behalf. These contracts set forth the scope of work to be completed at a fixed fee or amount per patient enrolled. Payments under these contracts depend on performance criteria such as the successful enrollment of patients or the completion of clinical trial milestones as well as time-based fees. Expenses are accrued based on contracted amounts applied to the level of patient enrollment and to activity according to the clinical trial protocol. Nonrefundable advance payments for goods or services that will be used or rendered for future research and development activities are deferred and capitalized. Such amounts are then recognized as an expense as the related goods are delivered or the services are performed, or when the goods or services are no longer expected to be provided.

Stock-Based Compensation

We recognize stock-based compensation expense for awards of equity instruments to employees and directors based on the grant-date fair value of those awards. The grant-date fair value of the award is recognized as compensation expense ratably over the requisite service period, which generally equals the vesting period of the award, and if applicable, is adjusted for expected forfeitures. We also grant performance-based stock options to employees. The grant-date fair value of the performance-based stock options is recognized as compensation expense over the implicit service period using the accelerated attribution method once it is probable that the performance condition will be achieved. Stock-based compensation expense is included in both research and development expenses and general and administrative expenses in the Consolidated Statements of Comprehensive Loss.

The following table summarizes the assumptions used in determining the fair value of stock options granted during the years ended December 31, 2017, 2016 and 2015:

	2017	2016	2015
Volatility	71% - 79%	74% - 77%	78% - 82%
Risk-free interest rate	1.73% - 2.13%	1.00% - 1.90%	1.31% - 1.75%
Dividend yield	0.0%	0.0%	0.0%
Expected option term (in years)	6.25	6.25	6.25

For the years ended December 31, 2017, 2016 and 2015, the volatility factor was based on our historical volatility during the expected term or since the closing of our merger with Transave, Inc. in December 2010. The risk-free interest rate is based on the US Treasury yield in effect at the date of grant. Estimated forfeitures were based on the actual percentage of option forfeitures since the closing of the Company's merger with Transave, Inc. in December 2010 for the years ended December 31, 2016 and 2015. Beginning with the year ended December 31, 2017, estimated forfeitures were based on the actual percentage of option forfeitures over the expected option term.

Identifiable Intangible Assets

Identifiable intangible assets are measured at their respective fair values and are not amortized until commercialization. Once commercialization occurs, these intangible assets will be amortized over their estimated useful lives. The fair values assigned to our intangible assets are based on reasonable estimates and assumptions given available facts and circumstances. Unanticipated events or circumstances may occur that may require us to review the assets for impairment. Events or circumstances that may require an impairment assessment include negative clinical trial results, the non-approval of a new drug application by a regulatory agency, material delays in our development program or a sustained decline in market capitalization.

Indefinite-lived intangible assets are not subject to periodic amortization. Rather, indefinite-lived intangibles are reviewed for impairment by applying a fair value based test on an annual basis or more frequently if events or circumstances indicate impairment may have occurred. Events or circumstances that may require an interim impairment assessment are consistent with those described above. We perform our annual impairment test as of October 1 of each year.

We use the income approach to derive the fair value of in-process research and development assets. This approach calculates fair value by estimating future cash flows attributable to the assets and then discounting these cash flows to a present value using a risk-adjusted discount rate. A market based valuation approach was not considered given a lack of revenues and profits by us. This approach requires significant management judgment with respect to unobservable inputs such as future volume, revenue and expense growth rates, changes in working capital use, appropriate discount rates and other assumptions and estimates. The estimates and assumptions used are consistent with our business plans.

Accrued Expenses

We are required to estimate accrued expenses as part of our process of preparing financial statements. This process involves estimating the level of service performed on our behalf and the associated cost incurred in instances where we have not been invoiced or otherwise notified of actual costs. Examples of areas in which subjective judgments may be required include costs associated with services provided by contract organizations for preclinical development, clinical trials and manufacturing of clinical materials. We accrue for expenses associated with these external services by determining the total cost of a given study based on the terms of the related contract. We accrue for costs incurred as the services are being provided by monitoring the status of the trials and the invoices received from our external service providers. In the case of clinical trials, the estimated cost normally relates to the projected costs of having subjects enrolled in our trials, which we recognize over the estimated term of the trial according to the number of subjects enrolled in the trial on an ongoing basis, beginning with subject enrollment. As actual costs become known to us, we adjust our accruals. To date, the number of clinical trials and related research service agreements has been relatively limited and our estimates have not differed significantly from the actual costs incurred.

New Accounting Pronouncements—Adopted

In August 2014, the Financial Accounting Standards Board (FASB) issued Accounting Standards Update (ASU) No. 2014-15, *Presentation of Financial Statements—Going Concern: Disclosure of Uncertainties about an Entity's Ability to Continue as a Going Concern,* which requires management to evaluate whether there is substantial doubt about the entity's ability to continue as a going concern and, if so, provide certain footnote disclosures. This ASU was effective for the annual period ended December 31, 2016, and interim reporting periods thereafter. The adoption of this standard did not have an impact on our consolidated financial statements and related footnote disclosures.

In November 2015, the FASB issued ASU 2015-17, *Income Taxes (Topic 740): Balance Sheet Classification of Deferred Taxes*, which updated and simplified the presentation of deferred income taxes. Current generally accepted accounting principles require an entity to separate deferred income tax liabilities and assets into current and noncurrent amounts in a classified statement of financial position. To simplify the presentation of deferred income taxes, the amendments in this update require that deferred tax liabilities and assets be classified as noncurrent in a classified statement of financial position. The amendments in this update are effective for financial statements issued for annual periods beginning after December 15, 2016 and interim periods within those annual periods. Earlier application was permitted and we adopted the update effective with our annual reporting period ended December 31, 2015. The adoption of this update did not have a significant impact on our consolidated financial statements.

In March 2016, the FASB issued ASU 2016-9, Improvements to Employee Share-Based Payment Accounting, which amends Accounting Standards Codification (ASC) Topic 718, Compensation—Stock Compensation. ASU 2016-9 simplifies several aspects of the accounting for share-based payment transactions, including the income tax consequences, classification of awards as either equity or liabilities, and classification on the statement of cash flows. ASU 2016-9 was effective for fiscal years beginning after December 15, 2016, and interim periods within those fiscal years. The Company adopted ASU 2016-9 in the first quarter of 2017. The impact of the adoption was not material to the consolidated financial statements.

Recent Accounting Pronouncements—Not Yet Adopted

In May 2014, the FASB issued ASU 2014-09, *Revenue from Contracts with Customers (Topic 606)* which amended the existing accounting standards for revenue recognition. ASU 2014-09 establishes principles for recognizing revenue upon the transfer of promised goods or services to customers, in an amount that reflects the expected consideration received in exchange for those goods or services. In July 2015, the FASB deferred the effective date for annual reporting periods beginning

after December 15, 2017. We will adopt ASU 2014-09 in the first quarter of 2018 and the impact of adoption will not be material to our consolidated financial statements.

In February 2016, the FASB issued ASU 2016-02, *Leases (Topic 842)* in order to increase transparency and comparability among organizations by recognizing lease assets and lease liabilities on the balance sheet for those leases classified as operating leases under previous GAAP. ASU 2016-02 requires that a lessee should recognize a liability to make lease payments (the lease liability) and a right-of-use asset representing its right to use the underlying asset for the lease term on the balance sheet. ASU 2016-02 is effective for fiscal years beginning after December 15, 2018 (including interim periods within those periods) using a modified retrospective approach and early adoption is permitted. We expect to adopt ASU 2016-02 in the first quarter of 2019 and are in the process of evaluating the impact of adoption on our consolidated financial statements.

ITEM 7A. QUANTITATIVE AND QUALITATIVE DISCLOSURES ABOUT MARKET RISK

As of December 31, 2017, our cash and cash equivalents were in cash accounts or were invested in money funds. Such accounts or investments are not insured by the federal government.

As of December 31, 2017, we had $55.0 million of fixed rate borrowings bearing interest at 9.25% outstanding under the A&R Loan Agreement with Hercules. If a 10% change in interest rates was to have occurred on December 31, 2017, this change would not have had a material effect on the fair value of our debt as of that date, nor would it have had a material effect on our future earnings or cash flows.

The majority of our business is conducted in US dollars. However, we do conduct certain transactions in other currencies, including Euros, British Pounds and Japanese Yen. Fluctuations in foreign currency exchange rates do not materially affect our results of operations. During 2017, 2016 and 2015, our results of operations were not materially affected by fluctuations in foreign currency exchange rates.

ITEM 8. FINANCIAL STATEMENTS AND SUPPLEMENTARY DATA

The information required by Item 8 is included in our Financial Statements and Supplementary Data listed in Item 15 of Part IV of this 2017 Annual Report.

ITEM 9. CHANGES IN AND DISAGREEMENTS WITH ACCOUNTANTS ON ACCOUNTING AND FINANCIAL DISCLOSURE

None.

ITEM 9A. CONTROLS AND PROCEDURES

Evaluation of Disclosure Controls and Procedures

Our management, with the participation of our principal executive officer and principal financial officer, evaluated the effectiveness of our disclosure controls and procedures as of December 31, 2017. The term "disclosure controls and procedures," as defined in Rules 13a-15(e) and 15d- 15(e) under the Exchange Act, means controls and other procedures that are designed to provide reasonable assurance that information required to be disclosed by us in the periodic reports that we file or submit with the SEC is recorded, processed, summarized and reported, within the time periods specified in the SEC's rules and forms, and to ensure that such information is accumulated and communicated to our management, including our Chief Executive Officer and Chief Financial Officer, as appropriate, to allow timely decisions regarding required disclosure. Based on that evaluation, as of December 31, 2017, our Chief Executive Officer and Chief Financial Officer have concluded that our disclosure controls and procedures are effective at the reasonable assurance level.

Management's Report on Internal Control Over Financial Reporting

Our management is responsible for establishing and maintaining adequate internal control over financial reporting. Internal control over financial reporting is defined in Rule 13a-15(f) and 15d-15(f) under the Exchange Act , as a process designed by, or under the supervision of, our principal executive and principal financial and accounting officers and effected by our board of directors and management to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles and includes those policies and procedures that:

- Pertain to the maintenance of records that in reasonable detail accurately and fairly reflect the transactions and dispositions of our assets;
- Provide reasonable assurance that transactions are recorded as necessary to permit preparation of financial statements in accordance with US generally accepted accounting principles, and that receipts and expenditures of our company are being made only in accordance with authorizations of our management and board of directors; and
- Provide reasonable assurance regarding prevention or timely detection of unauthorized acquisition, use or disposition of our assets that could have a material effect on the financial statements.

Because of its inherent limitations, internal control over financial reporting may not prevent or detect misstatements. Projections of any evaluation of effectiveness to future periods are subject to the risks that controls may become inadequate because of changes in conditions, or that the degree of compliance with the policies or procedures may deteriorate. Our management assessed the effectiveness of our internal control over financial reporting as of December 31, 2017, based on the criteria set forth by the Committee of Sponsoring Organizations of the Treadway Commission (COSO) in Internal Control—Integrated Framework. A material weakness is a deficiency, or a combination of deficiencies, in internal control over financial reporting, such that there is a reasonable possibility that a material misstatement of a company's annual or interim financial statements will not be prevented or detected on a timely basis. Based on management's assessment, management concluded that the Company's internal control over financial reporting was effective as of December 31, 2017.

Ernst & Young LLP, our independent registered public accounting firm, issued an attestation report on our internal control over financial reporting. The report of Ernst & Young LLP is contained in Item 15 of Part IV of this Annual Report on Form 10-K.

ITEM 9B. OTHER INFORMATION

None

PART III

ITEM 10. DIRECTORS, EXECUTIVE OFFICERS AND CORPORATE GOVERNANCE

The information required by Item 10 of Form 10-K is incorporated by reference from the discussion responsive thereto under the captions *Election of Directors, Corporate Governance* and *Section 16(a) Beneficial Ownership Reporting Compliance* in our definitive proxy statement for our 2018 annual meeting of shareholders to be filed with the SEC no later than 120 days after the close of the fiscal year covered by this Annual Report.

ITEM 11. EXECUTIVE COMPENSATION

The information required by Item 11 of Form 10-K is incorporated by reference from the discussion responsive thereto under the captions *Compensation Discussion and Analysis*, *Compensation Committee Report*, *Compensation Committee Interlocks and Insider Participation* and *Director Compensation* in our definitive proxy statement for our 2018 annual meeting of shareholders to be filed with the SEC no later than 120 days after the close of the fiscal year covered by this Annual Report.

ITEM 12. SECURITY OWNERSHIP OF CERTAIN BENEFICIAL OWNERS AND MANAGEMENT AND RELATED STOCKHOLDER MATTERS

The information required by Item 12 of Form 10-K is incorporated by reference from the discussion responsive thereto under the captions *Compensation Discussion and Analysis*, *Security Ownership of Certain Beneficial Owners, Directors and Management* in our definitive proxy statement for our 2018 annual meeting of shareholders to be filed with the SEC no later than 120 days after the close of the fiscal year covered by this Annual Report.

ITEM 13. CERTAIN RELATIONSHIPS AND RELATED TRANSACTIONS AND DIRECTOR INDEPENDENCE

The information required by Item 13 of Form 10-K is incorporated by reference from the discussion responsive thereto under the captions *Election of Class II Directors* and *Certain Relationships and Related Transactions* in our definitive proxy statement for our 2018 annual meeting of shareholders to be filed with the SEC no later than 120 days after the close of the fiscal year covered by this Annual Report.

ITEM 14. PRINCIPAL ACCOUNTANT FEES AND SERVICES

The information required by Item 14 of Form 10-K is incorporated by reference from the discussion responsive thereto under the caption *Corporate Governance* and *Ratification of Independent Registered Public Accounting Firm* in our definitive proxy statement for our 2018 annual meeting of shareholders to be filed with the SEC no later than 120 days after the close of the fiscal year covered by this Annual Report.

PART IV

ITEM 15. EXHIBITS AND FINANCIAL STATEMENT SCHEDULES

(a) Documents filed as part of this report.

1. FINANCIAL STATEMENTS. The following consolidated financial statements of the Company are set forth herein, beginning on page 84:

(i) Reports of Independent Registered Public Accounting Firm

(ii) Consolidated Balance Sheets as of December 31, 2017 and 2016

(iii) Consolidated Statements of Comprehensive Loss for the Years Ended December 31, 2017, 2016 and 2015

(iv) Consolidated Statements of Shareholders' Equity for the Years Ended December 31, 2017, 2016 and 2015

(v) Consolidated Statements of Cash Flows for the Years Ended December 31, 2017, 2016 and 2015

(vi) Notes to Consolidated Financial Statements

2. FINANCIAL STATEMENT SCHEDULES.

None required.

3. EXHIBITS.

The exhibits that are required to be filed or incorporated by reference herein are listed in the Exhibit Index.

EXHIBIT INDEX

2.1	Agreement and Plan of Merger, dated December 1, 2010, among Insmed Incorporated, River Acquisition Co., Transave, LLC Transave, Inc. and TVM V Life Science Ventures GmbH & Co. KG (incorporated by reference from Exhibit 2.1 to Insmed Incorporated's Current Report on Form 8-K filed on December 2, 2010 (SEC file no. 000-30739)).
3.1	Articles of Incorporation of Insmed Incorporated, as amended through June 14, 2012 (incorporated by reference from Exhibit 3.1 to Insmed Incorporated's Annual Report on Form 10-K filed on March 18, 2013).
3.2	Amended and Restated Bylaws of Insmed Incorporated (incorporated by reference from Exhibit 3.1 to Insmed Incorporated's Quarterly Report on Form 10-Q filed on August 6, 2015).
4.1	Specimen stock certificate representing common stock, $0.01 par value per share, of the Registrant (incorporated by reference from Exhibit 4.2 to Insmed Incorporated's Registration Statement on Form S-4/A (Registration No. 333-30098) filed on March 24, 2000).
4.2	Indenture, dated as of January 26, 2018, by and between the Company and Wells Fargo Bank, National Association (incorporated by reference from Exhibit 4.1 to Insmed Incorporated’s Current Report on Form 8-K filed on January 26, 2018).
4.3	First Supplemental Indenture, dated as of January 26, 2018, by and between the Company and Wells Fargo Bank, National Association (incorporated by reference from Exhibit 4.2 to Insmed Incorporated’s Current Report on Form 8-K filed on January 26, 2018).
4.4	Form of 1.75% Convertible Senior Note due 2025 (included in Exhibit 4.3).
10.1**	Insmed Incorporated Amended and Restated 2000 Stock Incentive Plan (incorporated by reference from Exhibit 10.3 to Insmed Incorporated's Form 10-Q filed on May 7, 2013).
10.2**	Insmed Incorporated 2013 Incentive Plan (incorporated by reference from Exhibit 99.1 to Insmed Incorporated's Registration Statement on Form S-8 filed on May 24, 2013).
10.3**	Insmed Incorporated 2015 Incentive Plan (incorporated by reference from Exhibit 99.1 to Insmed Incorporated's Registration Statement on Form S-8 filed on May 28, 2015).

10.4**	Insmed Incorporated 2017 Incentive Plan (incorporated by reference from Exhibit 10.3 to Insmed Incorporated's Form 10-Q filed August 3, 2017).
10.5**	Form of Award Agreement for Restricted Stock Units issued to employees pursuant to the Insmed Incorporated 2013 Incentive Plan (incorporated by reference from Exhibit 10.3 to Insmed Incorporated's Form 10-K filed on March 6, 2014).
10.6**	Form of Award Agreement for Restricted Stock Units issued to directors pursuant to the Insmed Incorporated 2013 Incentive Plan (incorporated by reference from Exhibit 10.4 to Insmed Incorporated's Form 10-K filed on March 6, 2014).
10.7**	Form of Award Agreement for Restricted Stock Units issued to directors pursuant to the Insmed Incorporated 2015 Incentive Plan (incorporated by reference from Exhibit 10.1 to Insmed Incorporated's Form 10-Q filed May 3, 2017).
10.8**	Form of Restricted Unit Award Agreement under the Insmed Incorporated 2017 Incentive Plan (incorporated by reference from Exhibit 10.4 to Insmed Incorporated's Form 10-Q filed August 3, 2017).
10.9**	Form of Award Agreement for an Incentive Stock Option pursuant to the Insmed Incorporated 2013 Incentive Plan (incorporated by reference from Exhibit 10.5 to Insmed Incorporated's Form 10-K filed on March 6, 2014).
10.10**	Form of Award Agreement for a Non-Qualified Stock Option pursuant to the Insmed Incorporated 2013 Incentive Plan (incorporated by reference from Exhibit 10.6 to Insmed Incorporated's Form 10-K filed on March 6, 2014).
10.11**	Form of Award Agreement for a Non-Qualified Stock Option pursuant to the Insmed Incorporated 2015 Incentive Plan (incorporated by reference from Exhibit 10.2 to Insmed Incorporated's Form 10-Q filed May 3, 2017).
10.12**	Form of Non-Qualified Stock Option Agreement Under the Insmed Incorporated 2017 Incentive Plan (incorporated by reference from Exhibit 10.5 to Insmed Incorporated's Form 10-Q filed August 3, 2017).
10.13**	Form of Non-Qualified Stock Option Inducement Award Agreement (incorporated by reference from Exhibit 10.6 to Insmed Incorporated's Form 10-Q filed August 3, 2017).
10.14**	Employment Agreement, effective as of September 10, 2012, between Insmed Incorporated and William Lewis (incorporated by reference from Exhibit 10.1 to Insmed Incorporated's Current Report on Form 8-K filed on September 11, 2012).
10.15	Amended and Restated Loan and Security Agreement, dated as of September 30, 2016, by and between Insmed Incorporated, Celtrix Pharmaceuticals, the subsidiaries joined thereto, the lenders party thereto and Hercules Capital, Inc., as agent (incorporated by reference from Exhibit 10.1 to Insmed Incorporated's Quarterly Report on Form 10-Q filed on November 3, 2016).
10.16	Settlement, license and development agreement, dated March 5, 2007, between Insmed Incorporated, Insmed Therapeutic Proteins, Inc., Celtrix Pharmaceuticals, Tercica Inc., and Genentech, Inc. (incorporated by reference from Exhibit 10.1 to Insmed Incorporated's Quarterly Report on 10-Q filed on May 10, 2007 (SEC file no. 000-30739)).
10.17	License agreement, dated April 25, 2008, between Transave, Inc. and PARI Pharma GmbH, and Amendments No. 1-4 thereto (incorporated by reference from Exhibit 10.22 to Insmed Incorporated's Annual Report on Form 10-K filed on March 18, 2013).
10.17.1	Amendment No. 5 to License Agreement between Transave, Inc. and PARI Pharma GmbH, effective as of October 5, 2015 (incorporated by reference from Exhibit 10.14.1 to Insmed Incorporated's Annual Report on Form 10-K filed on February 25, 2016).
10.17.2	Amendment No. 6 to License Agreement between Transave, Inc. and PARI Pharma GmbH, effective as of October 9, 2015 (incorporated by reference from Exhibit 10.14.2 to Insmed Incorporated's Annual Report on Form 10-K filed on February 25, 2016).
10.18**	Employment Agreement, effective as of July 29, 2013, between Insmed Incorporated and Christine Pellizzari (incorporated by reference from Exhibit 10.1 to Insmed Incorporated's Form 10-Q filed on November 5, 2013).
10.19**	Insmed Incorporated Senior Executive Bonus Plan (incorporated by reference from Exhibit 10.2 to Insmed Incorporated's Form 10-Q filed on November 5, 2013).

10.20	Lease, dated December 31, 2013, between Denver Road, LLC and Insmed Incorporated (incorporated by reference from Exhibit 10.1 to Insmed Incorporated's Current Report on Form 8-K filed on January 3, 2014).
10.20.1	First Amendment to Lease, dated April 29, 2014, between Denver Road, LLC and Insmed Incorporated (incorporated by reference from Exhibit 10.17.1 to Insmed Incorporated's Annual Report on Form 10-K filed on February 25, 2016).
10.20.2	Second Amendment to Lease, dated November 20, 2015, between Denver Road, LLC and Insmed Incorporated (incorporated by reference from Exhibit 10.17.2 to Insmed Incorporated's Annual Report on Form 10-K filed on February 25, 2016).
10.21	Form of Indemnification Agreement entered into with each of the Company's directors and officers (incorporated by reference from Exhibit 10.1 to Insmed Incorporated's Current Report on Form 8-K filed on January 16, 2014).
10.22	Contract Manufacturing Agreement, dated February 7, 2014, between Insmed Incorporated and Therapure Biopharma Inc. (incorporated by reference from Exhibit 10.1 to Insmed Incorporated's Form 10-Q filed on May 8, 2014).
10.23	Amending Agreement, dated March 13, 2014, between Insmed Incorporated and Therapure Biopharma Inc. (incorporated by reference from Exhibit 10.2 to Insmed Incorporated's Form 10-Q filed on May 8, 2014).
10.24	Commercialization Agreement dated July 8, 2014 between Insmed Incorporated and PARI Pharma GmbH (incorporated by reference from Exhibit 10.1 to Insmed Incorporated's Form 10-Q filed on November 6, 2014).
10.25	Stock Purchase Agreement, dated as of December 15, 2014, by and between Insmed Incorporated and Hercules Technology Growth Capital, Inc. (incorporated by reference from Exhibit 10.28 to Insmed Incorporated's Form 10-K filed on February 27, 2015).
10.26	Master Agreement for Services, dated as of August 27, 2014, by and between Insmed Incorporated and SynteractHCR, Inc. (incorporated by reference from Exhibit 10.29 to Insmed Incorporated's Form 10-K filed on February 27, 2015).
10.27	Work Order 1, dated as of December 30, 2014, by and between Insmed Incorporated and SynteractHCR, Inc. (incorporated by reference from Exhibit 10.30 to Insmed Incorporated's Form 10-K filed on February 27, 2015).
10.28	Change in Scope 1 to Work Order 1, dated as of May 27, 2016, by and between Insmed Incorporated and SynteractHCR, Inc. (incorporated by reference from Exhibit 10.2 to Insmed Incorporated's Form 10-Q filed August 4, 2016).
10.29**	Employment Agreement, effective as of January 2, 2013, between Insmed Incorporated and S. Nicole Schaeffer (incorporated by reference from Exhibit 10.2 to Insmed Incorporated's Form 10-Q filed on May 7, 2015).
10.30	Commercial Fill/Finish Services Agreement between Insmed Incorporated and Ajinomoto Althea, Inc., dated as of September 15, 2015 (incorporated by reference from Exhibit 10.1 to Insmed Incorporated's Form 10-Q filed November 6, 2015).
10.31	Lease Agreement, effective as of July 1, 2016, by and between Insmed Incorporated and CIP II/AR Bridgewater Holdings, LLC (incorporated by reference from Exhibit 10.1 to Insmed Incorporated's Form 10-Q filed August 4, 2016).
10.32**	Employment Agreement, effective as of September 27, 2016, between Insmed Incorporated and Roger Adsett (incorporated by reference from Exhibit 10.2 to Insmed Incorporated's Form 10-Q filed November 3, 2016).
10.33*	License Agreement, dated October 4, 2016, between Insmed Incorporated and AstraZeneca AB (incorporated by reference from Exhibit 10.29 to Insmed Incorporated’s Form 10-K filed February 23, 2017).
10.34	Extension of Commercial Fill/Finish Services Agreement between Insmed Incorporated and Ajinomoto Althea, Inc., dated as of November 30, 2016 (incorporated by reference from Exhibit 10.30 to Insmed Incorporated’s Form 10-K filed February 23, 2017).
10.35	Amendment to Employment Agreement, effective as of September 26, 2016, between Insmed Incorporated and Christine Pellizzari (incorporated by reference from Exhibit 10.31 to Insmed Incorporated’s Form 10-K filed February 23, 2017).

10.36	Amendment to Employment Agreement, effective as of September 26, 2016, between Insmed Incorporated and S. Nicole Schaeffer (incorporated by reference from Exhibit 10.32 to Insmed Incorporated's Form 10-K filed February 23, 2017).
10.37	Employment Agreement, effective as of June 1, 2017, between Insmed Incorporated and Paolo Tombesi (incorporated by reference from Exhibit 10.1 to Insmed Incorporated's Form 10-Q filed August 3, 2017).
10.38	Employment Agreement, effective as of June 1, 2017, between Insmed Incorporated and Paul D. Streck (incorporated by reference from Exhibit 10.2 to Insmed Incorporated's Form 10-Q filed August 3, 2017).
10.39*	Manufacturing and Supply Agreement between Insmed Incorporated and Patheon UK Limited, dated as of October 20, 2017 (filed herewith).
10.40*	Technology Transfer Agreement between Insmed Incorporated and Patheon UK Limited, dated as of October 20, 2017 (filed herewith).
21.1	Subsidiaries of Insmed Incorporated (filed herewith).
23.1	Consent of Ernst & Young LLP (filed herewith).
31.1	Certification of William H. Lewis, Chief Executive Officer of Insmed Incorporated, pursuant to Rules 13a-14(a) and 15d-14(a) promulgated under the Securities Exchange Act of 1934, as adopted pursuant to Section 302 of the Sarbanes Oxley Act of 2003 (filed herewith).
31.2	Certification of William H. Lewis, Chief Executive Officer of Insmed Incorporated, pursuant to 18 USC Section 1350, as adopted pursuant to Section 906 of the Sarbanes Oxley Act of 2003 (filed herewith).
32.1	Certification of Paolo Tombesi, Chief Financial Officer (Principal Financial and Accounting Officer) of Insmed Incorporated, pursuant to Rules 13a-14(a) and 15d-14(a) promulgated under the Securities Exchange Act of 1934, as adopted pursuant to Section 302 of the Sarbanes Oxley Act of 2003 (filed herewith).
32.2	Certification of Paolo Tombesi, Chief Financial Officer (Principal Financial and Accounting Officer) of Insmed Incorporated, pursuant to 18 USC Section 1350, as adopted pursuant to Section 906 of the Sarbanes Oxley Act of 2003 (filed herewith).
101.INS	XBRL Instance Document
101.SCH	XBRL Taxonomy Extension Schema Document
101.CAL	XBRL Taxonomy Extension Calculation Linkbase Document
101.DEF	XBRL Taxonomy Extension Definition Linkbase Document
101.LAB	XBRL Taxonomy Extension Label Linkbase Document
101.PRE	XBRL Taxonomy Extension Presentation Linkbase Document

*	Confidential treatment has been requested for certain portions of this exhibit. The confidential portions of this exhibit have been omitted and filed separately with the Securities and Exchange Commission.
**	Management contract or compensatory plan or arrangement of the Company required to be filed as an exhibit.

ITEM 16. FORM 10-K SUMMARY

Not applicable.

SIGNATURES

Pursuant to the requirements of Section 13 or 15(d) of the Securities Exchange Act of 1934, the Registrant has duly caused this report to be signed on its behalf by the undersigned, thereunto duly authorized on February 23, 2018.

INSMED INCORPORATED
a Virginia corporation
(Registrant)

By: /s/ WILLIAM H. LEWIS
William H. Lewis
President and Chief Executive Officer (Principal Executive Officer) and Director

Pursuant to the requirements of the Securities Exchange Act of 1934, this report has been signed below by the following persons on behalf of the Registrant and in the capacities indicated on February 23, 2018.

Signature	Title
/s/ WILLIAM H. LEWIS William H. Lewis	President and Chief Executive Officer (Principal Executive Officer) and Director
/s/ PAOLO TOMBESI Paolo Tombesi	Chief Financial Officer (Principal Financial Officer and Principal Accounting Officer)
/s/ DONALD HAYDEN, JR. Donald Hayden, Jr.	Chairman of the Board of Directors
/s/ ALFRED F. ALTOMARI Alfred F. Altomari	Director
/s/ DAVID R. BRENNAN David R. Brennan	Director
/s/ STEINAR J. ENGELSEN, M.D. Steinar J. Engelsen, M.D.	Director
/s/ DAVID W.J. MCGIRR David W.J. McGirr	Director
/s/ MYRTLE POTTER Myrtle Potter	Director
/s/ MELVIN SHAROKY, M.D. Melvin Sharoky, M.D.	Director

Report of Independent Registered Public Accounting Firm

To the Shareholders and the Board of Directors of Insmed Incorporated

Opinion of the Financial Statements

We have audited the accompanying consolidated balance sheets of Insmed Incorporated (the Company) as of December 31, 2017 and 2016, the related consolidated statements of comprehensive loss, shareholders' equity and cash flows for each of the three years in the period ended December 31, 2017, and the related notes (collectively referred to as the "financial statements"). In our opinion, the financial statements present fairly, in all material respects, the consolidated financial position of the Company at December 31, 2017 and 2016, and the consolidated results of its operations and its cash flows for each of the three years in the period ended December 31, 2017, in conformity with U.S. generally accepted accounting principles.

We also have audited, in accordance with the standards of the Public Company Accounting Oversight Board (United States) (PCAOB), the Company's internal control over financial reporting as of December 31, 2017, based on criteria established in Internal Control-Integrated Framework issued by the Committee of Sponsoring Organizations of the Treadway Commission (2013 framework), as and our report dated February 23, 2018 expressed an unqualified opinion thereon.

Basis for Opinion

These financial statements are the responsibility of the Company's management. Our responsibility is to express an opinion on the Company's financial statements based on our audits. We are a public accounting firm registered with the PCAOB and are required to be independent with respect to the Company in accordance with the U.S. federal securities laws and the applicable rules and regulations of the Securities and Exchange Commission and the PCAOB.

We conducted our audits in accordance with the standards of the PCAOB. Those standards require that we plan and perform the audit to obtain reasonable assurance about whether the financial statements are free of material misstatement, whether due to error or fraud. Our audits included performing procedures to assess the risks of material misstatement of the financial statements, whether due to error or fraud, and performing procedures that respond to those risks. Such procedures included examining, on a test basis, evidence regarding the amounts and disclosures in the financial statements. Our audits also included evaluating the accounting principles used and significant estimates made by management, as well as evaluating the overall presentation of the financial statements. We believe that our audits provide a reasonable basis for our opinion.

/s/ Ernst & Young LLP

We have served as the Company's auditor since at least 1999, but we are unable to determine the specific year.

Iselin, New Jersey
February 23, 2018

Report of Independent Registered Public Accounting Firm

To the Shareholders and the Board of Directors of Insmed Incorporated

Opinion on Internal Control over Financial Reporting

We have audited Insmed Incorporated's internal control over financial reporting as of December 31, 2017, based on criteria established in Internal Control - Integrated Framework issued by the Committee of Sponsoring Organizations of the Treadway Commission (2013 framework), (the COSO criteria). In our opinion, Insmed Incorporated (the Company) maintained, in all material respects, effective internal control over financial reporting as of December 31, 2017, based on the COSO criteria**.**

We also have audited, in accordance with the standards of the Public Company Accounting Oversight Board (United States) (PCAOB), the consolidated balance sheets of the Company as of December 31, 2017 and 2016, and the consolidated statements of comprehensive loss, shareholders' equity and cash flows for each of the three years in the period ended December 31, 2017 of the Company and our report dated February 23, 2018 expressed an unqualified opinion thereon.

Basis for Opinion

The Company's management is responsible for maintaining effective internal control over financial reporting and for its assessment of the effectiveness of internal control over financial reporting included in the accompanying Management's Report on Internal Control Over Financial Reporting. Our responsibility is to express an opinion on the Company's internal control over financial reporting based on our audit. We are a public accounting firm registered with the PCAOB and are required to be independent with respect to the Company in accordance with the U.S. federal securities laws and the applicable rules and regulations of the Securities and Exchange Commission and the PCAOB.

We conducted our audit in accordance with the standards of the PCAOB. Those standards require that we plan and perform the audit to obtain reasonable assurance about whether effective internal control over financial reporting was maintained in all material respects.

Our audit included obtaining an understanding of internal control over financial reporting, assessing the risk that a material weakness exists, testing and evaluating the design and operating effectiveness of internal control based on the assessed risk, and performing such other procedures as we considered necessary in the circumstances. We believe that our audit provides a reasonable basis for our opinion.

Definition and Limitations of Internal Control Over Financial Reporting

A company's internal control over financial reporting is a process designed to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles. A company's internal control over financial reporting includes those policies and procedures that (1) pertain to the maintenance of records that, in reasonable detail, accurately and fairly reflect the transactions and dispositions of the assets of the company; (2) provide reasonable assurance that transactions are recorded as necessary to permit preparation of financial statements in accordance with generally accepted accounting principles, and that receipts and expenditures of the company are being made only in accordance with authorizations of management and directors of the company; and (3) provide reasonable assurance regarding prevention or timely detection of unauthorized acquisition, use, or disposition of the company's assets that could have a material effect on the financial statements.

Because of its inherent limitations, internal control over financial reporting may not prevent or detect misstatements. Also, projections of any evaluation of effectiveness to future periods are subject to the risk that controls may become inadequate because of changes in conditions, or that the degree of compliance with the policies or procedures may deteriorate.

/s/ Ernst & Young LLP

Iselin, New Jersey
February 23, 2018

INSMED INCORPORATED
Consolidated Balance Sheets
(in thousands, except par value and share data)

	As of December 31,	
	2017	**2016**
Assets		
Current assets:		
Cash and cash equivalents	$ 381,165	$ 162,591
Prepaid expenses and other current assets	8,279	5,816
Total current assets	389,444	168,407
In-process research and development	58,200	58,200
Fixed assets, net	12,432	10,020
Other assets	1,971	1,329
Total assets	$ 462,047	$ 237,956
Liabilities and shareholders' equity		
Current liabilities:		
Accounts payable	$ 14,671	$ 10,439
Accrued expenses	29,339	16,822
Other current liabilities	646	728
Total current liabilities	44,656	27,989
Debt, long-term	55,567	54,791
Other long-term liabilities	765	693
Total liabilities	100,988	83,473
Shareholders' equity:		
Common stock, $0.01 par value; 500,000,000 authorized shares, 76,610,508 and 62,019,889 issued and outstanding shares at December 31, 2017 and December 31, 2016, respectively	766	620
Additional paid-in capital	1,318,181	919,164
Accumulated deficit	(957,885)	(765,236)
Accumulated other comprehensive loss	(3)	(65)
Total shareholders' equity	361,059	154,483
Total liabilities and shareholders' equity	$ 462,047	$ 237,956

See accompanying notes to consolidated financial statements

INSMED INCORPORATED
Consolidated Statements of Comprehensive Loss
(in thousands, except per share data)

	2017	2016	2015
Revenues	$ —	$ —	$ —
Operating expenses:			
Research and development	109,749	122,721	74,277
General and administrative	79,171	50,679	43,216
Total operating expenses	188,920	173,400	117,493
Operating loss	(188,920)	(173,400)	(117,493)
Investment income	1,624	604	261
Interest expense	(5,925)	(3,498)	(2,889)
Other income (expense), net	300	119	(33)
Loss before income taxes	(192,921)	(176,175)	(120,154)
Income tax (benefit) provision	(272)	98	(1,971)
Net loss	$ (192,649)	$ (176,273)	$ (118,183)
Basic and diluted net loss per share	$ (2.89)	$ (2.85)	$ (2.02)
Weighted average basic and diluted common shares outstanding	66,576	61,892	58,633
Net loss	$ (192,649)	$ (176,273)	$ (118,183)
Other comprehensive income (loss):			
Foreign currency translation gains (losses)	62	(65)	—
Total comprehensive loss	$ (192,587)	$ (176,338)	$ (118,183)

See accompanying notes to audited consolidated financial statements

INSMED INCORPORATED
Consolidated Statements of Shareholders' Equity
(in thousands)

	Common Stock		Additional Paid-in Capital	Accumulated Deficit	Accumulated Other Comprehensive Loss	Total
	Shares	Amount				
Balance at January 1, 2015	49,806	$ 498	$ 656,519	$ (470,780)	$ —	$ 186,237
Comprehensive loss:						
Net loss				(118,183)		(118,183)
Exercise of stock options	481	5	5,107			5,112
Net proceeds from issuance of common stock	11,500	115	222,827			222,942
Issuance of common stock for vesting of RSUs	27					—
Stock compensation expense			15,590			15,590
Balance at December 31, 2015	61,814	$ 618	$ 900,043	$ (588,963)	$ —	$ 311,698
Comprehensive loss:						
Net loss				(176,273)		(176,273)
Other comprehensive loss					(65)	(65)
Exercise of stock options	162	2	1,082			1,084
Issuance of common stock for vesting of RSUs	44					—
Stock compensation expense			18,039			18,039
Balance at December 31, 2016	62,020	$ 620	$ 919,164	$ (765,236)	$ (65)	$ 154,483
Comprehensive loss:						
Net loss				(192,649)		(192,649)
Other comprehensive income					62	62
Exercise of stock options	379	4	3,429			3,433
Net proceeds from issuance of common stock	14,123	141	377,515			377,656
Issuance of common stock for vesting of RSUs	89	1				1
Stock compensation expense			18,073			18,073
Balance at December 31, 2017	76,611	$ 766	$ 1,318,181	$ (957,885)	$ (3)	$ 361,059

See accompanying notes to audited consolidated financial statements

INSMED INCORPORATED
Consolidated Statements of Cash Flows
(in thousands)

	Years ended December 31,		
	2017	**2016**	**2015**
Operating activities			
Net loss	$(192,649)	$(176,273)	$(118,183)
Adjustments to reconcile net loss to net cash used in operating activities:			
Depreciation and amortization	2,901	2,438	1,982
Stock-based compensation expense	18,073	18,039	15,590
Amortization of debt issuance costs	118	281	458
Accrual of the end of term charge on the debt	658	171	76
Changes in operating assets and liabilities:			
Prepaid expenses and other assets	(2,783)	191	(1,484)
Accounts payable	3,604	2,767	(1,781)
Accrued expenses and other	10,461	5,678	2,642
Net cash used in operating activities	(159,617)	(146,708)	(100,700)
Investing activities			
Purchase of fixed assets	(3,001)	(4,200)	(3,454)
Net cash used in investing activities	(3,001)	(4,200)	(3,454)
Financing activities			
Proceeds from issuance of debt	—	30,000	—
Proceeds from issuance of common stock	377,656	—	222,942
Proceeds from exercise of stock options	3,433	1,084	5,112
Payment of debt issuance costs	—	(411)	(250)
Net cash provided by financing activities	381,089	30,673	227,804
Effect of exchange rates on cash and cash equivalents	103	(50)	—
Net increase (decrease) in cash and cash equivalents	218,574	(120,285)	123,650
Cash and cash equivalents at beginning of period	162,591	282,876	159,226
Cash and cash equivalents at end of period	$ 381,165	$ 162,591	$ 282,876
Supplemental disclosures of cash flow information:			
Cash paid for interest	$ 5,165	$ 3,608	$ 2,948
Cash paid (received) for income taxes, net	$ 166	$ 85	$ (3,008)

See accompanying notes to audited consolidated financial statements

INSMED INCORPORATED

NOTES TO CONSOLIDATED FINANCIAL STATEMENTS

1. Description of Business and Basis of Presentation

Description of Business—Insmed is a global biopharmaceutical company focused on the unmet needs of patients with rare diseases. The Company's lead product candidate is amikacin liposome inhalation suspension (ALIS) (formerly known as liposomal amikacin for inhalation), which is in late-stage development for adult patients with treatment refractory nontuberculous mycobacteria (NTM) lung disease caused by Mycobacterium avium complex (MAC), a rare and often chronic infection that can cause irreversible lung damage and can be fatal. The Company's earlier clinical-stage pipeline includes INS1007, a novel oral reversible inhibitor of dipeptidyl peptidase 1, and INS1009, an inhaled nanoparticle formulation of a treprostinil prodrug.

In recent years, the Company has funded its operations through public offerings of securities and debt financings. The Company expects to continue to incur losses both in its US and certain international entities, as the Company plans to fund research and development activities and commercial launch activities. The Company may need to raise additional capital to fund its operations, to develop and commercialize ALIS, to develop INS1007 and INS1009, and to develop, acquire, in-license or co-promote other products that address orphan or rare diseases. The Company believes it currently has sufficient funds to meet its financial needs for at least the next 12 months.

The Company was incorporated in the Commonwealth of Virginia on November 29, 1999 and its principal executive offices are located in Bridgewater, New Jersey. The Company has legal entities in the United States (US), Ireland, Germany, France, the United Kingdom (UK), the Netherlands and Japan.

Basis of Presentation—The consolidated financial statements include the accounts of the Company and its wholly-owned subsidiaries, Insmed Limited, Celtrix Pharmaceuticals, Inc., Insmed Holdings Limited, Insmed Ireland Limited, Insmed France SAS, Insmed Germany GmbH, Insmed Netherlands B.V. and Insmed Godo Kaisha. All intercompany transactions and balances have been eliminated in consolidation.

2. Summary of Significant Accounting Policies

Use of Estimates—The preparation of the consolidated financial statements in conformity with accounting principles generally accepted in the United States (GAAP) requires management to make estimates and assumptions that affect the amounts reported in the consolidated financial statements and accompanying notes. The Company bases its estimates and judgments on historical experience and on various other assumptions. The amounts of assets and liabilities reported in the Company's balance sheets and the amounts of expenses reported for each period presented are affected by estimates and assumptions, which are used for, but not limited to, the accounting for stock-based compensation, income taxes, loss contingencies, and accounting for research and development costs. Actual results could differ from those estimates.

Investment Income and Interest Expense—Investment income consists of interest and dividend income earned on the Company's cash and cash equivalents. Interest expense consists primarily of interest costs related to the Company's debt.

Cash and Cash Equivalents—The Company considers cash equivalents to be highly liquid investments with maturities of three months or less from the date of purchase.

Fixed Assets, Net—Fixed assets are recorded at cost and are depreciated on a straight-line basis over the estimated useful lives of the assets. Estimated useful lives of three years to five years are used for computer equipment. Estimated useful lives of seven years are used for laboratory equipment, office equipment, manufacturing equipment and furniture and fixtures. Leasehold improvements are amortized over the shorter of the lease term or the estimated useful life of the asset. Long-lived assets are reviewed for impairment whenever events or changes in circumstances indicate that the carrying amount of an asset may not be recoverable. Recoverability of assets to be held and used is measured by a comparison of the carrying amount of an asset to estimated undiscounted future cash flows expected to be generated by the asset. If the carrying amount of an asset exceeds its estimated future cash flows, then an impairment charge is recognized for the amount by which the carrying value of the asset exceeds the fair value of the asset.

Identifiable Intangible Assets—Identifiable intangible assets are measured at their respective fair values and are not amortized until commercialization. Once commercialization occurs, these intangible assets will be amortized over their estimated useful lives. The fair values assigned to the Company's intangible assets are based on reasonable estimates and assumptions given available facts and circumstances. Unanticipated events or circumstances may occur that may require the Company to review the assets for impairment. Events or circumstances that may require an impairment assessment include

INSMED INCORPORATED

NOTES TO CONSOLIDATED FINANCIAL STATEMENTS (Continued)

2. Summary of Significant Accounting Policies (Continued)

negative clinical trial results, the non-approval of a new drug application by a regulatory agency, material delays in the Company's development program or a sustained decline in market capitalization.

Indefinite-lived intangible assets are not subject to periodic amortization. Rather, indefinite-lived intangibles are reviewed for impairment by applying a fair value based test on an annual basis or more frequently if events or circumstances indicate impairment may have occurred. Events or circumstances that may require an interim impairment assessment are consistent with those described above. The Company performs its annual impairment test as of October 1 of each year.

The Company uses the income approach to derive the fair value of in-process research and development assets. This approach calculates fair value by estimating future cash flows attributable to the assets and then discounting these cash flows to a present value using a risk-adjusted discount rate. This approach requires significant management judgment with respect to unobservable inputs such as future volume, revenue and expense growth rates, changes in working capital use, appropriate discount rates and other assumptions and estimates. The estimates and assumptions used are consistent with the Company's business plans. A market based valuation approach was not considered given a lack of revenues and profits for the Company.

Debt Issuance Costs—Debt issuance costs are amortized to interest expense using the effective interest rate method over the term of the debt. Debt issuance costs paid to the lender and third parties are reflected as a discount to the debt in the consolidated balance sheets. Unamortized debt issuance costs associated with extinguished debt are expensed in the period of the extinguishment.

Fair Value Measurements—The Company categorizes its financial assets and liabilities measured and reported at fair value in the financial statements on a recurring basis based upon the level of judgments associated with the inputs used to measure their fair value. Hierarchical levels, which are directly related to the amount of subjectivity associated with the inputs used to determine the fair value of financial assets and liabilities, are as follows:

- Level 1—Inputs are unadjusted, quoted prices in active markets for identical assets or liabilities at the measurement date.
- Level 2—Inputs (other than quoted prices included in Level 1) are either directly or indirectly observable for the assets or liability through correlation with market data at the measurement date and for the duration of the instrument's anticipated life.
- Level 3—Inputs reflect management's best estimate of what market participants would use in pricing the asset or liability at the measurement date. Consideration is given to the risk inherent in the valuation technique and the risk inherent in the inputs to the model.

Each major category of financial assets and liabilities measured at fair value on a recurring basis is categorized based upon the lowest level of significant input to the valuations. The fair value hierarchy also requires an entity to maximize the use of observable inputs and minimize the use of unobservable inputs when measuring fair value. Financial instruments in Level 1 generally include US treasuries and mutual funds listed in active markets.

The Company's only assets and liabilities which were measured at fair value as of December 31, 2017 and December 31, 2016 were its cash and cash equivalents of $381.2 million and $162.6 million, respectively. These amounts were measured at Level 1 using quoted prices in active markets for identical assets at the measurement date. The Company's cash and cash equivalents permit daily redemption and the fair values of these investments are based upon the quoted prices in active markets provided by the holding financial institutions. Cash equivalents consist of liquid investments with a maturity of three months or less from the date of purchase and the short-term investments consist of instruments with maturities greater than three months.

The Company recognizes transfers between levels within the fair value hierarchy, if any, at the end of each quarter. There were no transfers in or out of Level 1, Level 2 or Level 3 during 2017 and 2016.

As of December 31, 2017 and 2016, the Company held no securities that were in an unrealized loss or gain position.

The Company reviews the status of each security quarterly to determine whether an other-than-temporary impairment has occurred. In making its determination, the Company considers a number of factors, including: (1) the significance of the decline; (2) whether the securities were rated below investment grade; (3) how long the securities have been in an unrealized loss position; and (4) the Company's ability and intent to retain the investment for a sufficient period of time for it to recover.

INSMED INCORPORATED

NOTES TO CONSOLIDATED FINANCIAL STATEMENTS (Continued)

2. Summary of Significant Accounting Policies (Continued)

Foreign Currency—The Company has operations in the US, Ireland, Germany, France, the UK and the Netherlands. The results of its non-US dollar based functional currency operations are translated to US dollars at the average exchange rates during the period. Assets and liabilities are translated at the exchange rate prevailing at the balance sheet date. Equity is translated at the prevailing exchange rate at the date of the equity transaction. Translation adjustments are included in shareholders' equity, as a component of other comprehensive loss.

The Company realizes foreign currency transaction gains (losses) in the normal course of business based on movements in the applicable exchange rates. These gains (losses) are included as a component of other income (expense), net.

Concentration of Credit Risk—Financial instruments that potentially subject the Company to concentrations of credit risk consist primarily of cash and cash equivalents. The Company places its cash equivalents with high credit-quality financial institutions and may invest its short-term investments in US treasury securities, mutual funds and government agency bonds. The Company has established guidelines relative to credit ratings and maturities that seek to maintain safety and liquidity.

The Company relies on third-party manufacturers and suppliers for manufacturing and supply of its products. The inability of the suppliers or manufacturers to fulfill supply requirements of the Company could materially impact future operating results. A change in the relationship with the suppliers or manufacturer, or an adverse change in their business, could materially impact future operating results.

Other Income—In 2015, the French National Agency for Medicines and Health Products Safety (ANSM) granted ALIS a Temporary Authorizations for Use (Autorisation Temporaire d'Utilisation or ATU). Pursuant to this program, the Company shipped product to pharmacies after receiving requests from physicians for patients in France. For the years ended December 31, 2017, 2016 and 2015, the revenue recorded was immaterial and is included as a component of other income (expense), net. The Company is initiating expanded access programs (EAPs) in other select territories in Europe, some of which may be fully reimbursed. EAPs are intended to make products available on a named patient basis before they are commercially available in accordance with local regulations.

Research and Development—Research and development expenses consist primarily of salaries, benefits and other related costs, including stock-based compensation, for personnel serving in the Company's research and development functions, and other internal operating expenses, the cost of manufacturing a drug candidate, including the medical devices for drug delivery, for clinical study, the cost of conducting clinical studies, and the cost of conducting preclinical and research activities. In addition, research and development expenses include payments to third parties for the license rights to products in development (prior to marketing approval). The Company's expenses related to manufacturing its drug candidate and medical devices for clinical study are primarily related to activities at contract manufacturing organizations that manufacture ALIS, INS1007, and INS1009 and the medical devices for the Company's use. The Company's expenses related to clinical trials are primarily related to activities at contract research organizations that conduct and manage clinical trials on the Company's behalf. These contracts set forth the scope of work to be completed at a fixed fee or amount per patient enrolled. Payments under these contracts primarily depend on performance criteria such as the successful enrollment of patients or the completion of clinical trial milestones as well as time-based fees. Expenses are accrued based on contracted amounts applied to the level of patient enrollment and to activity according to the clinical trial protocol. Nonrefundable advance payments for goods or services that will be used or rendered for future research and development activities are deferred and capitalized. Such amounts are then recognized as an expense as the related goods are delivered or the services are performed, or when the goods or services are no longer expected to be provided.

Stock-Based Compensation—The Company recognizes stock-based compensation expense for awards of equity instruments to employees and directors based on the grant-date fair value of those awards. The grant-date fair value of the award is recognized as compensation expense ratably over the requisite service period, which generally equals the vesting period of the award, and if applicable, is adjusted for expected forfeitures. The Company also grants performance-based stock options to employees. The grant-date fair value of the performance-based stock options is recognized as compensation expense over the implicit service period using the accelerated attribution method once it is probable that the performance condition will be achieved. Stock-based compensation expense is included in both research and development expenses and general and administrative expenses in the Consolidated Statements of Comprehensive Loss.

Income Taxes—The Company accounts for income taxes under the asset and liability method. Deferred tax assets and liabilities are recognized for the future tax consequences attributable to differences between the financial statement carrying

INSMED INCORPORATED

NOTES TO CONSOLIDATED FINANCIAL STATEMENTS (Continued)

2. Summary of Significant Accounting Policies (Continued)

amounts of existing assets and liabilities and their respective tax bases and operating loss carry forwards. Deferred tax assets and liabilities are measured using enacted tax rates expected to apply to taxable income in the years in which those temporary differences are expected to be recovered or settled. The effect on deferred tax assets and liabilities of a change in tax rates is recognized in income in the period that includes the enactment date.

A valuation allowance is recorded to reduce the deferred tax assets to the amount that is expected to be realized. In evaluating the need for a valuation allowance, the Company takes into account various factors, including the expected level of future taxable income and available tax planning strategies. If actual results differ from the assumptions made in the evaluation of a valuation allowance, the Company records a change in valuation allowance through income tax expense in the period such determination is made.

The Company uses a comprehensive model for how it measures, presents and discloses an uncertain tax position taken or expected to be taken in a tax return. The Company may recognize the tax benefit from an uncertain tax position only if it is more likely than not that the tax position will be sustained on examination by taxing authorities, based solely on the technical merits of the position. The tax benefits recognized in the financial statements from such a position should be measured based on the largest benefit that has a greater than 50% likelihood to be sustained upon ultimate settlement. The Company had no uncertain tax positions as of December 31, 2017 and 2016 that qualified for either recognition or disclosure in the consolidated financial statements.

The Company's policy for interest and penalties related to income tax exposures is to recognize interest and penalties as a component of the income tax (benefit) provision in the Consolidated Statements of Comprehensive Loss.

Tax Cuts and Jobs Act

On December 22, 2017, the US government enacted comprehensive tax legislation, referred to as the Tax Cuts and Jobs Act (the Tax Act). The Tax Act significantly revises US tax law by, among other provisions, lowering the US federal statutory income tax rate from 35% to 21%, imposing a mandatory one-time transition tax on previously deferred foreign earnings, and eliminating or reducing certain income tax deductions.

ASC 740, *Income Taxes* requires the effects of changes in tax laws to be recognized in the period in which the legislation is enacted. However, due to the complexity and significance of the Tax Act's provisions, the SEC staff issued Staff Accounting Bulletin No. 118 (SAB 118), which allows companies to record the tax effects of the Tax Act on a provisional basis based on a reasonable estimate, and then, if necessary, subsequently adjust such amounts during a limited measurement period as more information becomes available. The measurement period ends when a company has obtained, prepared, and analyzed the information necessary to finalize its accounting, but cannot extend beyond one year from enactment.

The provisional amounts recorded for the Tax Act did not have a material impact on the Company's financial statements as of December 31, 2017, because its deferred temporary differences are fully offset by a valuation allowance and the Company does not have any significant offshore earnings from which to record the mandatory transition tax. However, given the significant complexity of the Tax Act, anticipated guidance from the US Treasury about implementing the Tax Act, and the potential for additional guidance from the SEC or the FASB related to the Tax Act, these estimates may be adjusted during the measurement period. The provisional amounts disclosed in our footnotes were based on the Company's present interpretations of the Tax Act and current available information, including assumptions and expectations about future events, such as its projected financial performance, and are subject to further refinement as additional information becomes available (including the Company's actual full Fiscal 2018 results of operations, as well as potential new or interpretative guidance issued by the FASB or the Internal Revenue Service and other tax agencies) and further analyses are completed. The Company continues to analyze the changes in certain income tax deductions, assess calculations of earnings and profits in certain foreign subsidiaries, including if those earnings are held in cash or other assets and gather additional data to compute the full impacts on the Company's deferred and current tax assets and liabilities.

Net Loss Per Common Share—Basic net loss per common share is computed by dividing net loss attributable to common shareholders by the weighted average number of common shares outstanding during the period. Diluted net loss per common share is computed by dividing net loss by the weighted average number of common shares and other dilutive securities outstanding during the period. Potentially dilutive securities from stock options and restricted stock units would be anti-dilutive as the Company incurred a net loss in all periods presented. Potentially dilutive common shares resulting from the assumed exercise of outstanding stock options are determined based on the treasury stock method.

INSMED INCORPORATED

NOTES TO CONSOLIDATED FINANCIAL STATEMENTS (Continued)

2. Summary of Significant Accounting Policies (Continued)

The following table sets forth the reconciliation of the weighted average number of shares used to compute basic and diluted net loss per share for the years ended December 31, 2017, 2016 and 2015.

	Years Ended December 31,		
	2017	2016	2015
	(in thousands, except per share amounts)		
Numerator:			
Net loss	$ (192,649)	$ (176,273)	$ (118,183)
Denominator:			
Weighted average common shares used in calculation of basic net loss per share:	66,576	61,892	58,633
Effect of dilutive securities:			
Common stock options	—	—	—
Restricted stock and restricted stock units	—	—	—
Weighted average common shares outstanding used in calculation of diluted net loss per share	66,576	61,892	58,633
Net loss per share:			
Basic and Diluted	$ (2.89)	$ (2.85)	$ (2.02)

The following potentially dilutive securities have been excluded from the computations of diluted weighted average common shares outstanding as of December 31, 2017, 2016 and 2015 as their effect would have been anti-dilutive (in thousands).

	2017	2016	2015
Stock options to purchase common stock	8,609	7,117	5,274
Restricted stock and restricted stock units	47	89	44

Segment Information—The Company currently operates in one business segment, which is the development and commercialization of therapies for patients with rare diseases. A single management team that reports to the Chief Executive Officer comprehensively manages the entire business. The Company does not operate separate lines of business with respect to its products or product candidates. Accordingly, the Company does not have separate reportable segments.

New Accounting Pronouncements (Adopted)—In August 2014, the Financial Accounting Standards Board (FASB) issued Accounting Standards Update (ASU) No. 2014-15, *Presentation of Financial Statements—Going Concern: Disclosure of Uncertainties about an Entity's Ability to Continue as a Going Concern,* which requires management to evaluate whether there is substantial doubt about the entity's ability to continue as a going concern and, if so, provide certain footnote disclosures. This ASU was effective for the annual period ended December 31, 2016, and interim reporting periods thereafter. The adoption of this standard did not have an impact on the Company's consolidated financial statements and related footnote disclosures.

In March 2016, the FASB issued ASU 2016-9, *Improvements to Employee Share-Based Payment Accounting*, which amends ASC Topic 718, *Compensation—Stock Compensation*. ASU 2016-9 simplifies several aspects of the accounting for share-based payment transactions, including the income tax consequences, classification of awards as either equity or liabilities, and classification on the statement of cash flows. ASU 2016-9 is effective for fiscal years beginning after December 15, 2016, and interim periods within those fiscal years. The Company adopted ASU 2016-9 in the first quarter of 2017. ASU 2016-9 did not have a material impact on its consolidated financial statements.

New Accounting Pronouncements (Not Yet Adopted)—In May 2014, the FASB issued ASU 2014-9, *Revenue from Contracts with Customers (Topic 606)* which amended the existing accounting standards for revenue recognition. ASU 2014-9 establishes principles for recognizing revenue upon the transfer of promised goods or services to customers, in an amount that reflects the expected consideration received in exchange for those goods or services. In July 2015, the FASB deferred the

INSMED INCORPORATED

NOTES TO CONSOLIDATED FINANCIAL STATEMENTS (Continued)

2. Summary of Significant Accounting Policies (Continued)

effective date for annual reporting periods beginning after December 15, 2017. The Company will adopt ASU 2014-9 in the first quarter of 2018 and expects the impact of adoption will not be material to its consolidated financial statements.

In February 2016, the FASB issued ASU 2016-2, *Leases (Topic 842)* in order to increase transparency and comparability among organizations by recognizing lease assets and lease liabilities on the balance sheet for those leases classified as operating leases under previous GAAP. ASU 2016-2 requires that a lessee should recognize a liability to make lease payments (the lease liability) and a right-of-use asset representing its right to use the underlying asset for the lease term on the balance sheet. ASU 2016-2 is effective for fiscal years beginning after December 15, 2018 (including interim periods within those periods) using a modified retrospective approach and early adoption is permitted. The Company expects to adopt ASU 2016-2 in the first quarter of 2019 and is in the process of evaluating the impact of adoption on its consolidated financial statements.

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NOTES TO CONSOLIDATED FINANCIAL STATEMENTS (Continued)

3. Accrued Expenses

Accrued expenses consist of the following:

	As of December 31,	
	2017	2016
	(in thousands)	
Accrued clinical trial expenses	$ 7,837	$ 6,683
Accrued compensation	12,197	6,937
Accrued professional fees	4,500	1,992
Accrued technical operation expenses	2,182	591
Accrued interest payable	423	438
Accrued construction costs	1,719	—
Other accrued expenses	481	181
	$ 29,339	$ 16,822

4. Identifiable Intangible Assets

The Company's only identifiable intangible asset was in-process research and development (IPRD) related to ALIS as of December 31, 2017 and 2016. The total intangible IPRD asset was $58.2 million as of December 31, 2017 and 2016, which resulted from the initial amount recorded at the time of the Company's merger with Transave in 2010 and subsequent adjustments in the value. The Company uses the income approach to derive the fair value of in-process research and development assets. This approach calculates fair value by estimating future cash flows attributable to the assets and then discounting these cash flows to a present value using a risk-adjusted discount rate. Identifiable intangible assets are measured at their respective fair values and will not be amortized until commercialization. If commercialization occurs, intangible assets will be amortized over their estimated useful lives. As of December 31, 2017, the Company did not identify any indicators of impairment of its in-process research and development intangible assets and the implied value of the intangible assets was more than 100% greater than the book value.

5. Fixed Assets, net

Fixed assets are stated at cost and depreciated using the straight-line method, based on useful lives as follows:

Asset Description	Estimated Useful Life (years)	As of December 31, 2017	2016
		(in thousands)	
Lab equipment	7	$ 7,055	$ 5,662
Furniture and fixtures	7	1,937	1,903
Computer hardware and software	3 - 5	2,325	2,251
Office equipment	7	65	65
Manufacturing equipment	7	1,436	1,148
Leasehold improvements	lease term	6,939	6,735
Construction in Progress (CIP)	—	3,320	—
		23,077	17,764
Less accumulated depreciation		(10,645)	(7,744)
Fixed assets, net		$ 12,432	$ 10,020

Depreciation expense was $2.9 million, $2.4 million and $2.0 million for the years ended December 31, 2017, 2016 and 2015, respectively.

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NOTES TO CONSOLIDATED FINANCIAL STATEMENTS (Continued)

6. Debt

On June 29, 2012, the Company and its domestic subsidiaries, as co-borrowers, entered into a Loan and Security Agreement with Hercules Technology Growth Capital, Inc. (as subsequently amended, the Prior Loan Agreement) under which the Company borrowed an aggregate of $25.0 million at an interest rate of 9.25%. The Company was required to pay an "end of term" charge of $390,000 in January of 2016, which was charged to interest expense (and accreted to the debt) using the effective interest method over the life of the Prior Loan Agreement.

On September 30, 2016, the Company and its domestic subsidiaries, as co-borrowers, entered into an Amended and Restated Loan and Security Agreement (the A&R Loan Agreement) with Hercules Capital, Inc. (Hercules). The A&R Loan Agreement included a total commitment from Hercules of up to $55.0 million, of which $25.0 million was previously outstanding. The amount of borrowings was increased by $10.0 million to an aggregate total of $35.0 million on September 30, 2016. An additional $20.0 million was available at the Company's option through June 30, 2017 subject to certain conditions, including the payment of a facility fee of 0.375%. The Company exercised this option in early October 2016 and borrowed an additional $20.0 million in connection with its upfront payment obligation under the License Agreement with AstraZeneca (see *Note 10*). The interest rate for the term is floating and is defined as the greater of (i) 9.25% or (ii) 9.25% plus the sum of the US prime rate minus 4.50%, along with a backend fee of 4.15% of the aggregate principal amount outstanding and an aggregate facility fee of $337,500. The maturity date of the loan facility was also extended to October 1, 2020. In connection with the Company generating and announcing top-line data from the CONVERT study on September 5, 2017 that supports the filing of a New Drug Application (NDA), along with the completion of the equity financing, the interest-only period was automatically extended through May 1, 2019 and the Company's requirement to have a consolidated minimum cash liquidity in an amount no less than $25.0 million was eliminated.

In connection with the A&R Loan Agreement, the Company granted Hercules a first position lien on all of the Company's assets, excluding intellectual property. Prepayment of the loans made pursuant to the A&R Loan Agreement is subject to penalty. The backend fee of 4.15% on the aggregate outstanding principal balance will be charged to interest expense (and accreted to the debt) using the effective interest method over the original life of the A&R Loan Agreement. Debt issuance fees paid to Hercules were recorded as a discount on the debt and are being amortized to interest expense using the effective interest method over the life of the A&R Loan Agreement.

The A&R Loan Agreement also contains representations and warranties by the Company and Hercules and indemnification provisions in favor of Hercules and customary covenants (including limitations on other indebtedness, liens, acquisitions, investments and dividends, and a minimum liquidity covenant), and events of default (including payment defaults, breaches of covenants following any applicable cure period, a material impairment in the perfection or priority of the lender's security interest or in the collateral, and events relating to bankruptcy or insolvency). Upon the occurrence of an event of default, a default interest rate of an additional 5% may be applied to the outstanding loan balances, and the lender may terminate its lending commitment, declare all outstanding obligations immediately due and payable, and take such other actions as set forth in the A&R Loan Agreement.

The following table presents the components of the Company's debt balance as of December 31, 2017 (in thousands):

Debt:		
Note payable under A&R Loan Agreement	$	55,000
Accretion of end of term charge		828
Issuance fees paid to lender		(261)
Current portion of long-term debt		—
Long-term debt	$	55,567

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NOTES TO CONSOLIDATED FINANCIAL STATEMENTS (Continued)

6. Debt (Continued)

Future principal repayments of the Company's long-term debt are as follows (in thousands):

Year Ending in December 31:	
2018	$ —
2019	13,399
2020	41,601
	$ 55,000

The estimated fair value of the debt (categorized as a Level 2 liability for fair value measurement purposes) is determined using current market factors and the ability of the Company to obtain debt at comparable terms to those that are currently in place. As of December 31, 2017 and 2016, the fair value of the Company's debt approximates the carrying amount.

In February 2018, the Company notified Hercules that it will repay the A&R Loan Agreement in full on February 28, 2018. The total aggregate cash payable to Hercules for the early prepayment of debt, inclusive of accrued interest, the backend fee and an early payment penalty will be approximately $58.0 million.

7. Shareholders' Equity

Common Stock—As of December 31, 2017, the Company had 500,000,000 shares of common stock authorized with a par value of $0.01 and 76,610,508 shares of common stock issued and outstanding. In addition, as of December 31, 2017, the Company had reserved 8,608,921 shares of common stock for issuance upon the exercise of outstanding common stock options and 46,914 shares of common stock for issuance upon the vesting of restricted stock units.

In September 2017, the Company completed an underwritten public offering of 14,123,150 shares of the Company’s common stock, which included the underwriter’s exercise in full of its over-allotment option of 1,842,150 shares, at a price to the public of $28.50 per share. The Company’s net proceeds from the sale of the shares, after deducting underwriting discounts and offering expenses of $24.8 million, were approximately $377.7 million.

In April 2015, the Company completed an underwritten public offering of 11,500,000 shares of the Company's common stock, which included the underwriter's exercise in full of its over-allotment option of 1,500,000 shares, at a price to the public of $20.65 per share. The Company's net proceeds from the sale of the shares, after deducting underwriting discounts and offering expenses of $14.5 million, were approximately $222.9 million.

Preferred Stock—As of December 31, 2017 and 2016, the Company had 200,000,000 shares of preferred stock authorized with a par value of $0.01 and no shares of preferred stock were issued and outstanding.

8. Stock-Based Compensation

The Company’s current equity compensation plan, the 2017 Incentive Plan, was approved by shareholders at the Company’s Annual Meeting of Shareholders on May 18, 2017. The 2017 Incentive Plan is administered by the Compensation Committee and the Board of Directors of the Company. Under the terms of the 2017 Incentive Plan, the Company is authorized to grant a variety of incentive awards based on its common stock, including stock options (both incentive stock options and non-qualified stock options), RSUs, performance options/shares and other stock awards, as well as pay incentive bonuses to eligible employees and non-employee directors. On May 18, 2017, upon the approval of the 2017 Incentive Plan by shareholders, 5,000,000 shares were authorized for issuance thereunder, plus any shares subject to then-outstanding awards under the 2015 Incentive Plan and the 2013 Incentive Plan that subsequently were canceled, terminated unearned, expired, were forfeited, lapsed for any reason or were settled in cash without the delivery of shares. As of December 31, 2017, 4,910,002 shares remained for future issuance under the 2017 Incentive Plan. The 2017 Incentive Plan will terminate on April 3, 2027 unless it is extended or terminated earlier pursuant to its terms. In addition, from time to time, the Company makes inducement grants of stock options. These awards are made pursuant to the Nasdaq inducement grant exception as a component of new hires’ employment compensation in connection with the Company’s equity grant program. During the twelve months ended December 31, 2017 and 2016, the Company granted inducement stock options covering 266,230 and 88,060, respectively, shares of the Company's common stock to new employees.

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NOTES TO CONSOLIDATED FINANCIAL STATEMENTS (Continued)

8. Stock-Based Compensation (Continued)

Stock Options—The Company calculates the fair value of stock options granted using the Black-Scholes valuation model. The following table summarizes the grant date fair value and assumptions used in determining the fair value of all stock options granted, including grants of inducement options, during the years ended December 31, 2017, 2016 and 2015.

	2017	2016	2015
Volatility	71% - 79%	74% - 77%	78% - 82%
Risk-free interest rate	1.73% - 2.13%	1.00% - 1.90%	1.31% - 1.75%
Dividend yield	0.0%	0.0%	0.0%
Expected option term (in years)	6.25	6.25	6.25
Weighted average fair value of stock options granted	$10.52	$8.77	$14.20

For the years ended December 31, 2017, 2016 and 2015, the volatility factor was based on the Company's historical volatility during the expected option term. Estimated forfeitures were based on the actual percentage of option forfeitures since the closing of the Company's merger with Transave, Inc. in December 2010 for the years ended December 31, 2016 and 2015. Beginning with the year ended December 31, 2017, estimated forfeitures were based on the actual percentage of option forfeitures over the expected option term.

From time to time, the Company grants performance-condition options to certain employees. Vesting of these options is subject to the Company achieving certain performance criteria established at the date of grant and the individuals fulfilling a service condition (continued employment). As a result of the Marketing Authorization Application (MAA) acceptance for ALIS, which was received from the European Medicines Agency (EMA) in February 2015, the vesting of performance options totaling $1.5 million were recorded as non-cash compensation expense in the first quarter of 2015. As of December 31, 2017, the Company had performance options totaling 133,334 shares outstanding.

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NOTES TO CONSOLIDATED FINANCIAL STATEMENTS (Continued)

8. Stock-Based Compensation (Continued)

The following table summarizes stock option activity for stock options granted for the years ended December 31, 2017, 2016 and 2015 as follows:

	Number of Shares	Weighted Average Exercise Price	Weighted Average Remaining Contractual Life in Years	Aggregate Intrinsic Value (in '000)
Options outstanding at January 1, 2015	4,400,106	$ 10.59		
Granted	1,902,850	20.45		
Exercised	(481,140)	10.62		
Forfeited and expired	(548,094)	15.43		
Options outstanding at December 31, 2015	5,273,722	$ 13.64		
Vested and expected to vest at December 31, 2015	5,059,645	13.46		
Exercisable at December 31, 2015	1,991,141	8.70		
Options outstanding at December 31, 2015	5,273,722	$ 13.64		
Granted	2,532,675	12.96		
Exercised	(162,340)	6.68		
Forfeited and expired	(527,351)	17.08		
Options outstanding at December 31, 2016	7,116,706	$ 13.30		
Vested and expected to vest at December 31, 2016	6,850,658	13.25		
Exercisable at December 31, 2016	3,113,998	11.28		
Options outstanding at December 31, 2016	7,116,706	$ 13.30		
Granted	2,284,710	15.92		
Exercised	(378,275)	9.08		
Forfeited and expired	(414,220)	15.50		
Options outstanding at December 31, 2017	8,608,921	$ 14.08	7.4	$ 147,260
Vested and expected to vest at December 31, 2017	8,325,255	$ 14.03	7.4	$ 142,783
Exercisable at December 31, 2017	4,229,478	$ 12.71	6.3	$ 78,138

The total intrinsic value of stock options exercised during the years ended December 31, 2017, 2016 and 2015 was $4.3 million, $1.0 million and $4.7 million, respectively.

As of December 31, 2017, there was $29.7 million of unrecognized compensation expense related to unvested stock options, which is expected to be recognized over a weighted average period of 2.6 years. Included above in unrecognized compensation expense was $1.1 million related to outstanding performance-based options. The following table summarizes the range of exercise prices and the number of stock options outstanding and exercisable as of December 31, 2017:

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NOTES TO CONSOLIDATED FINANCIAL STATEMENTS (Continued)

8. Stock-Based Compensation (Continued)

Outstanding as of December 31, 2017					Exercisable as of December 31, 2017	
Range of Exercise Prices		Number of Options	Weighted Average Remaining Contractual Term (in years)	Weighted Average Exercise Price	Number of Options	Weighted Average Exercise Price
$ 3.03	$ 4.55	973,195	4.65	$ 3.60	973,195	$ 3.60
$ 6.90	$ 6.90	137,577	5.22	$ 6.90	100,077	$ 6.90
$ 6.96	$ 10.85	1,077,621	8.29	$ 10.76	420,374	$ 10.62
$ 11.14	$ 12.58	1,088,035	6.39	$ 12.17	781,991	$ 12.18
$ 12.66	$ 13.67	1,043,273	8.74	$ 13.59	101,126	$ 13.26
$ 13.94	$ 15.91	862,300	7.76	$ 14.97	406,441	$ 14.53
$ 16.07	$ 16.16	1,008,750	7.69	$ 16.13	463,629	$ 16.12
$ 16.35	$ 17.24	868,650	9.24	$ 17.13	23,999	$ 16.85
$ 17.36	$ 22.76	1,415,700	7.14	$ 21.18	927,334	$ 21.23
$ 22.84	$ 31.78	133,820	8.86	$ 27.47	31,312	$ 23.74

Restricted Stock and Restricted Stock Units—The Company may grant Restricted Stock (RS) and Restricted Stock Units (RSUs) to employees and non-employee directors. Each share of RS vests upon and each RSU represents a right to receive one share of the Company's common stock upon the completion of a specific period of continued service or achievement of a certain milestone. RS and RSU awards granted are valued at the market price of the Company's common stock on the date of grant. The Company recognizes noncash compensation expense for the fair values of these RS and RSUs on a straight-line basis over the requisite service period of these awards.

The following table summarizes RSU awards granted during the years ended December 31, 2017, 2016 and 2015:

	Number of RSUs	Weighted Average Grant Price
Outstanding at January 1, 2015	20,502	$ 19.47
Granted	49,776	16.07
Released	(26,724)	(18.68)
Forfeited	—	—
Outstanding at December 31, 2015	43,554	$ 19.47
Granted	89,194	10.85
Released	(43,554)	(16.07)
Forfeited	—	—
Outstanding at December 31, 2016	89,194	$ 10.85
Granted	46,914	17.16
Released	(89,194)	(10.85)
Forfeited	—	—
Outstanding at December 31, 2017	46,914	$ 17.16

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NOTES TO CONSOLIDATED FINANCIAL STATEMENTS (Continued)

8. Stock-Based Compensation (Continued)

The following table summarizes the stock-based compensation recorded in the Consolidated Statements of Comprehensive Loss related to stock options and RSUs during the years ended December 31, 2017, 2016 and 2015:

	2017	2016	2015
	(in millions)		
Research and development expenses	$ 6.5	$ 6.2	$ 4.0
General and administrative expenses	11.6	11.8	11.6
Total (1)	$ 18.1	$ 18.0	$ 15.6

(1) Includes $0.0 million, $1.7 million and $2.3 million for the years ended December 31, 2017, 2016 and 2015, respectively, for the remeasurement of certain stock options and RSUs that occurred during May 2013.

9. Income Taxes

The income tax (benefit) provision was $(0.3) million, $0.1 million and $(2.0) million and the effective rates were approximately 0%, 0% and 2% for the years ended December 31, 2017, 2016 and 2015, respectively. The income tax (benefit) for the year ended December 31, 2017 reflects the reversal of the valuation allowance related to alternative minimum tax (AMT) that the Company paid in 2009. As a result of the Tax Act, the Company recorded a noncurrent receivable to reflect the refund due to the Company in future periods relating to the previously paid AMT. In addition, the income tax (benefit) provision for the years ended December 31, 2017 and 2016 reflected current income tax expense recorded as a result of the taxable income in certain of the Company's subsidiaries in Europe. The income tax benefit recorded and the effective tax rates for the year ended December 31, 2015 primarily reflected the reversal of valuation allowances previously recorded against the Company's New Jersey State net operating losses (NOLs) that resulted from the Company's sale of $24.3 million of its New Jersey State NOLs under the State of New Jersey's Technology Business Tax Certificate Transfer Program (the Program) for cash of $2.0 million, respectively, net of commissions. The Program allows qualified technology and biotechnology businesses in New Jersey to sell unused amounts of NOLs and defined research and development tax credits for cash. In 2015, the Company reached the lifetime maximum cap of NOLs that can be sold to the State of New Jersey.

The Company is subject to US federal and state income taxes and the statute of limitations for tax audit is open for the federal tax returns for the years ended 2014 and later, and is generally open for certain states for the years 2013 and later. The Company has incurred net operating losses since inception, except for the year ended December 31, 2009. Such loss carryforwards would be subject to audit in any tax year in which those losses are utilized, notwithstanding the year of origin.

The Company's policy is to recognize interest accrued related to unrecognized tax benefits and penalties in income tax expense. The Company has recorded no such expense. As of December 31, 2017 and 2016, the Company has recorded no reserves for unrecognized income tax benefits, nor has it recorded any accrued interest or penalties related to uncertain tax positions. The Company does not anticipate any material changes in the amount of unrecognized tax positions over the next 12 months.

For the years ended December 31, 2017 and 2016, the Company was also subject to foreign income taxes as a result of legal entities established for activities in Europe. The Company's loss before income taxes in the US and globally was as follows (in thousands):

	Years Ended December 31,		
	2017	2016	2015
US	$ (136,682)	$ (140,354)	$ (100,278)
Foreign	(56,239)	(35,821)	(19,876)
Total	$ (192,921)	$ (176,175)	$ (120,154)

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NOTES TO CONSOLIDATED FINANCIAL STATEMENTS (Continued)

9. Income Taxes (Continued)

The Company's income tax (benefit) provision consisted of the following (in thousands):

	Years Ended December 31,		
	2017	**2016**	**2015**
Current:			
Federal	$ —	$ —	$ —
State	3	3	(2,015)
Foreign	142	95	44
	145	98	(1,971)
Deferred:			
Federal	(417)	—	—
State	—	—	—
Foreign	—	—	—
	(417)	—	—
Total	$ (272)	$ 98	$ (1,971)

The reconciliation between the federal statutory tax rate of 34% and the Company's effective tax rate is as follows:

	Years Ended December 31,		
	2017	**2016**	**2015**
Statutory federal tax rate	34 %	34 %	34 %
Permanent items	(3)%	(3)%	(4)%
State income taxes, net of federal benefit	4 %	4 %	4 %
R&D and other tax credits	8 %	8 %	12 %
Foreign income taxes	(6)%	(4)%	(1)%
Impact of 2017 Tax Act	(49)%	— %	— %
Change in valuation allowance	12 %	(39)%	(43)%
Other	— %	— %	— %
Effective tax rate	— %	— %	2 %

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NOTES TO CONSOLIDATED FINANCIAL STATEMENTS (Continued)

9. Income Taxes (Continued)

Deferred tax assets and liabilities are determined based on the difference between financial statement and tax bases using enacted tax rates in effect for the year in which the differences are expected to reverse. The components of the deferred tax assets and liabilities consist of the following:

	As of December 31,	
	2017	**2016**
Deferred tax assets:		
Net operating loss carryforwards	$ 186,342	$ 228,729
General business credits	66,371	50,648
Product license	7,730	11,783
Alternative minimum tax (AMT) credit	—	418
Other	17,217	16,265
Gross deferred tax assets	$ 277,660	$ 307,843
Deferred tax liabilities:		
In-process research and development	$ (16,360)	$ (23,245)
Deferred tax liabilities	$ (16,360)	$ (23,245)
Net deferred tax assets	$ 261,300	$ 284,598
Valuation allowance	(261,300)	(284,598)
Net deferred tax assets	$ —	$ —

The net deferred tax assets (prior to applying the valuation allowance) of $261.3 million and $284.6 million at December 31, 2017 and 2016, respectively, primarily consist of net operating loss carryforwards for income tax purposes. Due to the Company's history of operating losses, the Company recorded a full valuation allowance on its net deferred tax assets by decreasing the valuation allowance by $23.3 million in 2017 and increasing by $68.4 million in 2016, respectively, as it was more likely than not that such tax benefits will not be realized. As of December 31, 2017, the Company's gross deferred tax assets were also impacted by the Tax Act which required the change to a 21% US tax rate (see below for further discussion on the Tax Act).

At December 31, 2017, the Company had federal net operating loss carryforwards for income tax purposes of approximately $721.8 million. Due to the limitation on NOLs as more fully discussed below, $544.0 million of the NOLs are available to offset future taxable income, if any. The NOL carryovers and general business tax credits expire in various years beginning in 2018. For state tax purposes, the Company has approximately $296.0 million of New Jersey NOLs available to offset against future taxable income. The Company also has California and Virginia NOLs that are entirely limited due to Section 382 (as discussed below), in addition to changing state apportionment allocations, as the Company is now 100% resident in New Jersey.

During 2014, the Company completed an Internal Revenue Code Section 382 (Section 382) analysis in order to determine the amount of losses that are currently available for potential offset against future taxable income, if any. It was determined that the utilization of the Company's NOL and general business tax credit carryforwards generated in tax periods up to and including December 2010 were subject to substantial limitations under Section 382 due to ownership changes that occurred at various points from the Company's original organization through December 2010. In general, an ownership change, as defined by Section 382, results from transactions increasing the ownership of shareholders that own, directly or indirectly, 5% or more of a corporation's stock, in the stock of a corporation by more than 50 percentage points over a testing period (usually 3 years). Since the Company's formation, it has raised capital through the issuance of common stock on several occasions which, combined with the purchasing shareholders' subsequent disposition of those shares, resulted in multiple changes in ownership, as defined by Section 382 since the Company's formation in 1999. These ownership changes resulted in substantial limitations on the use of the Company's NOLs and general business tax credit carryforwards up to and including December 2010. The Company continues to track all of its NOLs and tax credit carryforwards but has provided a full valuation allowance to offset those amounts.

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NOTES TO CONSOLIDATED FINANCIAL STATEMENTS (Continued)

9. Income Taxes (Continued)

On December 22, 2017, the US government enacted the Tax Act. The Tax Act significantly revises US tax law by, among other provisions, lowering the US federal statutory income tax rate from 35% to 21%, imposing a mandatory one-time transition tax on previously deferred foreign earnings, and eliminating or reducing certain income tax deductions.

The Tax Act

ASC 740, *Income Taxes* requires the effects of changes in tax laws to be recognized in the period in which the legislation is enacted. However, due to the complexity and significance of the Tax Act's provisions, the SEC staff issued SAB 118, which allows companies to record the tax effects of the Tax Act on a provisional basis based on a reasonable estimate, and then, if necessary, subsequently adjust such amounts during a limited measurement period as more information becomes available. The measurement period ends when a company has obtained, prepared, and analyzed the information necessary to finalize its accounting, but cannot extend beyond one year from enactment.

The Tax Act did not have a material impact on the Company's financial statements because its deferred temporary differences are fully offset by a valuation allowance and the Company does not have any significant offshore earnings from which to record the mandatory transition tax. However, given the significant complexity of the Tax Act, anticipated guidance from the US Treasury about implementing the Tax Act, and the potential for additional guidance from the SEC or the FASB related to the Tax Act, these estimates may be adjusted during the measurement period. The provisional amounts disclosed in our footnotes were based on the Company's present interpretations of the Tax Act and current available information, including assumptions and expectations about future events, such as its projected financial performance, and are subject to further refinement as additional information becomes available (including the Company's actual full year 2018 results of operations, as well as potential new or interpretative guidance issued by the FASB or the Internal Revenue Service and other tax agencies) and further analyses are completed. The Company continues to analyze the changes in certain income tax deductions, assess calculations of earnings and profits in certain foreign subsidiaries, including if those earnings are held in cash or other assets, and gather additional data to compute the full impacts on the Company's deferred and current tax assets and liabilities.

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NOTES TO CONSOLIDATED FINANCIAL STATEMENTS (Continued)

10. License and Other Agreements

In-License Agreements

PARI Pharma GmbH—In April 2008, the Company entered into a licensing agreement with PARI Pharma GmbH (PARI) for use of the optimized eFlow Nebulizer System for delivery of ALIS in treating patients with NTM lung infections, CF and bronchiectasis. Under the licensing agreement, the Company has rights under several US and foreign issued patents and patent applications involving improvements to the optimized eFlow Nebulizer System, to exploit such system with ALIS for the treatment of such indications, but the Company cannot manufacture such nebulizers except as permitted under the Commercialization Agreement with PARI. Under the licensing agreement, the Company paid PARI an upfront license fee and PARI is entitled to receive milestone payments up to an aggregate of €4.3 million either in cash, qualified stock or a combination of both, at PARI's discretion, based on achievement of certain future milestone events including first acceptance of MAA submission (or equivalent) in the US of ALIS and the device, first receipt of marketing approval in the US for ALIS and the device, and first receipt of marketing approval in a major EU country for ALIS and the device. In addition, PARI is entitled to receive royalty payments in the mid-single digits on the annual global net sales of ALIS, pursuant to the licensing agreement, subject to certain specified annual minimum royalties. In October 2017, the Company exercised an option to buy-down the future royalties that will be payable to PARI on ALIS net sales, if approved. The royalty buy-down will reduce the Company's future royalty payments due to PARI. The payment to PARI was included as a component of general and administrative expenses in the fourth quarter of 2017. See below for information related to the commercialization agreement with PARI.

Other Agreements

Cystic Fibrosis Foundation Therapeutics, Inc.—In 2004 and 2009, the Company entered into research funding agreements with Cystic Fibrosis Foundation Therapeutics, Inc. (CFFT) whereby it received $1.7 million and $2.2 million for each respective agreement in research funding for the development of ALIS. If ALIS becomes an approved product for CF in the US, the Company will owe a payment to CFFT of up to $13.4 million that is payable over a three-year period after approval as a commercialized drug in the US. Furthermore, if certain global sales milestones are met within five years of the drug's commercialization, the Company would owe an additional payment of $3.9 million. Since there is significant development and regulatory risk associated with ALIS, including with respect to the CF indication, the Company has not accrued these obligations.

Therapure Biopharma Inc.—In February 2014, the Company entered into a contract manufacturing agreement with Therapure Biopharma Inc. (Therapure) for the manufacture of ALIS at a 200 kg scale. Pursuant to the agreement, the Company and Therapure collaborated to construct a production area for the manufacture of ALIS in Therapure's existing manufacturing facility in Canada. Therapure manufactures ALIS for the Company on a non-exclusive basis. The agreement has an initial term of five years from the first date on which Therapure delivers ALIS to the Company after it obtains permits related to the manufacture of ALIS, and will renew automatically for successive periods of two years each, unless terminated by either party by providing the required two years' prior written notice to the other party. Notwithstanding the foregoing, the parties have rights and obligations under the agreement prior to the commencement of the initial term. Under the agreement, the Company is obligated to pay certain minimum amounts for the batches of ALIS produced each calendar year. Costs incurred under this agreement will be recorded as a component of research and development expense until such time as the Company receives regulatory approvals for ALIS.

PARI Pharma GmbH—In July 2014, the Company entered into a Commercialization Agreement with PARI for the manufacture and supply of eFlow nebulizer systems and related accessories (the Device) as optimized for use with ALIS. Under the Commercialization Agreement, PARI manufactures the Device except in the case of certain defined supply failures, when the Company will have the right to make the Device and have it made by third parties (but not certain third parties deemed under the Commercialization Agreement to compete with PARI). The Commercialization Agreement has an initial term of fifteen years from the first commercial sale of ALIS pursuant to the licensing agreement (the Initial Term). The term of the agreement may be extended by the Company for an additional five years by providing written notice to PARI at least one year prior to the expiration of the Initial Term. Notwithstanding the foregoing, the parties have certain rights and obligations under the agreement prior to the commencement of the Initial Term.

SynteractHCR, Inc.—In December 2014, the Company entered into a services agreement with SynteractHCR, Inc. (Synteract) pursuant to which the Company retained Synteract to perform implementation and management services in connection with the 212 study. The Company anticipates that aggregate costs relating to all work orders for the 212 study will

INSMED INCORPORATED

NOTES TO CONSOLIDATED FINANCIAL STATEMENTS (Continued)

10. License and Other Agreements (Continued)

be approximately $45 million over the period of the study. In April 2015, the Company entered into a work order with Synteract to perform implementation and management services for the 312 study. The Company anticipates that aggregate costs relating to all work orders for the 312 study will be approximately $25 million over the period of the study.

Ajinomoto Althea, Inc.—In September 2015, the Company entered into a Commercial Fill/Finish Services Agreement (the Fill/Finish Agreement) with Ajinomoto Althea, Inc., a Delaware corporation (Althea), for Althea to produce, on a non-exclusive basis, ALIS in finished dosage form at a 50 kg scale. Under the Fill/Finish Agreement, the Company is obligated to pay a minimum of $2.7 million for the batches of ALIS produced by Althea each calendar year during the term of the Fill/Finish Agreement. The Fill/Finish Agreement became effective as of January 1, 2015, and had an initial term that was to end on December 31, 2017. In 2016, the Company signed an extension of the Fill/Finish Agreement through December 31, 2019, and it may be extended for additional two year periods upon mutual written agreement of the Company and Althea at least one year prior to the expiration of its then-current term. The Company has expensed at least the required minimum in each year of the contract.

AstraZeneca—In October 2016, the Company entered into a license agreement (AZ License Agreement) with AstraZeneca AB, a Swedish corporation (AstraZeneca). Pursuant to the terms of the AZ License Agreement, AstraZeneca granted the Company exclusive global rights for the purpose of developing and commercializing AZD7986 (renamed INS 1007). In consideration of the licenses and other rights granted by AstraZeneca, the Company made an upfront payment of $30.0 million, which was included as research and development expense in the fourth quarter of 2016. The Company is also obligated to make a series of contingent milestone payments totaling up to an additional $85.0 million upon the achievement of clinical development and regulatory filing milestones. If the Company elects to develop INS1007 for a second indication, the Company will be obligated to make an additional series of contingent milestone payments to AstraZeneca totaling up to $42.5 million. The Company is not obligated to make any additional milestone payments for additional indications. In addition, the Company will pay AstraZeneca tiered royalties ranging from a high single-digit to mid-teen on net sales of any approved product based on INS1007 and one additional payment of $35.0 million upon the first achievement of $1.0 billion in annual net sales. The AZ License Agreement provides AstraZeneca with the option to negotiate a future agreement with the Company for commercialization of INS1007 in chronic obstructive pulmonary disease or asthma.

Patheon UK Limited—In October 2017, the Company entered into certain agreements with Patheon UK Limited (Patheon) related to increasing its long-term production capacity for ALIS commercial inventory. The agreements provide for Patheon to manufacture and supply ALIS for its anticipated commercial needs. Under these agreements, the Company is required to deliver to Patheon the required raw materials, including active pharmaceutical ingredients, and certain fixed assets needed to manufacture ALIS. Patheon's supply obligations will commence once certain technology transfer and construction services are completed. The Company's manufacturing and supply agreement with Patheon will remain in effect for a fixed initial term, after which it will continue for successive renewal terms unless either we or Patheon have given written notice of termination. The technology transfer agreement will expire when the parties agree that the technology transfer services have been completed. The agreements may also be terminated under certain other circumstances, including by either party due to a material uncured breach of the other party or the other party's insolvency. These early termination clauses may reduce the amounts due to the relevant parties. The investment in our long-term production capacity build-out, including under the Patheon agreements and related agreements or purchase orders with third parties for raw materials and fixed assets, is estimated to be approximately $60.0 million and will be incurred over the next three to four years.

11. Commitments and Contingencies

Commitments

The Company has an operating lease for office and laboratory space located in Bridgewater, NJ for which the initial lease term expires in November 2019. Future minimum rental payments under this lease are $2.0 million. In July 2016, the Company signed an operating lease for additional laboratory space located in Bridgewater, NJ for which the initial lease term expires in September 2021. Future minimum rental payments under this lease are $1.9 million.

Rent expense charged to operations was $1.5 million, $1.2 million, and $0.8 million for the years ended December 31, 2017, 2016 and 2015, respectively. Rent expense is recorded on a straight-line basis over the term of the

INSMED INCORPORATED

NOTES TO CONSOLIDATED FINANCIAL STATEMENTS (Continued)

11. Commitments and Contingencies (Continued)

applicable leases. Future minimum rental cash payments required under the Company's operating leases as of December 31, 2017 are as follows (in thousands):

Year Ending on December 31:		
2018	$	1,521
2019		1,421
2020		477
2021		498
2022		—
	$	3,917

Legal Proceedings

On July 15, 2016, a lawsuit captioned Hoey v. Insmed Incorporated, et al, No. 3:16-cv-04323-FLW-TJB (D.N.J. July 15, 2016) was filed in the US District Court for the District of New Jersey on behalf of a putative class of investors who purchased the Company's common stock from March 18, 2013 through June 8, 2016. The complaint alleged that the Company and certain of its executives violated Sections 10(b) and 20(a) of the Securities Exchange Act of 1934 (Exchange Act) by misrepresenting and/or omitting the likelihood of the European Medicines Agency (EMA) approving the Company's European marketing authorization application (MAA) for use of ALIS in the treatment of NTM lung disease and the likelihood of commercialization of ALIS in Europe.

On October 25, 2016, the Court issued an order appointing Bucks County Employees Retirement Fund as lead plaintiff for the putative class. On December 15, 2016, the lead plaintiff filed an amended complaint that shortens the putative class period for the Exchange Act claims to March 26, 2014 through June 8, 2016 and adds claims under Sections 11, 12, and 15 of the Securities Act of 1933 (Securities Act) on behalf of a putative class of investors who purchased common stock in or traceable to the Company's March 31, 2015 public offering. The amended complaint names as defendants in the Securities Act claims the Company, certain directors and officers, and the investment banks who served as underwriters in connection with the secondary offering. The amended complaint alleges defendants violated the Securities Act by using a purportedly misleading definition of "culture conversion" and supposedly failing to disclose in the offering materials purported flaws in its Phase 2 study that made the secondary offering risky or speculative. The amended complaint seeks damages in an unspecified amount. The Company moved to dismiss the amended complaint on March 1, 2017. The lead plaintiff opposed the motion on May 17, 2017 and the Company provided its reply brief on July 11, 2017. On July 20, 2017, the plaintiff asked for leave to file a sur-reply in further opposition to the Company's motion to dismiss the amended complaint, which the Company had opposed.

On February 15, 2018, the Court issued a decision granting the Company's motion and dismissing the amended complaint without prejudice. The lead plaintiff has until March 19, 2018 to file a second amended complaint. If a second amended complaint is filed, the Company intends to continue to defend the lawsuit vigorously; however, there can be no assurance regarding the ultimate outcome of the lawsuit.

From time to time, the Company is a party to various other lawsuits, claims and other legal proceedings that arise in the ordinary course of business. While the outcomes of these matters are uncertain, management does not expect that the ultimate costs to resolve these matters will have a material adverse effect on the Company's consolidated financial position, results of operations or cash flows.

12. Quarterly Financial Data (Unaudited)

The following table summarizes unaudited quarterly financial data for the years ended December 31, 2017 and 2016 (in thousands, except per share data).

INSMED INCORPORATED

NOTES TO CONSOLIDATED FINANCIAL STATEMENTS (Continued)

	2017				
	First Quarter	Second Quarter	Third Quarter	Fourth Quarter*	Total*
Revenues	$ —	$ —	$ —	$ —	$ —
Operating loss	$ (35,969)	$ (43,515)	$ (44,083)	$ (65,353)	$ (188,920)
Net loss	$ (37,414)	$ (44,672)	$ (45,179)	$ (65,384)	$ (192,649)
Basic and diluted net loss per share	$ (0.60)	$ (0.72)	$ (0.69)	$ (0.85)	$ (2.89)

	2016				
	First Quarter	Second Quarter	Third Quarter	Fourth Quarter**	Total**
Revenues	$ —	$ —	$ —	$ —	$ —
Operating loss	$ (33,067)	$ (36,133)	$ (37,149)	$ (67,051)	$ (173,400)
Net loss	$ (33,532)	$ (36,579)	$ (37,760)	$ (68,402)	$ (176,273)
Basic and diluted net loss per share	$ (0.54)	$ (0.59)	$ (0.61)	$ (1.10)	$ (2.85)

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* Includes a one-time payment in October 2017 related to the buy-down of future royalties payable to PARI on the global net sales of ALIS, if approved.

** Includes a $30.0 million upfront payment to AstraZeneca under the AZ License Agreement related to INS1007, which was included as a component of research and development expense.

Basic and diluted net loss per share amounts included in the above table were computed independently for each of the quarters presented. Accordingly, the sum of the quarterly basic and diluted net loss per share amounts may not agree to the total for the year.

13. Retirement Plan

The Company has a 401(k) defined contribution plan for the benefit for all US employees and permits voluntary contributions by employees subject to IRS-imposed limitations. Beginning in April 2015, the Company matched 100% of eligible employee contributions on the first 3% of employee salary (up to the IRS maximum). Employer contributions for the year ended December 31, 2017, 2016 and 2015 were $0.8 million, $0.6 million and $0.4 million, respectively. Effective January 1, 2018, the Company is matching 100% of eligible employee contributions on the first 4% of employee salary (up to the IRS maximum).

14. Subsequent Event

In January 2018, the Company completed an underwritten public offering of 1.75% convertible senior notes due 2025 (the Convertible Notes) pursuant to an indenture dated as of January 26, 2018, between the Company and Wells Fargo Bank, National Association (Wells Fargo), as trustee, as supplemented by the first supplemental indenture, dated January 26, 2018 between the Company and Wells Fargo (as supplemented, the Indenture). The Company sold $450.0 million aggregate principal amount of Convertible Notes, including the exercise in full of the underwriters' option to purchase additional Convertible Notes of $50.0 million. The Company's net proceeds from the offering, after deducting underwriting discounts and commissions and other offering expenses of $14.2 million, were approximately $435.8 million. The Company is currently evaluating the accounting for the debt and equity components of the offering.

The Convertible Notes bear interest payable semiannually in arrears on January 15 and July 15 of each year, beginning on July 15, 2018. The Convertible Notes mature on January 15, 2025, unless earlier converted, redeemed, or repurchased. The Convertible Notes are convertible into common shares of the Company under certain circumstances described in the Indenture. The initial conversion rate is 25.5384 shares of common stock per $1,000 principal amount of Convertible Notes (equivalent to an initial conversion price of approximately $39.16 per share of common stock). The conversion rate will be subject to adjustment in some events but will not be adjusted for any accrued and unpaid interest.

Confidential

EXHIBIT 10.39

CONFIDENTIAL TREATMENT HAS BEEN REQUESTED AS TO CERTAIN PORTIONS OF THIS DOCUMENT. EACH SUCH PORTION, WHICH HAS BEEN OMITTED HEREIN AND REPLACED WITH ASTERISKS (***), HAS BEEN FILED SEPARATELY WITH THE SECURITIES AND EXCHANGE COMMISSION.

MANUFACTURING AND SUPPLY AGREEMENT

MANUFACTURING AND SUPPLY AGREEMENT

This **MANUFACTURING AND SUPPLY AGREEMENT** (this "Agreement") dated as of 20 October 2017 (the "Effective Date") is made by and between Insmed Incorporated, a Virginia corporation having its principal place of business at 10 Finderne Avenue, Building 10, Bridgewater, New Jersey 08807, USA (" Client"), and Patheon UK Limited, a company incorporated in England and Wales having its principal place of business at Kingfisher Drive, Covingham, Swindon, SN35BZ, United Kingdom ("Patheon"). Client and Patheon are sometimes referred to herein individually as a "Party" and collectively as the "Parties."

RECITALS

WHEREAS, Client has a commercial interest in the manufacture and commercialization of Amikacin Liposome Inhalation Suspension (ARIKAYCE®), a sterile, aqueous liposomal suspension designed for oral inhalation via nebulization which is manufactured using the Client Manufacturing Process (the "Product");

WHEREAS, Patheon has expertise and experience in manufacturing and packaging sterile pharmaceutical products and is interested in providing manufacturing services to Client in connection with the Product;

WHEREAS, in anticipation of this Agreement and the services that Patheon will supply hereunder, the Parties are executing an agreement pursuant to which Patheon would undertake certain technology transfer and construction services in order to validate Client's technology package and prepare Patheon's facilities for the manufacture of the Product; and

NOW, THEREFORE, in consideration of the foregoing, the mutual promises and covenants of the Parties contained herein and other good and valuable consideration, the receipt and sufficiency of which are hereby acknowledged, the Parties hereto, intending to be legally bound, do hereby agree as follows:

ARTICLE I. DEFINITIONS

The following terms shall have the meanings set forth below. Unless the context indicates otherwise, the singular shall include the plural and the plural shall include the singular.

"Additional Services" means any services requested and approved by Client that supplement Patheon's regular performance of the Manufacturing Services pursuant to this Agreement or that supplement Patheon's regular performance of the Transfer Services pursuant to the Technology Transfer Agreement, as applicable, as described in Schedule B.

"Affiliate" means, with respect to any Person, any other Person that directly, or indirectly through one or more intermediaries, controls, is controlled by, or is under common control with, such Person. For the purposes of this definition only, a Person will be regarded as in control of another Person if such Person owns, or directly or indirectly controls, more than 50% of the voting securities (or comparable equity interests) or other ownership interests

of the other Person, or if such Person directly or indirectly possesses the power to direct or cause the direction of the management or policies of the other Person, whether through the ownership of voting securities, by contract, or any other means whatsoever.

"Agreed Delivery Date" has the meaning set forth in Section 2.3(f).

"Agreement" has the meaning set forth in the Preamble hereto.

"API" means the active pharmaceutical ingredient amikacin sulfate.

"Applicable Law" means applicable United States and foreign federal, state, and local laws, orders, rules, regulations, guidelines, standards, customs and ordinances, including, without limitation, those (to the extent they are applicable) of the FDA and comparable foreign Regulatory Authorities, including the FDA Act.

"Base Fee" means the monthly fee paid by Client, as more specifically set forth in Schedule B. For the avoidance of doubt, Base Fees do not include Technology Transfer Fees or Capital Expenditures (both as defined in the Technology Transfer Agreement), Product Fees, Material Costs, Maintenance Costs, Disposal Costs or charges for Bill Back Items or Additional Services.

"Basic Engineering Design" means the basic engineering design to be conducted by Patheon as described in the Letter Agreement entered into by the Parties dated 16 June 2017.

"Bill Back Items" means the items and services set forth in Schedule B or other project-specific items that are used or necessary in connection with the Manufacture of the Products and that are not included as Materials.

"Certificate of Analysis" means a certificate evidencing the analytical tests conducted on a specific batch of Product or Material and setting forth, *inter alia*, the items tested, specifications, and test results.

"Certificate of Compliance" means a certificate stating that a specific batch of Product has been Manufactured in compliance with GMP and the Specifications.

"Claim" has the meaning set forth in Section 9.3(a).

"Client" has the meaning set forth in the Preamble hereto.

"Client Indemnified Parties" has the meaning set forth in Section 9.2.

"Client Manufacturing Equipment" means process equipment necessary to Manufacture the bulk Product that consists of equipment for the bulk Manufacturing, vial preparation, fill/finish, and in-process control testing of the Product and its intermediates as more fully set forth in Exhibit F of the Technology Transfer Agreement.

"Client Manufacturing Process" means the proprietary process owned or Controlled by Client for Manufacturing the Product, as disclosed by Client to Patheon, and each intermediate of the Product, as established as of the Effective Date, including without limitation, as set forth in the investigational new drug application filed with the FDA, and, when applicable, as set forth in the NDA as may be filed with, and approved by, the FDA.

"Client Manufacturing Process Improvements" has the meaning set forth in Section 5.1(e)(i).

"Client On Site Representative" has the meaning set forth in Section 3.5(a).

"Client Product Improvements" has the meaning set forth in Section 5.1(e)(i).

"Client Specification Improvements" has the meaning set forth in Section 5.1(e)(i).

"Client-Supplied Materials" has the meaning set forth in Section 2.2(a).

"Commercially Reasonable Efforts" means, with respect to the efforts to be expended by a Party to achieve any objective, the reasonable, diligent efforts to accomplish such objective as a similarly situated party (with respect to size, resources and assets) in the pharmaceutical industry would normally use to accomplish a similar objective in its own interests under similar circumstances.

"Confidentiality Agreement" has the meaning set forth in Section 7.1.

"Confidential Information" has the meaning set out in the Confidentiality Agreement.

"Control" or "Controlled" means ownership or the right by a Party to assign or grant a license or sublicense under Intellectual Property rights to the other Party of the scope set forth herein, without breaching the terms of any agreement with a Third Party.

"Deficiency Notice" has the meaning set forth in Section 2.8(b).

"Discretionary Manufacturing Changes" has the meaning set forth in Section 2.10(b)(ii).

"Disposal Costs" means the cost charged by a Third Party for disposal of waste from the Manufacture of the Product plus an [***]% handling fee.

"Effective Date" has the meaning set forth in the Preamble hereto

"EMA" means the European Medicines Agency.

"Equipment" means any equipment used in the Manufacture of the Product as more fully set forth in Exhibit F of the Technology Transfer Agreement.

"Existing Client Intellectual Property" has the meaning set forth in Section 5.1(a).

"Existing Patheon Intellectual Property" has the meaning set forth in Section 5.1(b).

"Expected Yield" has the meaning set forth in Section 2.9(a).

"Expert" has the meaning set forth in Section 2.8(d)(vi).

"Exploit" means to make, have made, import, use, sell, offer for sale, receive or otherwise dispose of a product or process, including the research, development (including the conduct of clinical trials), registration, modification, enhancement, improvement, Manufacture, storage, formulation, optimization, export, transport, distribution, promotion, or marketing of a product or process.

"Facility" means the facility of Patheon located at Kingfisher Drive, Swindon, Wiltshire SN3 5BZ, United Kingdom, or such other facility approved in accordance with Section 3.4(a).

"FDA" means the United States Food and Drug Administration and any successor organization thereto and all agencies under its direct control.

"FDA Act" means the US Federal Food, Drug, and Cosmetic Act, as amended.

"FDA Approval Date" means the date of receipt by Client of Regulatory Approval in the United States for Products Manufactured at the Manufacturing Suite.

"Filing Party" has the meaning set forth in Section 3.17(d).

"Final Filing" has the meaning set forth in Section 3.17(g).

"Forecast" has the meaning set forth in Section 2.3(a).

"GMP" means the current good manufacturing practices applicable from time to time to the Manufacturing of the Product, or any intermediate of the Product, pursuant to Applicable Law, including those promulgated under the FDA Act at 21 C.F.R. (Parts 210 and 211 and Part 4 as relevant for combination products), and those promulgated under Directive 2001/83/EC (as amended by Directive 2004/27/EC), Directive 2003/94/EC and EudraLex - Volume 4 of the Rules Governing Medicinal Products in the European Union entitled "EU Guidelines to Good Manufacturing Practice Medicinal Products for Human and Veterinary Use", together with the latest FDA, EMA and European Commission guidance documents pertaining to manufacturing and quality control practice, all as updated, amended and revised from time to time. Guidance in draft status will be considered as in effect for the purposes of this definition if this guidance has been adopted by Patheon at the Facility in relation to all its other clients and included as part of Patheon's Standard Operating Procedures or if it is agreed to be adopted by the Commercial Steering Committee.

"Indemnified Party" has the meaning set forth in Section 9.3(a).

"Indemnifying Party" has the meaning set forth in Section 9.3(a).

"Initial Draft" has the meaning set forth in Section 3.17(e).

"Initial Term" has the meaning set forth in Section 8.1.

"Intellectual Property" includes, without limitation, rights in patents, patent applications, formulae, trademarks, trademark applications, trade-names, Inventions, copyrights, designs, trade secrets, databases and rights in know how (whether or not any of these is registered or capable of registration and including applications for registration of any such thing) and all other similar rights or forms of protection of a similar nature or having equivalent or similar effect to any of these which may subsist anywhere in the world.

"Invention" means information about any innovation, improvement, development, discovery, computer program, device, trade secret, method, know-how, process, technique or the like, whether or not written or otherwise fixed in any form or medium, regardless of the media on which it is contained and whether or not patentable or copyrightable.

"Loss" means any claims, lawsuits, losses, damages, liabilities, penalties, costs, and expenses (including reasonable attorneys' fees and disbursements).

"Maintenance" means the maintenance of Equipment and the Facility in satisfactory operating condition, including the performance of systematic inspection and service of Equipment pursuant to the applicable Standard Operating Procedures of Patheon, as reviewed and agreed to by Client (the "Equipment Standard Operating Procedures"), or the manufacturer's terms of operation and recommended procedures.

"Maintenance Costs" means the cost charged by a Third Party for (a) routine Maintenance; or (b) revalidation of the Equipment, plus an [***]% handling fee.

"Make Good Costs" has the meaning set forth in Section 8.3(d).

"Manufacture" and "Manufacturing Services" means the manufacture of the Products, including without limitation the planning, purchasing and receipt of Patheon-Supplied Materials, planning (based on the Forecast), receipt of Client-Supplied Materials and the manufacturing, processing, formulating, filling, bulk packaging, bulk labelling, storage, handling, quality release of Products (Certificate of Compliance), together with all agreed sample retention, stability testing, quality control and assurance and waste disposal.

"Manufacturing Services Termination Costs" has the meaning set forth in Section 8.3(e).

"Manufacturing Suite" means the manufacturing suite at the Facility, whose footprint was determined pursuant to the Technology Transfer Agreement.

"Marketing Authorization" means an approved New Drug Application as defined in the FDA Act and the regulations promulgated thereunder, or any corresponding foreign application, registration, or certification, necessary or reasonably useful to market any Product in a country or regulatory jurisdiction other than the United States, including applicable pricing and reimbursement approvals, and all supplements and amendments thereto.

"Material Costs" has the meaning set forth in Section 2.2(b).

"Materials" means all API, excipients and processing aids, and processing, filling and packaging components listed in Schedule C, as amended from time to time by agreement in writing.

"NDA" means the US new drug application for a product, including the Product, requesting permission to place a drug on the market in accordance with 21 C.F.R. Part 314, and all supplements (SNDA) filed pursuant to the requirements of the FDA, including all documents, data, and other information filed concerning such product that are necessary for FDA approval to market such product in the Territory.

"Non-Conforming Product" means (a) a batch of Product that fails, or is aborted during processing; or (b) a Product Manufactured by Patheon that fails to [***].

"Non-Filing Party" has the meaning set forth in Section 3.17(d).

"Party" and "Parties" have the meanings set forth in the Preamble hereto.

"Patheon" has the meaning set forth in the Preamble hereto.

"Patheon Indemnified Parties" has the meaning set forth in Section 9.1.

"Patheon Independent Manufacturing Equipment Improvements" has the meaning set forth in Section 5.1(f)(i).

"Patheon Manufacturing Equipment" means any equipment, other than the Client Manufacturing Equipment, necessary to Manufacture the Product including as more fully set forth in Exhibit F of the Technology Transfer Agreement, waste handling systems and all building infrastructure and any and all improvements or additions made thereto, as approved in writing by Client.

"Patheon Nonconformance" has the meaning set forth in Section 2.8(d)(i).

"Patheon-Supplied Materials" has the meaning set forth in Section 2.2(a).

*** Certain information on this page has been omitted and filed separately with the Securities and Exchange Commission. Confidential treatment has been requested with respect to the omitted portions.

"Person" means an individual, sole proprietorship, partnership, limited partnership, limited liability partnership, corporation, limited liability company, business trust, joint stock company, trust, unincorporated association, joint venture, or other similar entity or organization, including a government or political subdivision, department, or agency of a government.

"Product" has the meaning set forth in the Recitals hereto in finished, bulk-packaged form according to the Specifications as described in Schedule A, as the same may be amended from time to time.

"Product Fee" has the meaning set forth in Section 2.4.

"Project Manager" and "Project Managers" have the meaning set forth in Section 3.5(b).

"Purchase Order" means a written purchase order that sets forth (a) the quantities of each presentation of Product to be delivered by Patheon to Client, (b) the requested delivery dates therefor, and (c) the bulk packaging to be used for such Product.

"Quality Agreement" has the meaning set forth in Section 3.1.

"Regulatory Approval" means any and all approvals (including pricing and reimbursement approvals), licenses, registrations, or authorizations of any Regulatory Authority necessary to Exploit the Product in any country in the Territory, including any approval of a Product, Marketing Authorization and supplements and amendments thereto.

"Regulatory Authority" means any applicable supra-national, federal, national, regional, state, provincial, or local regulatory agencies, departments, bureaus, commissions, councils, or other government entities regulating or otherwise exercising authority with respect to the Exploitation of a Product in the Territory.

"Regulatory Filings" has the meaning set forth in Section 3.17.

"Regulatory Obligations" has the meaning set forth in Section 3.17.

"Remediation Period" has the meaning set forth in Section 8.2(a)(vii).

"Reports" has the meaning set forth in Section 3.13.

"Required Manufacturing Changes" has the meaning set forth in Section 2.10(b)(i).

"Shipment Costs" has the meaning set forth in Section 2.8(d)(ii).

"Specifications" means the specifications for each presentation of Product (*i.e.*, the dosage forms in Schedule A) given by Client to Patheon relating to the specifications of the Materials; the manufacturing specifications, directions and processes; the storage requirements; all environmental, health and safety information for the Product including material safety data sheets and the finished Product specifications, specifications for bulk

and primary packaging and shipping requirements for the Product, as amended, modified, or supplemented from time to time.

"Technology Transfer Agreement" means the agreement executed on the date hereof between Client and Patheon in order for Patheon to be able to Manufacture the Products, as described in more detail in the third Recital.

"Term" has the meaning set forth in Section 8.1.

"Territory" means the United States and other territories agreed by the Parties pursuant to Section 2.2(t) from time to time.

"Third Party" means a Person who is neither a Party nor an Affiliate of a Party.

"Third Party Losses" means Losses incurred as a result of claims brought by Third Parties.

"Third Party Subcontractors" has the meaning set forth in Section 3.16.

ARTICLE II. MANUFACTURING SERVICES

2.1 Supply Obligations.

(a) Subject to the completion of the technology transfer and construction services under the Technology Transfer Agreement to validate Client's technology package and prepare Patheon's facilities for the manufacture of the Product, and the terms and conditions hereof, and in consideration for the payments set forth in Schedule B, Client appoints Patheon as a non-exclusive supplier of the Products and Patheon shall provide the Manufacturing Services and shall supply the Product to Client.

(b) Pursuant to the Technology Transfer Agreement, Client will develop and Patheon will confirm the Client Manufacturing Process. The Client Manufacturing Process is the Confidential Information of Client, subject to the terms of the Confidentiality Agreement, and accordingly Patheon may not allow Third Parties (other than relevant Regulatory Authorities or Third Party Subcontractors) to access the Manufacturing Suite or view documentation so describing the Manufacturing Process without Client's prior written consent, provided that third parties may view the filling line from outside the room in which it is housed.

(c) Patheon shall Manufacture all Products delivered hereunder:

(i) at the Manufacturing Suite;

(ii) in accordance with the Specifications, this Agreement and the Quality Agreement; and

(iii) in compliance with GMP and Applicable Laws.

(d) Patheon shall ensure that sufficient numbers of adequately educated and experienced staff are retained at the Facility in order to Manufacture the volumes of Product set out in the Forecast. Patheon shall perform all activities necessary to maintain a GMP compliant status of the manufacturing lines and areas of the Facility applicable to the Manufacture of the Product.

2.2 Materials, Bill Back Items and Additional Services.

(a) All Materials necessary for the Manufacture of the Product are set forth in Schedule C. Materials that will be purchased by Client and shipped to Patheon ("Client-Supplied Materials") are listed in Part A of Schedule C. Materials that will be purchased by Patheon ("Patheon-Supplied Materials") are listed in Part B of Schedule C.

(b) Patheon-Supplied Materials will be invoiced to Client [***] at the time of purchase by Patheon at cost plus an [***]% handling fee, in accordance with the invoicing procedure set forth in Article IV ("Material Costs"). Patheon shall obtain the prior written approval of Client on the cost of such Patheon-Supplied Materials if the cost of any individual item of Patheon-Supplied Material increases by more than (i) [***]%; or (ii) £[***], whichever is the lower. Where Client nominates a particular supplier to supply certain Patheon-Supplied Materials, Patheon shall purchase those Materials from that supplier subject to Section 2.2(d). All purchases of Patheon-Supplied Materials by Patheon shall be made on Patheon's own behalf and not as an agent for Client.

(c) Patheon shall store, handle, and protect the Materials with a reasonable level of care, which shall include taking all reasonable precautions to ensure that the Materials are not subject to contamination, deterioration, destruction, or theft. Patheon shall keep adequate records of its usage of the Materials during the Term.

(d) Client acknowledges that Patheon is required under GMP to follow certain verification and approval processes for all vendors used by Patheon in the procurement of Materials. In the event that Client requests Patheon to procure Materials from a vendor that is not currently verified by Patheon, Client will be liable for Patheon's fees for the performance of any auditing and verification activities by Patheon under this Section 2.2(d) as an Additional Service. Client will be responsible for validation of suppliers of Client-Supplied Materials unless otherwise agreed. Patheon will be responsible for validation of suppliers of Patheon-Supplied Materials. Any changes to a supplier of Materials proposed by either Party shall be subject to the change control procedure set out in Section 2.10(b) and may not be used until, as applicable, submission has been filed to necessary health authorities and where appropriate approvals obtained.

(e) Patheon shall be responsible for ordering and paying for the relevant quantities of Patheon-Supplied Materials necessary for the Manufacture of Products on such terms and conditions as Patheon may agree with relevant suppliers.

(f) The Commercial Steering Committee shall discuss and agree the process by which Patheon shall order from Client the relevant quantities of Client-Supplied Materials necessary for the Manufacture of Products during the Term. Client will keep Patheon informed of the standard lead time for and cost of Client-Supplied Materials and shall supply such Client-Supplied Materials free of charge on a consignment basis in response to orders placed by Patheon under this Agreement.

(g) Client will at its sole cost and expense, deliver Client-Supplied Materials to the Facility DDP (Incoterms 2010) at no cost to Patheon (with any VAT paid by Client) in the quantities and on the dates agreed with Patheon in response to orders placed pursuant to the process agreed under Section 2.2(f). If the Client-Supplied Materials are not received on the agreed date, Patheon may delay the Manufacture of Product for a period of time proportionate to such delay.

(h) All shipments of Client-Supplied Materials, if required, will be accompanied by Certificate(s) of Analysis from the Material manufacturer or Client confirming its compliance with the Material's specifications, together with all required documentation as specified in the Quality Agreement. Client or Client's designee will be the "Importer of Record" for Client-Supplied Materials imported to the Facility. Client-Supplied Materials will be held by Patheon on behalf of Client as set forth in this Agreement.

(i) Title to Client-Supplied Materials will at all times remain the property of Client. Risk in the Client-Supplied Materials shall remain with Patheon at all times from the point when the Client-Supplied Materials are delivered to Patheon until delivery of the Products to Client (or return of the Client-Supplied Materials to Client), at which time it shall pass to Client (or its relevant Affiliate). The transfer of risk in the Client-Supplied Materials to Patheon shall be without prejudice to Section 9.5 (to the extent that the terms and conditions of Patheon's policies of insurance do not cover any type of loss or damage to the Client-Supplied Materials) and shall be subject to any amounts recoverable by Patheon from its insurer provided that Patheon shall only insure Client-Supplied Materials up to the values recommended and provided to Patheon by Client. Patheon shall not be liable for any unrecoverable losses caused by the under-estimation of such values. The transfer of risk shall further be subject to any deductible amounts applied by Patheon's insurer and the terms and conditions and exclusions of Patheon's policies of insurance.

(j) Client-Supplied Materials will only be used by Patheon to perform the Manufacturing Services or associated activities necessary to perform the Manufacturing Services.

(k) Client shall supply the Client-Supplied Materials in accordance with the requirements of the Quality Agreement, the Specifications, the Marketing Authorization, and GMP.

(l) Patheon shall notify Client promptly in writing if, after having carried out the analysis and testing of Client-Supplied Materials as set out in the Quality Agreement or the

Specifications it considers that any delivered Client-Supplied Materials do not comply with Section 2.2(k), and shall provide samples of such delivery together with copies of any relevant analysis records. Upon receipt of notification pursuant to this Section 2.2(l) by Client, the Parties will use Commercially Reasonable Efforts to agree (each acting in good faith) whether or not the Client-Supplied Materials in question are compliant with the requirements set out in Section 2.2(k) and:

(i) Client shall be entitled at all reasonable times to inspect and/or analyse the delivery in question;

(ii) Patheon shall not use any of the Client-Supplied Materials in question in the Manufacture of Product until the matter has been resolved in accordance with this Section 2.2(l) and Section 2.2(m) unless agreed otherwise; and

(iii) at Patheon's request, Client shall deliver to Patheon replacement Client-Supplied Materials as soon as practicable, using Commercially Reasonable Efforts to enable continuity of Patheon's Manufacture of the relevant Products.

(m) In the event that the Parties do not agree on whether the Client-Supplied Materials in question are compliant with the requirements set out in Section 2.2(k), the matter may be referred to an Expert in accordance with the procedure in Section 2.8(d)(vi).

(n) If Client-Supplied Materials are not compliant (or are determined to be non-compliant) with the requirements set out in Section 2.2(k) and Patheon does not have sufficient quantity of released Client-Supplied Materials that are compliant, then Patheon will have no liability to Client if this results in delayed performance of any Manufacturing Services or cancellation or rescheduling of any manufacturing slots, provided that the non-compliance has not been caused by a breach of this Agreement by Patheon. Client will pay Patheon for the Purchase Order in accordance with Section 2.4 which payment will be credited against the Product Fees that are payable for future Purchase Orders.

(o) Where Patheon fails to carry out incoming analysis of Client-Supplied Materials in accordance with the Specifications and uses the Client-Supplied Materials in question in the Manufacture of Product and any such Client-Supplied Materials thereafter are agreed or determined pursuant to Section 2.8(d)(vi) to not comply with the requirements set out in Section 2.2(k), Patheon shall:

(i) provide the remedies set out in Section 2.8(d)(ii) for any Non-Conforming Product that is caused by such a failure (Patheon's obligation to reimburse Client-Supplied Materials incorporated into Non-Conforming Product caused by such a failure will be captured and calculated in the Yield Reimbursement Payment under Section 2.9 which shall be subject to the limitation of liability in Section 9.5(a)); and

(ii) at Client's option, subject to completion of any quality investigation, any sample retention requirements and the provisions of the Quality Agreement, take

all necessary action (at its own expense), to rework, reprocess (both of which shall be done promptly) or destroy any Non-Conforming Products caused by such a failure.

(p) Client will be responsible for paying for all Non-Conforming Product that arises from Client-Supplied Materials that do not comply with the requirements set out in Section 2.2(k) that could not be detected by Patheon carrying out the incoming analysis of Client-Supplied Materials in accordance with the Specifications.

(q) Patheon will provide free of charge sufficient storage capacity to support storage of the required quantity of Materials for the longer of up to [***] or the amount of time set forth for the applicable Material on Schedule C. Patheon will also provide free of charge sufficient storage capacity to support storage of Product for up to [***] after the release of the relevant Product. Any additional storage, or storage of Materials or Product beyond the applicable period stated herein, will be subject to the mutual agreement of the Parties to include the fees relating thereto. Patheon's standard storage fees as of the Effective Date are [***] per pallet, per [***] for storing the Materials or finished Product. Storage fees for Materials or Product that contain controlled substances or require refrigeration are charged at [***] per pallet per [***]. Storage fees are subject to a one pallet minimum charge per [***]. Storage fees will not apply to (i) any [***] for up to [***] after the Marketing Authorization for the United States has been granted; and (ii) any stocks of Products Manufactured during the first [***] after the Effective Date in anticipation of launch in the US, provided that where Patheon is unable to accommodate all or some of such launch quantities it may engage a Third Party Subcontractor to do so in accordance with Section 3.16.

(r) Bill Back Items will be charged to Client at Patheon's cost plus a [***] handling fee. Patheon shall invoice Client [***] for any Bill Back Items used in connection with the Manufacture of the Products during the preceding [***] in accordance with ARTICLE IV. Patheon may only invoice Bill Back Items that have been quoted to and approved in writing by an authorized person of Client in advance. The cost of any Bill Back Items where use is shared between Client and Patheon or other clients of Patheon will be apportioned in good faith in proportion to their use.

(s) If Client is interested in having Patheon perform Additional Services, Client will provide Patheon with a written request containing sufficient detail to enable Patheon to provide Client with a quote and proposal to provide such Additional Services. Patheon may only invoice for Additional Services that have been quoted to and approved in writing by an authorized person of Client in advance. Where a rate for Additional Services has been specified in Schedule B, such rates are calculated as at the Effective Date. These fees will be adjusted on 1st January of each year (first review [***]) to reflect any increase in the UK Consumer Price Index: All Items Index published by the Office for National Statistics (as published at www .ons.gov.uk) during the previous twelve (12) months (based on the average of the monthly changes over the 12-month period), provided that if the increase in the index exceeds [***] it will be implemented but the Parties shall meet and negotiate in good faith measures to mitigate the effect of the fee increase. Patheon shall invoice Client monthly for any Additional Services performed by Patheon during the preceding month in accordance with Article IV.

(t) If Client decides to have Patheon perform Manufacturing Services for the Product for a territory outside the United States, Japan and/or the European Union (including the United Kingdom), then Client will inform Patheon of the additional requirements for each new country and Patheon will prepare a quotation for consideration by Client of any additional costs for the Product destined for each new country. The agreed additional requirements and change to any Product Fees will be set out in a written amendment to this Agreement. The Product Fees for products supplied to Japan or the European Union (including the United Kingdom) shall be consistent with those for the United States save to the extent Additional Services are required in respect of such Products, *e.g.*, extra visual inspection for Japan, which shall be subject to Section 2.2(s).

(u) Patheon-Supplied Materials.

(i) If the Parties agree that Patheon is to source all or any of the Materials, Client understands and acknowledges that Patheon will rely on Client's Purchase Orders and Forecasts in ordering the Patheon-Supplied Materials required to meet the Purchase Orders. Accordingly, Client authorizes Patheon to purchase Patheon-Supplied Materials to satisfy the Manufacturing Services requirements for Products for the first [***] contemplated in the most recent Forecast or as set out in Schedule C. Patheon may make other purchases of Patheon-Supplied Materials to meet Manufacturing Services requirements for longer periods if agreed to in writing by the Parties. Client will give Patheon written authorization to order Patheon-Supplied Materials for any launch quantities of Product requested by Client which will be considered a Purchase Order when accepted by Patheon.

(ii) Client will reimburse Patheon for any destruction costs of any Patheon-Supplied Materials ordered by Patheon under Purchase Orders or under Section 2.2(u)(i) that are not included in finished Products Manufactured for Client on or before [***] after the forecasted month for which the purchases have been made (or for a longer period as the Parties may agree). If any non-expired Patheon-Supplied Materials are used in Products subsequently manufactured for Client, Client will receive credit for any costs of those Patheon-Supplied Materials previously paid to Patheon by Client.

(v) Waste Disposal. Patheon shall dispose of waste arising from the Manufacture of the Product. Disposal Costs will be invoiced to Client [***] in accordance with the invoicing procedure set forth in ARTICLE IV. Patheon may only invoice Disposal Costs that have been quoted to and approved in writing by an authorized person of Client in advance.

2.3 Forecasting, Order, and Delivery of Products.

(a) No later than [***] prior to the anticipated FDA Approval Date and thereafter at least [***] during the Term, Client shall deliver to Patheon a written good faith [***] forecast, calculated monthly for the first [***] and quarterly thereafter, estimating the quantities of each presentation of Product that Client expects to order from Patheon during such period (each, a "Forecast").

(b) If Patheon is unable to accommodate any portion of the Forecast, it will notify Client in writing setting out the reasons and the Parties will agree on any revisions to the Forecast. Without prejudice to Client's other rights and remedies under this Agreement, Patheon shall take all such actions as may be reasonably requested by Client to minimize the damage to Client (if any) caused by Patheon's inability to accommodate any portion of the Forecast, [***]. Taking these actions will not constitute an admission of liability by Patheon or any acceptance that an inability to accommodate any portion of the Forecast will cause damage to Client.

(c) Client shall update the Forecast on or before the first day of each calendar month on a rolling forward basis. Client shall also update the Forecast prior to the next monthly deadline if it determines that the volumes estimated in such Forecast have changed (or will change) by more than [***]. The most recent Forecast will prevail. Except as set forth in Section 2.3(e) below, each Forecast shall be non-binding and shall be used by Patheon for planning purposes only.

(d) When this Agreement is executed, Client will give Patheon a written [***] for strategic purposes, of the volume of Product Client then anticipates to purchase from Patheon for each year during such period (the "Long Term Forecast"). The Long Term Forecast will thereafter be updated every six months (as of June 1 and December 1) during the Term. If Patheon is unable to accommodate any portion of the Long Term Forecast, it will notify Client and the Parties will agree on any revisions to the Long Term Forecast.

(e) The first [***] of each Forecast shall be considered binding firm orders. Client will issue corresponding Purchase Order(s) on a monthly basis to purchase and, when accepted by Patheon, for Patheon to Manufacture and deliver the agreed quantity of the Product for each month of such [***] period, provided that the delivery lead time must be at least [***] from the date of Patheon's acceptance (or deemed acceptance) of the Purchase Order pursuant to Section 2.3(f) below. Expedited Purchase Orders will be subject to additional fees on reasonable terms that are consistent with those generally offered to Patheon's other customers.

(f) Patheon shall accept Purchase Orders by sending an acknowledgement to Client on or before [***] business days of its receipt of the Purchase Order. The acknowledgement will include confirmation of the quantity of Product ordered as set out in the Purchase Order and the delivery date(s) for the Product ordered as set out in the Purchase Order ("Agreed Delivery Date"). Upon receipt of such acknowledgement, each Purchase Order will be regarded by the Parties as a binding irrevocable commitment by Client to purchase from Patheon, and for Patheon to Manufacture and supply to Client, the relevant quantity of Product according to the requirements set out in such Purchase Order.

(g) Patheon shall only be required to provide a delivery month for any Purchase Orders or part thereof that do not relate to the first [***] of the applicable Forecast. The Agreed Delivery Date may be amended by agreement of the Parties. If Patheon fails to acknowledge receipt of a Purchase Order on or before the [***] business day period, the Purchase Order will be deemed to have been accepted by Patheon.

(h) Patheon shall deliver Product to Client EXW the Facility (as defined in Incoterms 2010) by the Agreed Delivery Date and in the quantities specified in the relevant Purchase Order. Client may accept deliveries in advance of the Agreed Delivery Date at its discretion. All Product shall be packed for shipping in accordance with the Specifications.

(i) Title to the Products shall vest in Client from [***]. Risk of loss to Product shall pass to Client (or a designated Client Affiliate) at the time when Patheon loads the Product onto the carrier's vehicle for shipment at the shipping point at the Facility. Neither payment for the Products by Client, nor passing of risk in the Products to Client, shall be deemed to constitute acceptance of such Products by Client.

(j) Each delivery of Product shall be accompanied by a Certificate of Analysis and a Certificate of Compliance and such other documents as may be required pursuant to the Quality Agreement. All Products shall be released for delivery on or before a quarterly average of [***], and no later than at [***], after the date that the API is combined with the excipients for the Product in accordance with the Client Manufacturing Process. If the quarterly average is greater than [***], the Parties shall engage in good faith discussions to agree a remediation plan describing the steps to be taken to improve shelf life performance. Patheon shall use Commercially Reasonable Efforts to implement such plan. If Product is released later than [***], Client may reject the same if in its reasonable opinion it will not be able to [***] that has been so released safely and at commercially reasonable rates. Any such rejected Product shall be regarded as [***]. The costs of all freight, insurance, handling fees, taxes, and other costs associated with the shipment of Product, as well as export licenses, import license, and customs formalities for the import and export of goods will be borne by Client. Client shall collect shipments from the Facility on the date specified in the relevant Purchase Order or otherwise following notification of availability for delivery from Patheon and agreement of a revised delivery date.

(k) If Client cancels any Purchase Order after acceptance thereof by Patheon or deemed acceptance as described in Section 2.3(f) or (g), Client will pay Patheon [***] of the Product Fee for the Purchase Order which payment will be credited against the Product Fees that are payable for future Purchase Orders.

(l) Patheon shall use Commercially Reasonable Efforts to satisfy, any changes in quantity, delivery phasing or dates requested by Client in respect of Purchase Orders or any additional orders. Any additional fees to reflect additional activities required to be conducted by Patheon as a result of these changes or additional orders shall be agreed by the Parties in advance.

2.4 Product Fees. The purchase price for Products Manufactured hereunder (the "Product Fee") shall be calculated according to the model as set forth in Schedule B. This means that the Product Fee payable per Product varies on an incremental basis as further described in

Schedule B. All purchases of Products will be invoiced at the applicable Product Fee based on the volume of Products expected to be supplied in that calendar year (or part thereof) based on most recent Forecast at the start of the calendar year. If the volume of Products ordered by Client during such calendar year falls into a different volume band then Patheon shall issue a corresponding invoice or credit note (as the case may be) by 31 March in the following calendar year. For the avoidance of doubt no Product Fees shall be payable for the aggregate total of [***] that are included in the Transfer Services as described in Exhibit C of the Technology Transfer Agreement. [***] are not included in the Technology Transfer Fees and therefore Product Fees shall be payable for these batches; any additional [***] shall be charged at the price specified in the Technology Transfer Agreement. Patheon shall invoice Client for the relevant Product Fee after the Products have been released by Patheon for delivery in accordance with Section 2.3(h). All Product Fees will be due and payable in accordance with the invoicing procedures set forth in ARTICLE IV.

2.5 Base Fees. Patheon will invoice Client [***] in advance for the Base Fees set forth Schedule B. All Base Fees will be due and payable in accordance with the invoicing procedures set forth in Article IV.

2.1 Fee Adjustment.

(a) The Base Fee and Product Fee stated herein are calculated as at the Effective Date and shall be fixed until [***]. Thereafter, starting on [***] the Base Fee and Product Fee shall be adjusted annually to reflect any change in the UK Consumer Price Index: All Items Index published by the Office for National Statistics (as published at www .ons.gov.uk) during the preceding twelve (12) months (based on the average of the monthly changes over the 12-month period) provided that if the increase in the index exceeds [***] it will be implemented but the Parties shall meet and negotiate in good faith measures to mitigate the effect of the fee increase.

(b) Patheon, in collaboration with Client, shall use Commercially Reasonable Efforts to identify and target potential areas of cost reduction (*e.g.*, efficiency savings as a result of increasing volumes, or changes in process, formulation or components relating to the Products) and process improvements (*e.g.*, cycle time reductions, inventory reductions, yield improvements or collaborative procurement) relating to its performance under this Agreement. The net benefits of cost savings and improved efficiencies achieved as a result of the same shall be allocated as follows:

(i) where benefits of cost reductions and improved efficiencies are only applicable to the Manufacture of the Product(s), the amount of such benefits shall be [***]; and

(ii) where benefits of cost reductions and improved efficiencies are applicable to the general manufacturing and supply chain costs of Patheon, such that Patheon and/or its customers generally benefit, the allocation of such benefits shall be [***].

(c) Exchange Rate Fluctuations

(i) Fees. On or before 1 November of each year the Parties will agree a forward exchange rate to be applied for the following year, effective 1 January, as defined by the Bloomberg.com one Year Forward Rate. Patheon will adjust the Base Fee, Product Fees, Technology Transfer Fees, any batch fees under the Technology Transfer Agreement and any other agreed fees such as fees for Additional Services to reflect the forward exchange rate (GBP value per contract at the forward rate) for each calendar year. The first adjustment will be effective from 1 January 2018. Prior to this date, Patheon will adjust the fees to reflect the USD/GBP exchange rate for the month in which the invoice is issued to Client as set out in Section 2.6(c)(ii).

At the end of the calendar year, the Parties will perform a true up based upon, (i) actual fees using the forward exchange rate and (ii) the theoretical fees had the Parties applied the monthly average USD/GBP exchange rate as published on OANDA.com during the calendar year. An example of the calculation is set out in Schedule G. Where the true up results in a positive or negative balance, Patheon shall issue a corresponding invoice or credit note in respect of the balance by 31 March in the following calendar year. Patheon will provide a report with its true up calculation for the year for Client to review and comment before any invoice or credit note is triggered. The first true up will be performed after 31 December 2018.

(ii) Costs. Patheon will also adjust the Capital Expenditures (as defined in the Technology Transfer Agreement), Material Costs, Maintenance Costs, Disposal Costs, charges for Bill Back Items and any other costs that are passed through to Client to reflect the USD/GBP exchange rate as published on Bloomberg.com for the month in which the invoice is issued to Client. This adjustment will be made and communicated to Client prior to being invoiced by Patheon.

2.2 Failure or Inability to Supply Product.

(a) Patheon shall ensure that Product is Manufactured and delivered to Client on a timely basis consistent with the terms of this Agreement (including the Forecast and Purchase Order procedures set forth in Section 2.3). In the event that Patheon, at any time during the Term, is unable or shall have reason to believe that it will be unable to supply Client with the full quantity of Product forecasted to be ordered or actually ordered by Client in a timely manner and in conformity with the warranty set forth in Section 6.3 (whether by reason of force majeure or otherwise), Patheon shall notify Client thereof in writing on or before [***] business days setting out the reasons for such inability to supply. Promptly thereafter, the Parties shall meet to discuss how Client shall obtain such full quantity of conforming Product and Patheon will take all such actions as may be reasonably agreed by the Parties to minimise any delay. Compliance by Patheon with this Section 2.7(a) shall not relieve Patheon of any other obligation or liability under this Agreement, including any obligation or liability under Section 2.7(c) below. If Patheon's inability to supply is partial, Patheon shall fulfill Purchase Orders with such quantities of Product as are available and the Client's payment obligations relating to the Product Fee shall be reduced accordingly. In the event Patheon's inability to meet Purchase Orders or forecasts is due to a shortage

*** Certain information on this page has been omitted and filed separately with the Securities and Exchange Commission. Confidential treatment has been requested with respect to the omitted portions.

of production capacity in the Manufacturing Suite, Patheon shall in addition to the foregoing requirements, promptly notify Client of such shortage of production capacity and the estimated date such shortage of production capacity is to end.

(b) The Parties acknowledge that following Completion of the Tech Transfer (as defined in the Technology Transfer Agreement), (i) the engineering approach and footprint agreed by the Parties for the Manufacturing Suite and utility requirements is intended to provide capacity for the Manufacture of [***] vials of Product per [***] and (ii) the provision of personnel supporting the Manufacturing Suite is intended to support the Manufacture of the volumes of Product as set out in the relevant Forecast. Patheon undertakes to maintain such capacity and associated support processes for the Term in order to be able to ramp up to manufacture of at least [***] vials of Product per year within any [***] period, subject to Client's provision of Forecasts for such volumes in accordance with Section 2.3(a). Patheon shall not without Client's prior written consent take any step that might reduce this capacity.

(c) If Patheon fails to Manufacture the full quantity of Product specified in a Purchase Order by the Agreed Delivery Date and in conformity with the warranty set forth in Section 6.3 (and such failure is directly due to the acts or omissions of Patheon where such acts or omission does not constitute a force majeure event pursuant to the terms of Section 10.2), and Patheon is unable to cure such failure on or before [***] days, in full and final settlement of such failure, Client, at its option, may cancel the unfulfilled portion of such Purchase Order, in which event Client shall have no liability with respect to the portion of such Purchase Order so cancelled. The cancelled portion of the Purchase Order shall count as ordered Product for the purposes of measuring On Time In Full Delivery Performance in accordance with Schedule D.

(d) On Time In Full Delivery. The Parties shall measure the delivery performance of Patheon under this Agreement after each anniversary of the initial batch of commercial Manufacture of Product, and make any shortfall or bonus credit based on Patheon's delivery performance as set out in Schedule D.

2.3 Non-Conforming Product.

(a) In the event Patheon discovers a potential Non-Conforming Product prior to delivery of such Product to Client, Patheon shall suspend any planned release or delivery of such Products in accordance with the Quality Agreement and provide written notice to Client as soon as practicable describing in detail the Non-Conforming Product and the potential cause of such Non-Conforming Product.

(b) Client will perform a customary inspection of the Products Manufactured by Patheon on receipt. Such inspection will be limited to a visual inspection of the shipment-ready packaged Products (and associated shipping documentation) and Client will not be obliged to perform any testing of the Product. Client shall (i) on or before [***] days after delivery thereof by Patheon or (ii) on or before [***] days after Client discovers or is informed of a discovery of nonconformity that could not reasonably have been detected by the customary inspection on delivery (but not after the expiration date of the Product), give Patheon notice of any Non-Conforming Product (including a sample of such Non-Conforming Product, if applicable) (a "Deficiency Notice"). Should Client fail to give Patheon the Deficiency Notice on or before the expiry of the applicable notice period, then the delivery will be deemed to have been accepted by Client. Patheon will have no liability whether pursuant to this Section 2.8, Section 3.12 or Section 3.14 or otherwise for any Non-Conforming Product for which it has not received a Deficiency Notice on or before the expiry of the applicable notice period.

(c) Following receipt of a Deficiency Notice Patheon shall conduct a root-cause analysis to verify whether a Product constitutes a Non-Conforming Product and, if found, to determine the cause of such Non-Conforming Product (including by undertaking an appropriate evaluation of a Non-Conforming Product sample, as applicable). Client shall provide reasonable cooperation to Patheon in connection with any such root-cause analysis and the payment obligation in relation to the Product Fee for such Product shall be suspended pending resolution of the issue. Patheon shall notify Client in writing of its determination regarding whether the Product constitutes a Non-Conforming Product on or before [***] days after either discovery of the Non-Conforming Product or receipt of such Deficiency Notice from Client, as applicable. Such notification shall include Patheon's good faith determination of the cause of the Non-Conforming Product. At Client's request and following the issue of a Purchase Order from Client, Patheon will use Commercially Reasonable Efforts to deliver a replacement delivery of the Product to Client as soon as practicable after receipt of the Deficiency Notice (subject to Client supplying Patheon with Client-Supplied Materials, if required) in order to ensure continuity of supply, and Client shall pay Patheon for such delivery in accordance with the terms of this Agreement.

(d) Patheon Nonconformance

(i) "Patheon Nonconformance" shall mean Patheon's failure to [***].

(ii) In the event of a Non-Conforming Product caused by a Patheon Nonconformance, Patheon shall reimburse Client for:

1. the Product Fees in respect of Non-Conforming Products; and

2. any shipment costs incurred by Client in the event that the Non-Conforming Product was shipped from the Facility at the time of the discovery of the Patheon Nonconformance ("Shipment Costs"); and

3. cost of losses of [***] incorporated into Non-Conforming Product,

in each case, to the extent applicable and/or already paid by Client.

(iii) Patheon's obligation to reimburse Client for Client-Supplied Materials incorporated into Non-Conforming Product caused by a Patheon Nonconformance will be captured and calculated in the Yield Reimbursement Payment under Section 2.9 which shall be subject to the limitation of liability in Section 9.5(a) herein.

(iv) [***] shall not apply in relation to (A) the internal expenses incurred by Patheon to supply conforming Product to Client pursuant to Section 2.8(c) if this is to replace Non-Conforming Product caused by a Patheon Nonconformance, or (B) the cost of any [***] or any Shipment Costs or the reimbursement of the Product Fee pursuant to Section 2.8(d)(ii). Client will not be liable to pay Product Fees for Non-Conforming Product caused by a Patheon Nonconformance and Patheon shall have no obligation to reimburse any unpaid Product Fees for Non-Conforming Product caused by a Patheon Nonconformance.

(v) If the Non-Conforming Product was caused by any reason other than a Patheon Nonconformance, as may be determined by an Expert in accordance with Section 2.8(d)(vi), Client shall be liable for all expected Product Fees for such Non-Conforming Product (to the extent not already paid), provided that where the cause of non-conformance is not identifiable but a Patheon Nonconformance has occurred, then Client shall be liable for [***] of the Product Fees.

(vi) If, following the root-cause analysis described in Section 2.8(c), Patheon notifies Client that it does not believe the Product is a Non-Conforming Product, or if the Parties disagree as to the cause of a Non-Conforming Product, the Parties shall first submit such dispute to the Project Managers for prompt resolution. If the Project Managers cannot resolve the dispute, the Parties shall submit the dispute to an independent expert or (if mutually agreed to by the Parties) a testing lab agreed by the Parties (an "Expert") for evaluation, provided that both Parties shall be entitled to observe and obtain copies of all results of such evaluation. The Expert shall determine (i) whether the Product is a Non-Conforming Product and (ii) the cause (or likely cause) of the Non-Conforming Product. Both Parties shall cooperate with the Expert's reasonable requests for assistance in connection with its evaluation hereunder. The findings of the Expert shall be binding on the Parties, absent fraud or manifest error. The Expert shall act as an expert and not as an arbitrator and (unless the Expert otherwise determines) the fees and expenses of the Expert shall be borne (1) by Patheon if the testing confirms the Non-Conforming Product and the cause or likely cause is found to be a Patheon Nonconformance; (2) by Client if the testing confirms the Non-Conforming Product and the cause or likely cause is found not to be a Patheon Nonconformance or if the cause or likely cause of such non-conformance is not identifiable; or (3) by the Party stating the Product was Non-

Conforming Product in the event the testing concludes that the Product meets the warranty set forth in Section 6.3. Costs of dealing with Product complaints and inquiries will be dealt with in accordance with Section 3.12. Costs of recalls will be dealt with in accordance with Section 3.14. Patheon shall have no liability for any Non-Conforming Product unless such Non-Conforming Product is identified as being due to a Patheon Nonconformance.

2.4 Yield reconciliation

(a) During its performance of the Manufacturing Services, on an annual basis Patheon is expected to produce a certain yield of Product using Client-Supplied Material (the "Expected Yield"). The initial Expected Yield shall be calculated and mutually agreed by the Parties after the first [***] batches of commercial Product Manufactured by Patheon. Pending such agreement, the Expected Yield shall be [***], but shall not be contractually binding and the Parties acknowledge that this may not be attainable due to the limited experience that Patheon will have in Manufacturing commercial Product. Accordingly the Yield Reimbursement Payment and credit set out in Section 2.9(c) shall not apply to the first [***] batches of commercial Product Manufactured by Patheon.

(b) On a [***] basis during the Term, Patheon shall provide Client with a report in respect of the previous [***] and [***] to date showing:

(i) the number of vials of Products released to be delivered to Client in accordance with the terms of this Agreement in the applicable periods;

(ii) Patheon's inventory of Client-Supplied Materials, quantity of Client-Supplied Materials that complies with Section 2.2(k) received at the Facility, Quantity Dispensed, Quantity Converted, and such additional information as the Parties may agree; and

(iii) the Achieved Yield in [***] and year to date, where "Achieved Yield" shall be calculated pursuant to an equation to be agreed by the Steering Committee taking into account Client-Supplied Materials that have expired as a result of a Patheon act or omission and any Client-Supplied Materials lost in the warehouse prior to and during Manufacture, but excluding (i) Client-Supplied Materials retained by Patheon as samples; (ii) Client-Supplied Materials contained in Product retained as samples; (iii) Client-Supplied Materials used in testing (if applicable); (iv) any agreed yield reductions arising from specific market related requirements such as visual inspection of the Product that are not part of normal processing and (v) Client-Supplied Materials received and used by Patheon pursuant to the Technical Transfer Agreement.

(c) In the event the Achieved Yield in any year after the date of Manufacture of the [***] of commercial Product is more than [***]% lower than the then-current Expected Yield for such year, (i) Patheon and Client will engage in good faith discussions to agree a remediation plan describing the steps to be taken to achieve the then-current Expected Yield and

(ii) Patheon will reimburse Client for excess [***] used by Patheon as a result of Patheon's failure to meet the Expected Yield in such batches (*i.e.*, reimbursement to Client for the actual costs of any [***]) subject to the limitation of liability in Section 9.5(a) (the "Yield Reimbursement Payment"). In the event the Achieved Yield in any year is more than [***]% greater than the then-current Expected Yield for such year, Patheon shall be entitled to reduce any Yield Reimbursement Payment to be made in the next year by an amount equal to the value of the excess [***] that would have been used by Patheon if the Achieved Yield for such calendar year was equal to the then-current Expected Yield in such batches.

(d) Patheon shall use Commercially Reasonable Efforts to drive year on year improvements in the Achieved Yield and the Expected Yield.

2.5 Equipment and Amendment of Product Specifications, Manufacturing Process, Equipment and Formulation.

(a) Equipment.

(i) Title to all Client Manufacturing Equipment will be held by Client or a Client Affiliate. Title to all Patheon Manufacturing Equipment will be held by Patheon.

(ii) Patheon is authorized to use the Client Manufacturing Equipment for the purposes of performing the Manufacturing Services for Client. Patheon may not move the Client Manufacturing Equipment from the Facility nor use the Client Manufacturing Equipment to perform manufacturing services for other clients without the Client's prior written consent.

(iii) Patheon will not sell or offer to sell, assign, pledge, lease or otherwise transfer or encumber the Client Manufacturing Equipment or any interest therein, without the prior written consent of Client. Patheon will not create any adverse lien, security interest or encumbrance in relation to the Client Manufacturing Equipment.

(iv) Patheon will use the Client Manufacturing Equipment in accordance with the Equipment Standard Operating Procedures or the relevant manufacturer's instructions and Client's direction (where agreed by the Parties, if any).

(v) During the Term, Patheon shall, at its cost, keep the Client Manufacturing Equipment secure.

(vi) Client shall be responsible for additions and replacement cost of any (i) Client Manufacturing Equipment and (ii) Patheon Manufacturing Equipment that is used only in connection with the Manufacture of the Product or that is used for Client and other clients of Patheon (the cost of any additions and replacement for Patheon Manufacturing Equipment that is used for Client and other clients of Patheon will be apportioned in good faith in proportion to their use). All replacement parts and repairs to the Client Manufacturing Equipment will become Client's property.

Patheon will not make any material alterations to the Equipment, the Manufacturing Suite or the Client Manufacturing Process used in the Manufacture of the Products without Client's prior written consent.

(vii) During the Term, Patheon shall provide all Maintenance for the Equipment and the Facility. Maintenance Costs will be invoiced to Client [***] in accordance with the invoicing procedure set forth in Article IV, provided that Patheon may only invoice Maintenance Costs that have been quoted to and approved in writing by an authorized person of Client in advance. Maintenance Costs relating to Patheon Manufacturing Equipment that is used for Client and other clients of Patheon will be apportioned in good faith in proportion to their use. Notwithstanding the foregoing, with respect to the Client Manufacturing Equipment and Patheon Manufacturing Equipment, Maintenance Costs do not include (A) the cost of spare parts (provided that Patheon shall keep such inventory of original manufacturer spare parts as the Parties agree is reasonably necessary to maintain the Client Manufacturing Equipment, to include at a minimum all critical spares recommended by the manufacturer of the Client Manufacturing Equipment), (B) Equipment breakdowns caused by any reason outside of Patheon's reasonable control (other than breakdowns caused by Patheon's gross negligence or failure to maintain the Equipment in accordance with the applicable Equipment Standard Operating Procedures of Patheon or the manufacturer's terms of operation and recommended procedures), or (C) specialized maintenance services not within Patheon's technical expertise or that requires specialist equipment where Patheon is required to utilize a Third Party contractor. Patheon's costs associated with such spare parts, Equipment breakdowns and Third Party contractors will be reimbursed by Client as a Bill Back Item, provided that where such spare parts, Equipment breakdowns and Third Party contractors relate to Patheon Manufacturing Equipment that is used for Client and other clients of Patheon, the costs will be apportioned in good faith in proportion to their use.

(viii) Patheon shall not be liable for ordinary wear and tear of the Client Manufacturing Equipment or Patheon Manufacturing Equipment; Patheon shall only be liable for the repair or replacement of any damage caused to Client Manufacturing Equipment or Patheon Manufacturing Equipment where such damage arises due to its gross negligence or willful misconduct or its failure to maintain Client Manufacturing Equipment or Patheon Manufacturing Equipment pursuant to the applicable Equipment Standard Operating Procedures of Patheon or the manufacturer's terms of operation and recommended procedures. Where this Section refers to costs relating to any Patheon Manufacturing Equipment, if the Patheon Manufacturing Equipment is used for Client and other clients of Patheon, these costs will be apportioned in good faith in proportion to their use.

(ix) Throughout the Term of this Agreement, Patheon shall maintain property insurance on all Equipment in the amount equal to at least the replacement value of such Equipment.

(x) Client may examine and inspect the Client Manufacturing Equipment at any reasonable time (wherever such Client Manufacturing Equipment is located in the Facility) so that Client can check the Client Manufacturing Equipment's existence, condition and proper maintenance.

(xi) Patheon shall ensure that at all times the Client Manufacturing Equipment is clearly marked in such a way as to identify that it is owned by Client. All Client Manufacturing Equipment shall be marked in such a way as to identify that it is for use only for Client.

(xii) If any item of the Client Manufacturing Equipment is lost, stolen or damaged, Patheon will promptly notify Client of such event.

(xiii) Client shall ensure that on delivery the Client Manufacturing Equipment complies with all EU mandatory requirements including without limitation, Supply of Machinery (Safety) Regulations 2008 (UK Regulations, Secondary UK Legislation), Electrical equipment of machines (General requirements BS EN 60204-1:2006+A1:2009) (British Product Standards), Machinery Directive 2006/42/EC (European Union Directive), Low Voltage Directive (LVD) 2006/95/EC (European Union Directive), and Electromagnetic Compatibility (EMC) Directive 2004/108/EC (European Union Directive).

(b) Change control

(i) For changes to the Specifications, Quality Agreement, the Client Manufacturing Process, the Equipment, the Manufacturing Services to be provided pursuant hereto, the Transfer Services to be provided pursuant to the Technology Transfer Agreement or the formulation of the Product that are required by Applicable Law (collectively, "Required Manufacturing Changes"), Patheon and Client shall cooperate to promptly make such changes within the required timeline and assess filing implications (prior approval, changes being effected, etc.).

(ii) For changes to the Specifications, Quality Agreement, the Client Manufacturing Process, the Equipment, the Manufacturing Services to be provided hereto, the Transfer Services to be provided pursuant to the Technology Transfer Agreement, or the formulation of the Product that are not Required Manufacturing Changes (collectively, "Discretionary Manufacturing Changes"), Patheon shall provide Client with an estimate of the timeframe and cost required to implement the same. Patheon and Client must each agree to any Discretionary Manufacturing Changes and shall cooperate in making such changes, and each agrees that it shall not unreasonably withhold or delay its consent to such Discretionary Manufacturing Changes. Once Client has approved the estimate in writing, Patheon shall implement the change within the agreed timeframe. Together Parties will assess filing implications, as for example, annual reportable status.

(iii) Notwithstanding the foregoing, all internal and external costs, including, without limitation, costs of obsolete Materials, work-in-process and Product associated with Required Manufacturing Changes shall be allocated between the Parties as follows: (x) to the extent that the change relates to the Product, the Specifications, the Client Manufacturing Process, the Equipment, the Manufacturing Services or the Manufacturing Suite or the Transfer Services to be provided pursuant to the Technology Transfer Agreement, Client shall pay the costs and expenses of implementing such change together with the actual cost of write-off (including waste disposal costs) of any inventory of Products or Materials rendered obsolete as a result of the change, provided that Client shall not be liable for the write-off costs of any Materials purchased in excess of those amounts needed to meet Purchase Orders or as otherwise agreed pursuant to Section 2.2(u); and (y) to the extent that the change results from a change in GMP or Applicable Laws that requires changes to the Facility or Manufacturing process (other than as a direct result of changes to the Product, the Specifications, the Client Manufacturing Process, the Equipment, the Manufacturing Services or the Manufacturing Suite or the Transfer Services to be provided pursuant to the Technology Transfer Agreement), the allocation of such benefits shall be discussed in good faith and allocated between the Parties as agreed at the time, having regard to any other Patheon customers who will benefit from the change.

(iv) The cost of implementing Discretionary Manufacturing Changes will be agreed by the Parties.

(v) In the event that Client changes the Specifications, Quality Agreement, the Client Manufacturing Process, the Equipment, the Manufacturing Services to be provided hereto, the Transfer Services to be provided pursuant to the Technology Transfer Agreement or the formulation of the Product, or consents to any change by Patheon, Patheon shall provide to Client at Client's cost as an Additional Service any such documentation or other information with respect thereto as they relate to the Manufacturing Services as Client may reasonably request in order to obtain or maintain any Regulatory Approval or comply with GMP or other Applicable Law.

(vi) Patheon shall not change the Specifications, the Materials or the Client Manufacturing Process used in the Manufacture of the Products, or make any other change which may reasonably be expected to have a regulatory impact on the Product, affect the Marketing Authorization or affect the quality or physical characteristics of the Product, without first obtaining written consent from Client.

ARTICLE III. REGULATORY, ACCESS, AND OTHER MATTERS

3.1 Quality Agreement. Prior to the expiry of the Technology Transfer Agreement, the Parties shall enter into a mutually agreed upon quality agreement ("Quality Agreement"). If there is any inconsistency between this Agreement and the Quality Agreement, the terms of the Quality

Agreement shall control solely with respect to quality issues, and this Agreement shall control with respect to all other issues.

3.2 Quality Assurance.

(a) Patheon shall at all times ensure that agreed quality assurance tests are adopted and that reference and retention samples are taken, analysed and retained in accordance with the Quality Agreement. Such samples shall (notwithstanding any termination of this Agreement) be retained by Patheon for the periods prescribed in the Quality Agreement at no additional cost.

(b) Unless otherwise specified in the Quality Agreement, Patheon shall provide to Client, in a timely manner, sufficient quantities of reference standards for the Products to enable Client to carry out and/or maintain the necessary testing capability to comply with its Regulatory Obligations and the obligations set out in the Quality Agreement throughout the Term.

(c) Patheon shall institute and maintain process controls during the Manufacture of the Products in accordance with GMP and shall maintain full records of such process controls which shall be made available to Client on request together with retained in-process samples. Such records must align with documentation set out in the Specifications and samples shall be retained by the Patheon for such period as may be specified in the Quality Agreement or as otherwise required by Applicable Law at no additional cost.

3.1 Release. All Product shall be released in accordance with the terms of the Quality Agreement.

3.2 Maintenance of Facility.

(a) Patheon shall Manufacture the Product exclusively at the Facility, unless Client has granted prior written consent to Manufacture the Product at any other facility, such consent to be granted by Client in its sole discretion.

(b) Subject to Section 2.10(b), Patheon shall at its own cost ensure that any and all necessary licenses, registrations, and (subject to any payments required under Section 3.10(b)) Regulatory Authority approvals have been obtained in connection with the Facility and Equipment used in connection with the Manufacture of the Product by Patheon.

(c) Subject to Section 2.10, Patheon shall maintain the Facility and Equipment in a state of repair and operating efficiency consistent with the requirements of the Specifications, the Regulatory Approvals, the Client Manufacturing Process, GMP, and all other Applicable Law. Prior to each use of Equipment in Manufacturing the Product, Patheon shall ensure that such Equipment is cleaned and consistent with any procedures reasonably established by Client and notified to Patheon, the Specifications, the Regulatory Approvals, the Client Manufacturing Process, GMP, and all other Applicable Law. Without limitation of the foregoing, Patheon agrees to implement, in connection with the Manufacture of the Product, quality assurance and quality

control procedures, including validation protocols and process change procedures that are reasonably satisfactory to Client.

(d) Patheon shall maintain in the Facility an adequate GMP and temperature controlled area for the Product, all intermediates thereof and Materials used in Manufacturing the Product in accordance with the Specifications, the Regulatory Approvals, the Client Manufacturing Process, any risk mitigation plan, the Quality Agreement, GMP, and all Applicable Law. All Product, intermediates and Materials (as applicable) shall be held by Patheon in a GMP and temperature controlled area (on a separate pallet and SAP reference from other products) until delivery to Client. In order for Patheon and Client to identify any potential effects on quality, safety or efficacy of the Products, subject to obligations of confidentiality that Patheon owes to Third Parties, Patheon shall disclose to Client (on a no-names basis) information relating to the nature of any other [***]. Client agrees that Patheon may, disclose information (on a no-names basis and subject to ARTICLE VII) relating to the nature of Client's Product to other clients of Patheon at the Facility if requested.

(e) Patheon shall only use qualified disposal services or sites that have appropriate environmental and operating permits and are in compliance with the Quality Agreement and Applicable Law.

(f) Patheon shall develop and put in place a disaster recovery and business continuity plan in respect of the Manufacture of Products at the Manufacturing Suite by 30 June 2018, and provide Client with a copy of the same on request. Client will provide Patheon with details of its requirements for these plans within a reasonable period from the Effective Date.

3.3 Client On Site Representatives; Project Managers; Steering Committee Meetings.

(a) For so long as Patheon is obliged to Manufacture and supply the Product for Client, Client shall have the right at all times throughout the Term to have [***] representatives present (or other number as mutually agreed to by the Parties) (each, a "Client On Site Representative") in that portion of Patheon's Manufacturing facilities that is being used to Manufacture the Product or store Materials to observe the procedures and processes used to Manufacture the Product. Subject to the following sentence, such representatives shall have full access to the Manufacturing Suite, to any other parts of the Facility that relate to the Manufacture of the Product, and to all non-financial records that relate to the Product, the Materials and Bill Back Items. Patheon shall provide reasonable (semi-permanent) on-site accommodations at the Facility for the Client On Site Representatives (*e.g.*, office space) provided that Client complies with the terms set out in Schedule E. For the avoidance of doubt, the term "non-financial records" as used in this Agreement does not include the Reports (defined in Section 3.13 below). Client On Site Representatives shall be appropriately trained by Client (*e.g.*, GMP training) and shall observe at all times Patheon's policies and procedures (as amended from time-to-time) as they pertain to the Facility, including policies relating to health and safety and compliance with GMP, and comply with all reasonable directions of Patheon in relation to the same; provided that Client is given notice of such policies and given a reasonable period of time to review and implement such policies. Patheon may refuse or limit in its sole discretion at any time admission to the Facility by any Client On Site Representative who fails to observe such policies or comply with such reasonable directions.

Client On Site Representatives shall have (i) no management authority over any Patheon employee and (ii) no authority to conclude contracts on behalf of Client.

(b) Patheon and Client will each appoint a project manager (each, a "Project Manager" and, together, the "Project Managers"), who will meet as needed to resolve any issues or problems arising in the performance of this Agreement. Client's Project Manager may be one of the Client On Site Representatives.

(c) Following completion of registration batches the Parties shall establish a steering committee in respect of commercial supply (the "Commercial Steering Committee"), which shall meet at least quarterly in order to manage the long term manufacturing and supply aspects of this Agreement. The responsibilities of the Commercial Steering Committee shall include without limitation:

(i) reviewing any ongoing development activities for the Products that may lead to changes in demand;

(ii) reviewing and discussing any trends or concerns in relation to delivery performance, Achieved Yields, usage of Client-Supplied Materials, quality related issues or plans to improve performance under the Agreement;

(iii) reviewing any potential restrictions on the availability of additional space within the Facility, which shall be notified by Patheon sufficiently far in advance of any proposed agreement with a Third Party in order for Client to be able assess its likely future requirements and for the Parties to have the opportunity to negotiate in good faith any reservation of the same; and

(iv) performing such other responsibilities as the Parties may agree.

Unless otherwise agreed by the Parties the Commercial Steering Committee shall follow the membership and procedural arrangements agreed for the steering committee under the Technology Transfer Agreement.

3.4 Notification of Regulatory Inspections. Patheon shall notify Client by telephone on or before [***], and in writing on or before [***], after learning of any proposed or unannounced visit or inspection of any part of the Facility which relates to the Manufacture of the Product by any Regulatory Authority, including the Occupational Safety and Health Administration or any equivalent governmental agencies of the country of Manufacture, and provide all relevant information known to Patheon regarding such investigation. Patheon shall permit Client or its agents to be present at the Facility to support Patheon during such visit or inspection if it impacts the Product or affects the Manufacturing Suite. The responsibility for conducting the inspection rests with Patheon. Patheon shall provide to Client in so far as it affects the Product or the Manufacturing Suite either a copy of or a summary of any report and other written communications received from such Regulatory Authority in connection with any visit or inspection, including FDA Form 483 observations and responses (or any equivalent observations and responses from any Regulatory Authority under Applicable Law). Such copy or summary shall be provided to

Client on or before [***] business days of Patheon's receipt thereof (and may be redacted as Patheon acting reasonably deems necessary to protect the confidentiality of matters not affecting the Product or the Manufacturing Suite or which are confidential to Patheon or to other clients of Patheon). Client shall have the right to review and comment on any communications with such Regulatory Authority pertaining to such inspection as set forth in Section 3.17. In the event that Client is subject to an inspection by any Regulatory Authority that relates to the Products or Patheon's performance of its obligations under this Agreement, Patheon shall provide Client and such Regulatory Authority with access to Patheon's non-financial records, the Products and those portions of the Facility used in the Manufacture of the Products or storage, testing, handling or receiving of the Materials as required by this Agreement or otherwise by Applicable Law, in each case subject to payment by Client of the fees set out in Section 3.10(b).

3.5 Manufacturing Records. Patheon shall maintain, or cause to be maintained, (a) all records necessary to comply with GMP and all other Applicable Law relating to the Manufacture of Product, (b) all Manufacturing records, standard operating procedures, equipment log books, batch records, laboratory notebooks, and all raw data relating to the Manufacturing of the Product, and (c) such other records as Client may reasonably require in order to ensure compliance by Patheon with the terms of this Agreement. The template, form and style of all records referred to herein are the exclusive property of Patheon; Client Confidential Information and all Product-specific related information contained in these records shall be deemed Confidential Information of Client and be retained for such period as may be required by GMP and all other Applicable Law.

3.6 Bulk Packaging. Client shall specify all bulk packaging to be used for the Product. Patheon agrees to use only such bulk packaging on the Product as set out in the Specifications.

3.7 Compliance with Applicable Laws. Patheon shall comply and shall cause each of its Materials and Bill Back Items suppliers to comply with the Quality Agreement, GMP and Applicable Law in carrying out the Manufacturing of the Product and its other duties and obligations under this Agreement.

3.8 Compliance Audits.

(a) With the exception of "for cause" audits (*e.g.*, audits arising in the event of regulatory issues or material Product conformity issues), Client and its designated representatives shall have the right to audit [***] all applicable non-financial records of Patheon for the purpose of determining Patheon's compliance with the obligations set forth in this Agreement, including Sections 2.2(a) and 6.2, and the terms of any Purchase Order. Such audit right shall include the right to inspect: (a) the Materials used in the Manufacture of the Product, (b) the holding facilities for such Materials, (c) the Manufacturing Suite and all Equipment used in the Manufacture of the Product, (d) all non-financial records relating to the Manufacturing Suite and the Manufacturing of the Product (subject to any other restrictions set forth in this Agreement) and (e) all other documentation set forth in the Quality Agreement, in order to carry out a GMP, quality and/or compliance audit of those parts of the Facility involved in, or which could affect, the Manufacture of the Products. Client shall provide Patheon with [***] days prior advance notice of its intention to conduct such audit and the Parties will determine a mutually agreeable date for such

audit. Client shall include no more than [***] of Client's representatives in each such audit, with each such audit lasting no more than [***] days, in each case without Patheon's prior written consent. Client shall also have the right to carry out follow up audits subject to payment by Client of the fees set out in Section 3.10(b) if any observations have been noted during any audit carried out pursuant to this Section 3.10(a) (excluding any "for cause" audits as described above or any audits where critical or major observations have been noted).

(b) Client may request additional GMP-type audits, additional audit days, or the participation of additional auditors subject to payment to Patheon of a fee of [***] for each additional audit day and [***] per audit day for each additional auditor. Patheon will support the first Product approval, including its inspection if required, of the FDA or equivalent regulatory launch for other jurisdictions (where applicable). Additional support (including, without limitation, subsequent regulatory launches or Product approval inspections/resulting reports for other jurisdictions) will be subject to additional fees.

(c) Patheon shall use Commercially Reasonable Efforts to ensure that any corrective or preventative actions identified in any audit carried out pursuant to this Section 3.10 that are agreed by the Parties are carried out in accordance with any agreed timeline and subject to payment by Client of any agreed fees.

(d) Patheon shall be responsible for ensuring the GMP compliance status of any authorised sub-contractors used in relation to the performance of its obligations under this Agreement as described in Section 2.2(d). Patheon shall assess each sub-contractor using Patheon's standard vendor assurance programme and shall report its findings to Client within [***] business days of a request from Client.

3.9 Inventory Reviews. Without limiting the foregoing, Client shall have the right, with Patheon's assistance, to conduct an annual inventory count of the Materials and of the Products. Following an audit or inventory, Client may discuss its observations and conclusions with Patheon, and Patheon shall promptly implement such corrective actions after notification thereof by Client. In the event the Parties are unable to agree upon whether or not corrective actions are necessary, such dispute shall be resolved pursuant to the terms of Section 10.10.

3.10 Product Inquiries and Complaints.

(a) With respect to Products Manufactured by Patheon, Patheon will promptly submit to Client any Product safety and efficacy inquiries, Product quality complaints, and adverse drug event reports that it receives, together with all available evidence and other information relating thereto, in accordance with procedures to be agreed upon by the Parties. Patheon will promptly advise Client of any occurrence or information which arises out of the Manufacture of Products which has or could be reasonably expected to have adverse regulatory compliance and/or reporting consequences concerning the Products, and provide relevant information to Client upon request. Except as otherwise required by, or to comply with, Applicable Law or the terms of this Agreement, Client, as the Party holding the applicable Marketing Authorization, will be responsible for investigating and responding to all such inquiries, complaints, and adverse events regarding the Product, and reporting to the FDA or any other Regulatory Authority.

(b) Pursuant to any reported complaint, adverse drug event or other issue which may pertain to the Manufacture of the Products Patheon will promptly conduct all such necessary internal investigations as may be necessary to determine the validity of such complaint, including performing analytical testing of corresponding Products or retention samples, and shall provide the results thereto to Client as soon as reasonably practicable, but no later than [***] days after Client's request. Such testing shall be performed using approved testing procedures as set forth in the applicable Regulatory Approval or the Quality Agreement. If such investigation or analytical testing concludes that the reported complaint or adverse drug event was the result of a Patheon Nonconformance, subject to Client having provided to Patheon a Deficiency Notice in accordance with the provisions of Section 2.8(b) including as to timing, Patheon shall [***] associated with such complaint or adverse drug event and incurred by Client with respect to such Non-Conforming Product, including reasonable [***]. Costs of recalls will be dealt with in accordance with Section 3.14. If such investigation or analytical testing concludes that the reported complaint or adverse drug event was not the result of a Patheon Nonconformance, Client shall compensate Patheon for all costs associated with such complaint or adverse drug event and incurred by Patheon with respect to such Non-Conforming Product, including costs of recalls, market withdrawals, returns, and destruction.

(c) If the Parties disagree as to which Party is responsible, Patheon and Client representatives shall attempt to resolve such dispute. If the representatives cannot resolve such dispute on or before [***] days, the retention samples shall be submitted by Patheon and Client to an Expert and Section 2.8(d)(vi) shall apply.

3.11 Reports. Prior to the start of Patheon's commercial Manufacture of the Product (or as reasonably requested by Client prior to such date), Patheon and Client will work together in good faith to develop and agree upon Patheon's ordinary course reporting obligations. Such reports ("Reports") will include those reports as necessary for Client to (a) manage Product inventory; (b) measure the Achieved Yield and whether all Products on agreed Purchase Orders order are delivered on time and in full; (c) manage its financial close and reporting; (d) monitor on-going Product and process performance for its internal analysis and reporting; and (e) comply with Applicable Law. Patheon will deliver such reports via electronic delivery methods, including by utilizing Patheon's existing IT systems as practicable.

3.12 Product Recalls.

(a) In the event (i) any Regulatory Authority issues a request, directive, or order that Product be recalled, (ii) a court of competent jurisdiction orders such a recall, or (iii) Client as holder of the applicable Marketing Authorization shall reasonably determine that Product should be recalled, withdrawn, or a field correction issued, the Parties shall take all appropriate corrective actions, and shall cooperate in the investigations surrounding the recall. In the event that Client or a Regulatory Authority determines that Product should be recalled, the recall strategy shall be developed by Client in consultation with Patheon to the extent possible and followed by Patheon. In the event of any Product recall, withdrawal, or field correction resulting from a Patheon Nonconformance, Patheon shall [***] associated with such recall, withdrawal, or field correction, which shall include [***] of the recalled Product and all other documented [***] incurred

in connection with such recall, plus reasonable [***] costs incurred by Client with respect to such Product, up to the maximum liability limits set forth in Section 9.5. In all other circumstances, all costs associated with any Product recall, withdrawal, or field correction shall be borne by Client.

(b) If there is any dispute concerning which Party's acts or omissions gave rise to such recall of Product, Patheon and Client representatives shall attempt to resolve such dispute. If the representatives cannot resolve such dispute on or before [***] days, the matter shall be submitted by Patheon and Client to an Expert and Section 2.8(d)(vi) shall apply.

3.13 Payment Audits.

(a) Upon [***] days' prior written notice, Client may audit any Third Party invoices subsequently invoiced to Client pertaining to Patheon's provision of Equipment, Materials, Bill Back Items and Additional Services hereunder; provided, however, that Client will not be entitled to more than one audit during any [***] month period. Such audits will be conducted during normal business hours, without undue disruption to Patheon's business, and may be conducted by Client, or by an independent public accounting firm designated by Client who is bound by confidentiality obligations at least as stringent as those set forth in the Confidentiality Agreement. Client will bear the full cost of the performance of any such audit.

(b) If, as a result of any audit of the Third Party invoices, it is shown that the payments or credits from one Party to the other under this Agreement with respect to the period of time audited were less than or more than the amount that should have been paid or credited, then the Parties will reconcile the amounts owed by each Party to the other.

3.14 Subcontractors. Patheon may arrange for Third Party subcontractors ("Third Party Subcontractors") to perform specific Manufacturing Services (such as testing or analysis) under this Agreement with Client's written consent or at Client's request. Patheon's liability for Third Party Subcontractors will remain subject to all limitations on Patheon's liability as set out in this Agreement. Patheon will have no liability arising from the performance of Manufacturing Services by Third Party Subcontractors, (i) to the extent that the Third Party Subcontractor is following the direct instructions of Client, or (ii) that are chosen or requested by Client and that provide a service or materials pursuant to their standard legal terms, provided that Patheon has used Commercially Reasonable Efforts to enforce such terms or (at Client's discretion and where possible to do so) to support Client in enforcing such terms. Patheon shall not be obliged to use a Third Party Subcontractor requested by Client if it does not comply with Patheon's supplier qualification requirements.

3.15 Regulatory Filing Obligations. (a) Except as otherwise set forth in this Agreement or the Technology Transfer Agreement, each Party will be responsible for all routine filings and communications with Regulatory Authorities ("Regulatory Filings") required with respect to such Party's Regulatory Obligations hereunder.

(a) "Regulatory Obligations" shall mean:

(i) with respect to Client, any Regulatory Filings pertaining to Regulatory Approvals; and

(ii) with respect to Patheon, any Regulatory Filings pertaining to the Manufacture of the Products at the Facility, including in connection with a Facility inspection by a Regulatory Authority (*e.g.*, those described in Section 3.6).

(b) Each Party shall have the sole responsibility for Regulatory Filings in respect of its Regulatory Obligations and shall provide the other with a copy of any Regulatory Approval relevant to this Agreement on request, to the extent reasonably required for its Regulatory Filings or in order to satisfy its obligations under Applicable Laws.

(c) Cooperation. Each Party ("Non-Filing Party") will provide reasonable assistance and cooperation free of charge to the other Party ("Filing Party") in connection with the Filing Party's Regulatory Obligations consistent with the terms of this Section 3.17 and the Non-Filing Party's obligations under this Agreement. The Filing Party shall notify the Non-Filing Party in writing of any written communications received by the Filing Party from a Regulatory Authority related to the other Party's Regulatory Obligations on or before [***] business days after receipt thereof. The Filing Party shall consult with the Non-Filing Party concerning the response of the Filing Party to each such communication, unless such filing is not relevant to the Non-Filing Party's Regulatory Obligations.

(d) Verification of Data. Prior to filing any documents or communications with a Regulatory Authority that incorporate or uses data generated by the Non-Filing Party or otherwise relate to the Non-Filing Party's Regulatory Obligations, the Filing Party will give the Non-Filing Party a draft of such document or communication ("Initial Draft") to give the Non-Filing Party the opportunity to verify the accuracy and regulatory validity of such Initial Draft. The Non-Filing Party shall be given a minimum of [***] calendar days to review the Initial Draft, but the Parties may mutually agree to a different time for the review as needed under the circumstances. The Initial Draft may be redacted by the Filing Party as reasonably deems necessary to protect the confidentiality of matters not affecting the Non-Filing Party or which are confidential to the Filing Party or to other clients or customers of the Non-Filing Party. The Parties agree that in reviewing the Initial Draft, the Non-Filing Party's role will be limited to verifying the accuracy of the description of its Regulatory Obligations or accuracy of its data or information in the Initial Draft.

(e) Inaccuracies. If the Non-Filing Party determines that any of its data or information in the Initial Draft is inaccurate or any other errors relating to the Non-Filing Party's Regulatory Obligations, the Non-Filing Party will notify Filing Party in writing of such inaccuracy and provide a recommendation to remediate the Initial Draft. Such notice shall also include documentation and data sufficient to substantiate the Non-Filing Party's claim that the Initial Draft is inaccurate to the Filing Party's reasonable satisfaction. The Non-Filing Party shall provide comments to the Initial Draft no later than [***] prior to the required filing date with the applicable Regulatory Authority. If the Non-Filing Party does not provide comments or notify the Filing Party of inaccuracies on or before such [***] period, the Non-Filing Party will be deemed to have approved any data or language related to its Regulatory Obligations in the Initial Draft. The Filing Party shall be required to incorporate the Non-Filing Party's recommendations to the extent they directly relate

to an error in the Non-Filing Party's data or information or the Non-Filing Party's Regulatory Obligations. The Parties will work together in good faith to resolve any inaccuracies contained in the Initial Draft as soon as practicable under the circumstances to prevent a delay or postponement of such filing (or any related inspections by such Regulatory Authority to which the filing relates).

(f) Responsibilities. The Filing Party shall deliver a copy of the final version of the filing ("Final Filing") to the Non-Filing Party at least [***] prior to the required filing date. Subject to the foregoing, the Non-Filing Party will not assume any responsibility for the accuracy of any other materials submitted by the Filing Party to a Regulatory Authority in connection with this Agreement. Except as otherwise set forth in this Agreement or the Technology Transfer Agreement, the Filing Party is solely responsible for the preparation and filing of any materials required by a Regulatory Authority with respect to such Party's Regulatory Obligations hereunder and any relevant costs will be borne by the Filing Party.

ARTICLE IV. FEES AND INVOICING

4.1 General. Patheon shall invoice Client for all applicable fees and charges incurred by Patheon. All invoices shall be sent electronically to [***]. Payment shall be due [***] days after receipt an undisputed invoice. All fees and costs in this Agreement are shown in British Pounds (GBP) but which shall be adjusted as described in Section 2.6(c) so that all invoices from Patheon and payments from Client to Patheon hereunder shall be in United States Dollars (USD).

4.2 Late Fees. In relation to all invoices issued by Patheon pursuant to this Agreement, if Client fails to make any payment due to Patheon by the due date for payment, then, without limiting Patheon's remedies under Article VIII or at law, Patheon may charge interest on past due accounts at [***] above the Bank of England Official Bank Rate per annum.

4.3 Disputed Invoices. If Client disputes any portion of an invoice, (a) Client shall provide Patheon with written notice of the disputed portion on or before [***] of receipt by Client of Patheon's invoice and its reasons therefor and shall not be obliged to pay such disputed portion unless and until such disputed portion is determined to be due and owing, and (b) Patheon shall cancel such invoice and issue a new invoice reflecting the undisputed invoiced amount, which shall be paid by Client on or before [***] after the date thereof. The Parties shall use Commercially Reasonable Efforts to resolve the dispute regarding the disputed amount promptly and in good faith, and if the Parties agree that a balance is due, Patheon shall issue an invoice for such balance, and payment shall be due [***] after receipt of such invoice. In the event of any inconsistency between an invoice and this Agreement, the terms of this Agreement shall control.

4.4 Taxes.

(a) VAT.

(i) Any payment due to Patheon under this Agreement in consideration for the provision of Manufacturing Services to Client by Patheon or any payment due to Patheon under the Technology Transfer Agreement in consideration for the provision of Transfer Services to Client by Patheon is exclusive of value added taxes, turnover taxes, sales taxes or similar taxes, including any related interest and penalties (hereinafter all referred to as "VAT"). If any VAT is payable on a Manufacturing Service supplied by Patheon to Client under this Agreement or a Transfer Service supplied by Patheon to Client under the Technology Transfer Agreement, this VAT will be added to the invoice amount and will be for the account of (and reimbursable to Patheon by) the Client.

(ii) If VAT on the supplies by Patheon is payable by Client under a reverse charge or withholding procedure (i.e., shifting of liability, accounting or payment requirement to recipient of supplies), Client will ensure that Patheon will not effectively be held liable for this VAT by the relevant taxing authorities or other parties.

(iii) Where applicable, Patheon will use its Commercially Reasonable Efforts to ensure that its invoices to Client are issued in such a way that these invoices meet the requirements for deduction of input VAT by Client, if Client is permitted by law to do so.

(iv) Each Party will provide the other with reasonable assistance to enable the recovery, as permitted by Applicable Law, of VAT resulting from payments made under this Agreement or the Technology Transfer Agreement, such recovery to be for the benefit of the Party bearing such VAT.

(v) If Patheon is acting as Client's buying agent, Patheon will always charge to the Client VAT in the relevant territory in addition to the amount paid by Patheon to supplier.

(vi) Reference to the Manufacturing Services or the Transfer Services in this Section also includes any element (or the entirety) of the Manufacturing Services or the Transfer Services characterised as a supply of goods by Patheon, its Third Party Subcontractors or any tax authority for VAT purposes.

(b) Duties. Client will bear the cost of all duties, levies, tariffs and similar charges (and any related interest and penalties) (together "Duties") however designated, arising from the performance of the Manufacturing Services or the Transfer Services by Patheon, including (without limitation) those imposed as a result of the shipping of Materials or Product to, from or between Patheon site(s). If these Duties are incurred by Patheon, then Patheon shall be entitled to invoice Client for these Duties at the time that they are incurred.

(c) Withholding Tax.

(i) Where any sum due to be paid to Patheon under this Agreement or the Technology Transfer Agreement is subject to any withholding or similar tax, Client will pay such withholding or similar tax to the appropriate government authority and deduct the amount paid from the amount then due to Patheon, in a timely manner and promptly transmit to Patheon an official tax certificate or other evidence of such withholding sufficient to enable Patheon to claim such payment of taxes. The Parties agree to cooperate with one another and use Commercially Reasonable Efforts to reduce or eliminate tax withholding or similar obligations in respect of royalties, milestone payments, and other payments made by Client to Patheon under this Agreement or the Technology Transfer Agreement.

(ii) Patheon will provide Client any tax forms that may be reasonably necessary in order for Client not to withhold tax or to withhold tax at a reduced rate under an applicable bilateral income tax treaty.

(iii) Each Party will provide the other with reasonable assistance to enable the recovery, as permitted by Applicable Law, of withholding taxes, or similar obligations resulting from payments made under this Agreement or the Technology Transfer Agreement, such recovery to be for the benefit of the Party bearing such withholding tax.

(d) No Offset. Any tax or Duty that Client pays, or is required to pay, but which Client believes should properly be paid by Patheon pursuant to this Agreement or the Technology Transfer Agreement may not be offset against sums due by Client to Patheon whether due pursuant to this Agreement or the Technology Transfer Agreement or otherwise.

ARTICLE V. INTELLECTUAL PROPERTY

5.1 Ownership.

(a) Client shall maintain ownership and Control of all of its technology and Intellectual Property rights existing prior to the Effective Date ("Existing Client Intellectual Property").

(b) Patheon shall maintain ownership and Control of all of its technology and Intellectual Property rights existing prior to the Effective Date ("Existing Patheon Intellectual Property").

(c) Existing Client Intellectual Property shall include and Client shall own all right, title, and interest in and to (i) the Product, (ii) the Specifications, and (iii) the Client Manufacturing Process.

(d) Existing Patheon Intellectual Property shall include and Patheon shall own all right, title, and interest in and to the Patheon Manufacturing Equipment as of the Effective Date.

(e) Client shall own all right, title, and interest in and to, all Intellectual Property with respect to, and any data with respect to:

(i) (A) any improvement of, modification of, change of, enhancement of, new indication for, new formula for, new formulation for, new ingredients for, new dosage for, new dosage strength for, new means of delivery for, or new packaging for, the Product ("Client Product Improvements"); (B) any improvement of, modification of, change of, or enhancement of the Specifications ("Client Specification Improvements"); (C) any improvement of, modification of, change of, enhancement of, new process for, new procedure for, new step for the Client Manufacturing Process (the "Client Manufacturing Process Improvements"); and (D) any improvements of, modification of, change of or enhancement of Client Manufacturing Equipment (the "Client Manufacturing Equipment Improvements") in each of case (A), (B), (C) and (D), (1) that is developed, conceived, or created after the Effective Date specifically as a result of or in connection with this Agreement, including Patheon's Manufacturing of the Product hereunder, (2) whether or not patentable, (3) whether developed, conceived, or created by employees of, or consultants to, Client or Patheon, alone or jointly with each other or with permitted Third Parties (including permitted sublicensees and subcontractors), and (4) that relates exclusively to the Product, Specifications, the Client Manufacturing Process or the Client Manufacturing Equipment as applicable; and

(ii) any Intellectual Property developed, conceived, or created by Client, alone or jointly with Third Parties (other than Patheon or its Affiliates, or their respective employees and consultants), in the course of conducting activities outside the scope of this Agreement and without any use of any Existing Patheon Intellectual Property, Patheon Improvements or Patheon Independent Manufacturing Equipment Improvements (as defined hereunder).

(f) Patheon shall own all right, title, and interest in and to, all Intellectual Property with respect to, and any data with respect to:

(i) any improvement of, modification of, change of, enhancement of any Patheon Manufacturing Equipment, (1) that is developed, conceived, or created as a result of or in connection with this Agreement, including Patheon's Manufacturing of the Product hereunder, (2) whether or not patentable, (3) whether developed, conceived, or created by employees of, or consultants to, Client or Patheon, alone or jointly with each other or with permitted Third Parties (including permitted sublicensees), and (4) that is of generic application rather than a specific solution that only has applicability to the Product, ("Patheon Independent Manufacturing Equipment Improvements");

(ii) any improvement of, modification of, change of, enhancement of manufacturing, processing, formulating, filling or packaging technology or equipment which is (x) generated or derived by Patheon, alone or jointly, and (y) of

generic application rather than specific to the Product ("Patheon Improvement"); and

(iii) any Intellectual Property developed, conceived, or created by Patheon, alone or jointly with Third Parties, in the course of conducting activities outside the scope of this Agreement and without any use of any Existing Client Intellectual Property, Client Product Improvements, Client Specification Improvements, Client Manufacturing Process Improvements or Client Manufacturing Equipment Improvements.

(g) Patheon shall, and shall cause its Affiliates to, promptly disclose in writing and in reasonable detail to Client any Client Product Improvements, Client Specification Improvements, Client Manufacturing Process Improvements or Client Manufacturing Equipment Improvements developed, conceived, or created by employees, consultants, or subcontractors of Patheon or its Affiliates, alone or jointly with employees, consultants or subcontractors of Client or its Affiliates. Such written notice will be treated as the Confidential Information of Client hereunder.

(h) Client shall, and shall cause its Affiliates to promptly disclose in writing and in reasonable detail to Patheon any potential Patheon Independent Manufacturing Equipment Improvements or Patheon Improvement developed, conceived, or created by employees, consultants, or subcontractors of Client or its Affiliates, alone or jointly with employees, consultants, or subcontractors of Patheon or its Affiliates. Such written notice will be treated as the Confidential Information of Patheon hereunder.

(i) The Specifications, the Client Manufacturing Process, and any and all information or material related to the Existing Client Intellectual Property, Client Product Improvements, Client Specification Improvements, Client Manufacturing Process Improvements or Client Manufacturing Equipment Improvements shall constitute Confidential Information of Client, which shall be deemed the disclosing party with respect to such Confidential Information.

(j) The Patheon Manufacturing Equipment and any and all information or material related to the Existing Patheon Intellectual Property, the Patheon Independent Manufacturing Equipment Improvements or Patheon Improvements shall constitute Confidential Information of Patheon, which shall be deemed the Disclosing Party with respect to such Confidential Information.

5.2 Licenses.

(a) Client hereby grants, for the purposes of this Agreement only, to Patheon a fully paid-up worldwide, non-exclusive license, under Client's entire right, title, and interest in and to the Existing Client Intellectual Property for Patheon to Manufacture the Products solely pursuant to the terms of this Agreement.

(b) Client hereby grants, for the purposes of this Agreement only, to Patheon a fully paid-up worldwide, non-exclusive license, under Client's entire right, title, and interest in and

to the Client Product Improvements, Client Specification Improvements, Client Manufacturing Process Improvements and Client Manufacturing Equipment Improvements, in each case to make Products solely pursuant to the terms of this Agreement.

(c) Patheon hereby grants to Client a fully paid-up perpetual worldwide, non-exclusive license, with the right to sublicense to Affiliates only, under Patheon's entire right, title, and interest in and to the Patheon Independent Manufacturing Equipment Improvements, the Existing Patheon Intellectual Property (to the extent incorporated in, or used in the Manufacture of, the Product) and the Patheon Improvements (to the extent incorporated in, or used in the Manufacture of, the Product) to make, use, offer for sale, sell, import, and otherwise dispose of the Product only.

5.3 Technology Transfer.

(a) Upon the request of Client at any time during the [***] period prior to expiry of this Agreement or in the event of a failure by Patheon to supply Products in accordance with the terms of this Agreement for a period exceeding [***] following notice of breach by Client and period of remedy by Patheon pursuant to Section 8.2(a)(vii), Patheon shall, at Client's cost (i) have its representatives meet with representatives of Client or its designee to enable Client or such designee to Manufacture the Product, and (ii) provide such other assistance as Client may reasonably request to enable Client or such designee to Manufacture the Product. Client shall reimburse Patheon for its fees and all documented out-of-pocket expenses reasonably incurred by Patheon in connection with such technology transfer, save where the technical transfer arises from a termination of this Agreement by Client pursuant to Section 8.2(a)(vii) following a uncured failure by Patheon to supply Products in accordance with the terms of this Agreement for a period exceeding [***], in which case Patheon will provide a [***] on its quotation referred to below up to a maximum of [***]. Such [***] shall count towards the Maximum Liability for that year pursuant to Section 9.5(a). Patheon will provide a quotation for the services which Client requires pursuant to this Section 5.3 as Additional Services and on acceptance by Client of the same, Patheon will provide the services stated therein. This Section is without prejudice to Client's obligations in Section 2.1(a).

(b) Following a request for technical transfer services pursuant to Section 5.3(a), Patheon shall:

(i) provide to Client copies of all technical documentation, Specifications, procedures and know-how in their possession or control that are reasonably required for the Manufacture of the Products in each case as agreed by the Parties in advance pursuant to Section 5.3;

(ii) make available to Client the services of such qualified and experienced scientists, production and quality assurance personnel, engineers, and quality checking personnel as may be necessary to support the technical transfer process and the establishment of the Manufacturing process for the Products in each case as agreed by the Parties in advance pursuant to Section 5.3, and at such convenient times as the Parties may reasonably agree; and

(iii) provide Client or its designee (but not any competitor of Patheon (i.e. a business that derives greater than [***] of its revenues from performing contract pharmaceutical development or commercial manufacturing services), with reasonable access to the Facility to observe the Manufacture of the Products at such times as the Parties may agree.

ARTICLE VI. REPRESENTATIONS AND WARRANTIES

6.1 Representations and Warranties of Each Party. Each Party hereby represents and warrants to the other Party as follows:

(a) Such Party (i) is duly formed and in good standing under the laws of the jurisdiction of its formation, (ii) has the power and authority and the legal right to enter into this Agreement and perform its obligations hereunder, and (iii) has taken all necessary action on its part required to authorize the execution and delivery of this Agreement and the performance of its obligations hereunder. This Agreement has been duly executed and delivered on behalf of such Party and constitutes a legal, valid, and binding obligation of such Party and is enforceable against it in accordance with its terms, subject to the effects of bankruptcy, insolvency, or other similar laws of general application affecting the enforcement of creditor rights and judicial principles affecting the availability of specific performance and general principles of equity, whether enforceability is considered a proceeding at law or equity.

(b) From FDA Approval Date, all necessary consents, approvals, and authorizations of all Regulatory Authorities, other governmental authorities, and other Persons required to be obtained by such Party in connection with the execution and delivery of this Agreement and the performance of its obligations hereunder have been obtained.

(c) The execution and delivery of this Agreement and the performance of such Party's obligations hereunder (i) do not and will not conflict with or violate any requirement of Applicable Law or any provision of the articles of incorporation, bylaws limited partnership agreement, or other constituent document of such Party and (ii) do not and will not conflict with, violate, or breach, or constitute a default or require any consent under, any contractual obligation or court or administrative order by which such Party is bound.

6.2 Additional Representations, Warranties, and Covenants of Patheon. Patheon warrants, represents, and covenants that:

(a) it has facilities, personnel, experience, and expertise sufficient in quality and quantity to perform its obligations hereunder;

(b) it shall perform its obligations hereunder in conformity with GMPs where applicable;

(c) it will comply with the Quality Agreement and comply with all agreed upon quality assurance, quality controls, and review procedures in the performance of its obligations hereunder;

(d) it has at the Effective Date and shall, during the Term of this Agreement and at its cost (subject to Section 2.10(b)), in connection with this Agreement, observe and comply with all Applicable Laws, including federal, state, and local laws, orders, regulations, rules, customs, and ordinances now in force or that may hereafter be in force, pertaining to the Facility and the performance of the Manufacturing Services and including, without limitation, (i) labor laws, orders, regulations, rules, customs, and ordinances of the country of Manufacture and (ii) those of the FDA pertaining to the Manufacturing Services and the Facility (but not those pertaining to non-Manufacturing matters relating to the Product, compliance with which shall be the responsibility of Client), and any laws, orders, regulations, rules, or ordinances issued in addition to, as a supplement to or as a replacement of Applicable Laws.

(e) as at the Effective Date, it has received no warning letter from any Regulatory Authority in relation to the Facility in the [***] period prior to the Effective Date (including in relation to the compliance of that Facility with all applicable requirements of GMP);

(f) as at the Effective Date, there are no outstanding FDA Form 483 observations (or any equivalent observations from any Regulatory Authority under Applicable Law) in relation to the Facility;

(g) none of it, its Affiliates, nor any Person under its direction or control (including Third Party Subcontractors), has ever been, nor will it engage suppliers which have to its actual knowledge, after due inquiry, been, (i) debarred or convicted of a crime for which a person can be debarred, under Section 335(a) or 335(b) of the FDA Act, or any equivalent Applicable Law of the country of Manufacture, (ii) threatened to be debarred under the FDA Act or any equivalent Applicable Law of the country of Manufacture or (iii) indicted for a crime or otherwise (to its actual knowledge after due inquiry) engaged in conduct for which a person can be debarred by the FDA or any equivalent Regulatory Authority pursuant to Applicable Law of the country of Manufacture, and Patheon agrees that it will promptly notify Client in the event it receives notification of any such debarment, conviction, threat or indictment. Should Patheon become aware of any suspected non-compliance with the foregoing, Patheon will notify Client in writing of such issue on or before [***]. For the purpose of this Section 6.2, suppliers and subcontractors engaged by Patheon to undertake the Manufacture of the Product shall be deemed to be under Patheon's direction or control;

(h) none of it, its Affiliates, nor any Person under its direction or control is currently excluded from a federal or state health care program under Sections 1128 or 1156 of the Social Security Act, 42 U.S.C. §§ 1320a-7, 1320c-5 or any equivalent Applicable Law of the country of Manufacture, as may be amended or supplemented;

(i) none of it, its Affiliates, nor any Person under its direction or control is otherwise currently excluded from contracting with the U.S. federal government or the government of the country of Manufacture;

(j) none of it, its Affiliates, nor any Person under its direction or control is otherwise currently excluded, suspended, or debarred from any U.S. or foreign governmental program;

(k) it shall immediately notify Client if, at any time during the Term, Patheon, its Affiliates, or any Person under its direction or control is convicted of an offense that would subject it or Client to exclusion, suspension, or debarment from any U.S. or foreign governmental program;

(l) it agrees to keep the Equipment free from all liens and encumbrances; and

(m) it will not enter into any agreement or arrangement with any other Third Party that would prevent its ability to perform its obligations hereunder

6.3 Warranty. Patheon warrants that:

(a) Products will be Manufactured in accordance with Section 2.1(c) of this Agreement, Quality Agreement, GMP, and all other Applicable Law;

(b) without prejudice to Section 2.8, at the time of delivery the Products will conform with the Specifications in accordance with the testing regime set out therein and will conform with the Certificate of Analysis therefor provided pursuant to Section 2.3(j);

(c) at the time of delivery title to such Product will pass to Client as provided herein free and clear of any security interest, lien, or other encumbrance;

(d) at the time of delivery such Product will not be adulterated or misbranded within the meaning of the FDA Act as a result of a Patheon Nonconformance; and

(e) at the time of delivery such Product will not be an article that, under the provisions of the FDA Act, may not be introduced into interstate commerce as a result of a Patheon Nonconformance.

6.4 Additional Representations, Warranties, and Covenants of Client. Client warrants, represents, and covenants that:

(a) Non-Infringement.

(i) to its knowledge, as at the Effective Date (1) it or its Affiliates Control all right, title, and interest in all Intellectual Property in the Client Manufacturing Process, the Client Manufacturing Equipment, the Product and the Specifications necessary for performance of the Manufacturing Services; and (2) it has the right to authorize Patheon to perform the Manufacturing Services, in each case in accordance with the terms and conditions hereof;

(ii) to its knowledge, as at the Effective Date, the performance of the Manufacturing Services hereunder, in accordance with the terms and conditions hereof and using the Client Manufacturing Process, or the manufacture, use, supply or other disposition of the Product by Patheon as may be required to perform its obligations under this Agreement or by Client, does not and will not result, in the infringement or misappropriation of any Third Party's Intellectual Property rights;

(iii) Client or its Affiliates Control and have the right to lawfully disclose the Specifications to Patheon and to authorize Patheon to use the Specification to perform the Manufacturing Services;

(iv) as of the Effective Date, so far as Client is aware there are no actions or other legal proceedings pending concerning the infringement of Third Party Intellectual Property rights related to any of the Specifications, the Client Manufacturing Process or any of the Materials, or the supply, use, or other disposition of any Product made in accordance with the Specifications.

(b) Quality and Compliance.

(i) during the Term, the Product, if Manufactured in accordance with the Specifications and in compliance with the Quality Agreement, applicable GMP and Applicable Laws, may be lawfully sold and distributed in every jurisdiction in which Client markets the Product; and

(ii) during the Term, on the date of shipment, the Client-Supplied Materials will conform to the specifications for the Client-Supplied Materials that Client has given to Patheon and the Client-Supplied Materials will be adequately contained, packaged, and labelled and will conform to the affirmations of fact on the container, provided that this shall not negate Patheon's obligations to perform any incoming inspections of Client-Supplied Materials as set out in the Specifications or the Quality Agreement.

(c) Client agrees that, as a pre-condition to the adding of any country to the Territory pursuant to Section 2.2(t), Client shall repeat the warranties above as at the date on which the country is added to the Territory.

6.5 **DISCLAIMER. THE FOREGOING EXPRESS WARRANTIES SET FORTH IN THIS ARTICLE VI ARE IN LIEU OF ALL OTHER WARRANTIES, EXPRESS OR IMPLIED, INCLUDING ANY WARRANTY OF MERCHANTABILITY, OR FITNESS FOR A PARTICULAR PURPOSE, OR NON-INFRINGEMENT, AND ALL OTHER WARRANTIES ARE HEREBY DISCLAIMED AND EXCLUDED BY EACH PARTY.**

ARTICLE VII. CONFIDENTIALITY

7.1 Confidentiality Obligations. The Parties agree that the terms of the Confidentiality Agreement dated 28 September 2016 between Client and Patheon Inc. (an Affiliate of Patheon), shall apply to all Confidential Information disclosed by a Party or its Affiliates to the other Party and are incorporated herein by this reference (the "Confidentiality Agreement"), provided that paragraph 5 of the Confidentiality Agreement shall be replaced with the following:

"Required Disclosure. The receiving Party may disclose Confidential Information to the extent that it is required by law or order of any governmental authority or agency or the rules and regulations of any securities authority or stock exchange on which securities issued by a Party or

its Affiliates are traded, including the Securities and Exchange Commission; provided that the receiving Party, using good faith efforts, shall apply for confidential treatment of such Confidential Information including Confidential Information contained in this Agreement or the Technology Transfer Agreement (if redacted versions of these agreements are required to be disclosed), shall provide the other Party a copy of the confidential treatment request far enough in advance and at least [***] business days, if possible, of its filing to give the other Party a meaningful opportunity to comment thereon and in order to provide the disclosing Party an opportunity to seek a protective order or the like with respect to certain Confidential Information, and shall incorporate in such confidential treatment request any reasonable comments of the other Party, in each case to the fullest extent permitted under applicable laws, rules or regulations."

7.2 Injunctive Relief. Each Party acknowledges that a breach by either Party of the Confidentiality Agreement or of this Article VII may not reasonably or adequately be compensated in damages in an action at law and that such a breach may cause the other Party irreparable injury and damage. By reason thereof, each Party agrees that the other Party may be entitled, in addition to any other remedies it may have under this Agreement or otherwise, to apply for preliminary and permanent injunctive and other equitable relief to prevent or curtail any breach of the Confidentiality Agreement or this Article VII; provided, however, that no specification in this Agreement of a specific legal or equitable remedy will be construed as a waiver or prohibition against the pursuing of other legal or equitable remedies in the event of such a breach. Each Party agrees that the existence of any claim, demand, or cause of action of it against the other Party, whether predicated upon this Agreement, or otherwise, will not constitute a defense to the enforcement by the other Party, or its successors or assigns, of the covenants contained in the Confidentiality Agreement and this Article VII.

ARTICLE VIII. TERM AND TERMINATION

8.1 Term. This Agreement shall commence as of the Effective Date and, unless earlier terminated in accordance with the terms hereof, shall expire on the seventh (7^{th}) anniversary of the FDA Approval Date (the "Initial Term"). Notwithstanding the foregoing, by mutual agreement, the Parties may commence discussions three (3) years prior to the end of the Initial Term with a view to extending the Initial Term for periods of two (2) years each (collectively, the Initial Term and any extensions thereof, the "Term").

8.2 Termination. In addition to any other provision of this Agreement expressly providing for termination of this Agreement, this Agreement may be terminated as follows:

(a) Client may terminate this Agreement by notice in writing to Patheon:

(i) at any time prior to the grant of the Marketing Authorization for the Product in the United States, by giving Patheon [***] prior written notice if: (A) Client's application for Marketing Authorization in the United States is rejected, or (B) any Regulatory Authority causes the clinical hold or permanent withdrawal of the Product;

(ii) at any time after the grant of the Marketing Authorization for the Product in the United States, by giving Patheon [***] prior written notice in the event that the Product is discontinued or withdrawn from (1) the United States, or (2) any other market in a country or countries of the Territory that represent [***] or more of Client's overall Product sales, for safety, quality or regulatory reasons;

(iii) if any Regulatory Approval naming Patheon as the Manufacturer of the Product is withdrawn by the applicable Regulatory Authority in relation to (1) the United States or (2) any other market in a country or countries of the Territory that represent [***] or more of Client's overall Product sales (for clarity, this does not refer to Patheon's manufacturer licence issued by the Medicines and Healthcare products Regulatory Agency in the United Kingdom);

(iv) if Patheon challenges Client's ownership of, or right to use, the Existing Client Intellectual Property by submission to a governmental authority responsible for Intellectual Property rights or to a court with jurisdiction over Intellectual Property rights provided that the performance of manufacturing or development services for other clients shall not be regarded as a challenge to Client's ownership of, or right to use, the Existing Client Intellectual Property;

(v) for convenience, at any time prior to the FDA Approval Date, with [***] written notice to Patheon;

(vi) for convenience, at any time after the FDA Approval Date, by giving Patheon (1) in the first [***] from the FDA Approval Date, [***] prior written notice; (2) in the [***] from the FDA Approval Date, [***] prior written notice; (3) in the [***] from the FDA Approval Date, [***] prior written notice; and (4) in any extension of this Agreement after the Initial Term, [***] prior written notice; or

(vii) at any time upon written notice in the event of any material default by Patheon in the performance of any of its obligations hereunder, which material default has not been cured by Patheon on or before [***] after receiving written notice thereof ("Remediation Period"), provided that (i) the Parties shall use Commercially Reasonable Efforts to agree a plan to remedy the material default within [***] days after written notice is given to Patheon and (ii) Patheon shall continue performing hereunder pursuant to the terms of Section 8.4 below. Client's right to terminate this Agreement for a particular breach under this Section 8.2(a)(vii) may only be exercised for a period of [***] following the expiry of the Remediation Period (where the breach has not been remedied) and, if the termination right is not exercised during this period, then Client will be deemed to have waived its right to terminate this Agreement for such breach.

(b) Patheon may terminate this Agreement at any time upon written notice in the event of (i) any material default by Client in the performance of any of its obligations hereunder (excluding payment), which default has not been cured by Client on or before [***] after receiving written notice thereof; or (ii) Client's default of its payment obligations in accordance with Article

IV in relation to undisputed invoices which default has not been cured by Client on or before [***] after receiving written notice thereof; provided, however, that, if Client fails to cure such payment default, Patheon may not terminate without first providing a second notice to the attention of Client's Chief Executive Officer and an additional [***] cure period.

(c) This Agreement may be terminated at any time by either Party immediately upon written notice to the other Party (A) pursuant to Section 10.2, in the event of a force majeure that remains uncured for the period provided in Section 10.2, or (B) if the other Party shall file in any court or agency, pursuant to any statute or regulation of any state or country, a petition in bankruptcy or insolvency or for reorganization or for arrangement or for the appointment of a receiver or trustee of the other Party or of its assets, or if the other Party proposes a written agreement of composition of its debts, or if the other Party shall be served with an involuntary petition against it, filed in any insolvency proceeding, and such petition is consented to by such Party or is not dismissed on or before [***] after the filing thereof, or if the other Party shall propose or be a party to any dissolution or liquidation, or if the other Party shall make an assignment for the benefit of its creditors.

(d) This Agreement will automatically terminate should either Client or Patheon exercise its right to terminate the Technology Transfer Agreement (but not in the event of an expiration of such agreement as set forth in Section 8.2 thereof) prior to the FDA Approval Date, in which case, any payment to Patheon will be made in accordance with the Technology Transfer Agreement.

8.3 Effect of Termination.

(a) The expiration or termination of this Agreement shall be without prejudice to any rights or obligations of the Parties that may have accrued prior to such termination, and the provisions of Sections 2.8, 3.7, 3.12, 3.14, 8.3 and 8.4, and ARTICLE I, ARTICLE IV, ARTICLE V, ARTICLE VII, ARTICLE IX and ARTICLE X shall survive the expiration or termination of this Agreement. Except as otherwise expressly provided herein, termination of this Agreement in accordance with the provisions hereof shall not limit remedies that may otherwise be available in law or equity.

(b) Upon expiration or termination of this Agreement, subject to the Parties' obligations under Section 8.4 below, each Party, at the request of the other, shall return all data, files, records, and other materials in its possession or control containing or comprising the other Party's Confidential Information.

(c) Upon expiration or termination of this Agreement for any reason, subject to the Parties' obligations under Section 8.4 below:

(i) all submitted but unfilled Purchase Orders with respect to which Patheon has (1) not begun Manufacture of Product shall be cancelled, or (2) begun Manufacture of the Product shall be completed, unless otherwise agreed;

(ii) Patheon will dismantle the Client Manufacturing Equipment and prepare and make it available for collection from the Facility according to a procedure agreed by the Parties (acting reasonably), following which Client shall remove all Client Manufacturing Equipment, Product and Materials from the Facility on or before the day [***] after the completion of said procedure, failing which Client will pay a fee equivalent to the aggregate monthly Base Fee for the Manufacturing Suite for each month or part month the Client Manufacturing Equipment, Product or Materials remain at the Facility after [***] post termination;

(iii) if Patheon has Manufactured any stocks of finished Product in addition to those ordered pursuant to a Purchase Order, or has ordered any Patheon-Supplied Materials in addition to those ordered as set out in Section 2.2(u), Client shall at its option place an order with Patheon for any of such finished Products and/or Patheon-Supplied Materials in accordance with the terms of this Agreement;

(iv) Patheon shall submit an invoice for any unpaid Material Costs, Maintenance Costs, Disposal Costs or any Bill Back Items which were ordered, purchased, produced or maintained by Patheon in contemplation of the Manufacture of the Product prior to the date of termination in accordance with Section 2.2, provided that Client shall not be liable for the costs of any Materials purchased in excess of those amounts needed to meet Purchase Orders (or such longer period as the Parties may have otherwise agreed);

(v) Client shall pay Patheon any earned but unpaid Product Fees, including those under any outstanding Purchase Order as described in Section 8.3(c)(i);

(vi) Client shall pay for any earned but undisputed and unpaid Base Fees, or fees for Additional Services; and

(vii) Client shall pay all due and outstanding invoices under Article IV.

(d) Upon expiration or termination of this Agreement for any reason other than by [***] pursuant to [***], subject to the Parties' obligations under Section 8.4 below, Client shall pay to Patheon all and any (i) dismantling costs, (ii) removal costs and (iii) Make Good Costs associated with the cessation of the Manufacturing Services or removal of the Client Manufacturing Equipment from the Facility. "Make Good Costs" means the reasonable costs required to clean, decontaminate or repair the Facility and return it to a clean, safe and useable area based on the contamination caused by the Manufacturing Services or repair of damage caused by the installation or removal of Client Manufacturing Equipment.

(e) Upon expiration or termination of this Agreement for any reason other than by [***] pursuant to [***], subject to the Parties' obligations under Section 8.4 below, Client shall pay to Patheon the following costs ("Manufacturing Services Termination Costs"): (i) all actual costs incurred by Patheon to complete activities associated with the completion, expiry or termination including, without limitation, disposal fees that may be payable for any Materials and supplies owned by Client to be disposed of by Patheon; and (ii) all and any direct costs and expenses, or wasted costs and expenses, or termination or cancellation fees payable by Patheon as a consequence of or arising from the termination of this Agreement, to include but not limited to, all and any redundancy costs of employees employed by Patheon to work solely or mainly in providing the Manufacturing Services and/or Manufacturing the Product, all and any termination costs in relation to subcontractors and agency staff working solely or mainly in providing the Manufacturing Services and/or Manufacturing the Product, any termination or cancellation fees payable to Third Party suppliers. Patheon will use Commercially Reasonable Efforts to mitigate the Manufacturing Services Termination Costs. Patheon will further provide Client with documentation in order to substantiate the Manufacturing Services Termination Costs.

(f) Upon termination (in whole) or expiry of this Agreement for any reason:

(i) the licences granted in Sections 5.2(a) and 5.2(b) shall terminate and Patheon shall not make any use for any purpose whatsoever of any of Client's Intellectual Property or any of Client's Confidential Information contained in the Quality Agreement except to the extent necessary to fulfil any Purchase Order or order placed by Client in accordance with Section 8.3(c)(iii) or to perform any other obligation under this Agreement;

(ii) any Yield Reimbursement Payment shall be paid which may be pro rata basis for any part year as applicable and which may be offset by any undisputed amounts owing to Patheon under this Agreement.

(g) Client acknowledges that no Patheon competitor (being a Person that derives greater than [***] of its revenues from performing contract pharmaceutical or biopharmaceutical development or commercial manufacturing services) will be permitted access to the Facility.

(h) In relation to any representatives of Client that are permitted access to the Facility pursuant to Section 8.3 or 8.4, Client shall ensure that such representatives are appropriately trained by Client (*e.g.*, GMP training) and shall observe at all times Patheon's policies and procedures (as amended from time-to-time) as they pertain to the Facility, including policies relating to health and safety and compliance with GMP, and comply with all reasonable directions of Patheon in relation to the same; provided that Client is given notice of such policies and given a reasonable period of time to review and implement such policies. Patheon may refuse or limit in its sole discretion at any time admission to the Facility by any of Client's representatives who fail to observe such policies or comply with such reasonable directions.

(i) The Parties agree that if any fees or charges are duplicated under this Agreement and the Technology Transfer Agreement, Client shall only be obligated to make such payment once.

8.4 Transition Assistance. Upon the delivery by either Party of a notice of termination of this Agreement for any reason other than by Patheon pursuant to Section 8.2(b) or (c), upon the request of Client, and subject to terms set forth in this Agreement, Patheon shall provide Client with the reasonable assistance of its staff and reasonable access to its other internal resources to provide Client with a reasonable level of technical assistance and consultation to transfer the Manufacture and the regulatory qualification of the Product to a supplier of Client's election, provided that Client will reimburse Patheon for its fees and all documented costs and out-of-pocket expenses incurred in connection with such assistance (Patheon would provide a quotation for the services which Client requires pursuant to this Section 8.4 as Additional Services and on acceptance by Client of the same, Patheon will provide the services stated therein).

ARTICLE IX. INDEMNIFICATION

9.1 Client Indemnification Obligations. Client shall indemnify Patheon, its Affiliates, and their respective directors, officers, employees, and agents (the "Patheon Indemnified Parties"), and defend and save each of them harmless, from and against:

(a) any and all Third Party Losses incurred by any of them in connection with, arising from, or occurring as a result of: (i) any gross negligence or willful misconduct by Client or any of its Affiliates; (ii) any claim made by any Person that the Manufacture and supply of the Product using the Client Manufacturing Process or any of Client's Intellectual Property, in each case in accordance with the terms hereof, infringes or misappropriates the Intellectual Property rights of such Person (other than to the extent arising as a result of any of Patheon's Intellectual Property used in accordance with the terms of this Agreement or the use by Patheon of any Third Party Intellectual Property); or (ii) any product liability claim made by any Person with respect to any Products which upon delivery conformed to and were Manufactured in accordance with the terms of Section 2.1(c); or

(b) any Loss incurred by any of them in connection with: (i) the negligence or willful misconduct of the Client On Site Representatives at the Facility; or (ii) any damage to Patheon's property or any claims of personal injury to any Patheon employees or Third Party Subcontractors caused as a result of Patheon's use of the Client Manufacturing Equipment in the performance of the Manufacturing Services provided that Patheon and its employees and Third Party Subcontractors have complied with all applicable Equipment Standard Operating Procedures or the manufacturer's terms of operation and recommended procedures for the Client Manufacturing Equipment, Specifications, and have not otherwise acted in a negligent manner or committed an act of willful misconduct in connection with the use and Maintenance of the Client Manufacturing Equipment;

except, in each case for (a) and (b), for those Losses for which Patheon has an obligation to indemnify the Client Indemnified Parties pursuant to Section 9.2, as to which Losses each Party shall indemnify the other to the extent of their respective liability for such Losses; and provided, however, that

Client will not be required to indemnify the Patheon Indemnified Parties with respect to any such Loss hereunder to the extent the same is caused by any breach of contract, negligent act or omission, or intentional misconduct by any Patheon Indemnified Parties. Client acknowledges that Patheon has not and will not conduct any freedom to operate searches in relation to the Product or the Client Manufacturing Process nor reviewed any Third Party patents in relation thereto and that Patheon's failure or omission to do so will not be considered negligence for the purposes of excluding or limiting a claim under this indemnity.

9.2 Patheon Indemnification Obligations. Patheon shall indemnify Client, its Affiliates, and their respective directors, officers, employees, and agents (the "Client Indemnified Parties"), and defend and save each of them harmless, from and against:

(a) any Third Party Losses incurred by any of them resulting from, or relating to, any claim of personal injury or property damage to the extent that the injury or damage is in connection with, arising from, or occurring as a result of: (i) any failure by Patheon to Manufacture and supply Products in accordance with the terms of in this Agreement; (ii) any gross negligence or willful misconduct by Patheon or any of its Affiliates; or (iii) any product liability claim made by any Person with respect to any Product Manufactured by Patheon to the extent any such liability is based on or caused by a Patheon Nonconformance; or

(b) any Third Party Losses incurred by any of them in connection with, arising from, or occurring as a result of a claim that any Existing Patheon Intellectual Property, Patheon Independent Manufacturing Improvement or Patheon Improvement used by Patheon in the Manufacture or supply of the Product infringes or misappropriates the Intellectual Property rights of such Person;

except in each case for (a) and (b) for which Client has an obligation to indemnify the Patheon Indemnified Parties pursuant to Section 9.1, as to which Losses each Party shall indemnify the other to the extent of their respective liability for such Losses; and provided, however, that Patheon will not be required to indemnify the Client Indemnified Parties with respect to any such Loss hereunder to the extent the same is caused by any breach of contract, negligent act or omission, or intentional misconduct by Client Indemnified Parties.

9.3 Indemnification Procedure.

(a) Indemnification Procedure. The indemnified Party (the "Indemnified Party") shall give the indemnifying Party (the "Indemnifying Party") prompt written notice of any Loss, action, or discovery of facts upon which such Indemnified Party intends to base a request for indemnification under Section 9.1 or 9.2 (a "Claim"), but in no event shall the Indemnifying Party be liable for any Losses that result from any delay in providing such notice. The Indemnified Party will: (i) use Commercially Reasonable Efforts to mitigate the effects of the Claim; (ii) reasonably cooperate with the Indemnifying Party in the defense of the Claim; and (iii) permit the Indemnifying Party to control the defense and settlement of the Claim, all at the Indemnifying Party's cost and expense.

(b) Settlement. With respect to any Losses (i) relating solely to the payment of money damages in connection with a Claim, (ii) that will not result in the Indemnified Party becoming subject to injunctive or other relief or otherwise adversely affect the business or reputation of the Indemnified Party in any manner, and (iii) as to which the Indemnifying Party has acknowledged in writing the obligation to indemnify the Indemnified Party hereunder, the Indemnifying Party shall have the sole right to consent to the entry of any judgment, enter into any settlement, or otherwise dispose of such Loss, on such terms as the Indemnifying Party, in its sole discretion, shall deem appropriate. With respect to all other Losses in connection with Claims, where the Indemnifying Party has assumed the defense of the Claim in accordance with Section 9.3(a), the Indemnifying Party shall have authority to consent to the entry of any judgment, enter into any settlement, or otherwise dispose of such Loss; provided that it obtains the prior written consent of the Indemnified Party, which consent shall not be unreasonably withheld or delayed. The Indemnifying Party shall not, without the prior written consent of the Indemnified Party, agree to any settlement or acquiesce to any judgment with respect to a Claim that obligates the Indemnified Party to pay any amount subject to indemnification by the Indemnifying Party or causes the Indemnified Party to admit to any civil or criminal liability.

9.4 Insurance. During the Term and for [***] thereafter, each Party shall procure and maintain at its own expense from a qualified and licensed insurer liability insurance or indemnity policies, in an amount not less than [***] in the aggregate, subject to such deductible or self-retention limits as either Party in its business discretion may elect. Such policies shall insure against liability on the part of each Party and any of its Affiliates, as their interests may appear, due to injury, disability, or death of any person or persons, or injury to property, arising from the distribution of the Products. Upon the execution of this Agreement and thereafter on January 1 of each year during the Term, each Party shall provide to the other a certificate of insurance (i) summarizing the insurance coverage and (ii) identifying any exclusions. Each Party shall promptly notify the other of any material adverse alterations to the terms of this policy or decreases in the amounts for which insurance is provided.

9.5 Limitation on Damages

(a) Maximum Liability. Except with respect to (i) [***], or (ii) a breach by [***] of its obligations under [***], Patheon's maximum liability to Client under this Agreement for any reason whatsoever, including, without limitation, any liability arising under Sections 2.2(o), 2.9, 3.12, 3.14 or 9.2 hereof or resulting from any and all breaches of its representations, warranties, or any other obligations under this Agreement in each calendar year will not exceed [***] of the total [***] received by or payable to Patheon pursuant to this Agreement in the [***] period prior to the month in which the underlying event occurred that gave rise to the liability (*e.g.*, the date of the incident or manufacture). For the first [***] period after the first commercial batch, as Patheon will not have received [***] for a full [***] period, the amount of the [***] for the purpose of the limitation of liability shall be calculated based on the volume of Product set out in the first [***] of the Forecast applicable on the date of Manufacture of the first commercial batch.

(b) Section 9.5(a) shall not apply to any reimbursement of the Product Fee, Shipment Costs or [***] pursuant to Section 2.8(d)(ii).

*** Certain information on this page has been omitted and filed separately with the Securities and Exchange Commission. Confidential treatment has been requested with respect to the omitted portions.

(c) Subject to Section 9.5(d), neither Party will be liable to the other in contract, tort, negligence, breach of statutory duty, equity, or otherwise for: (i) any direct or indirect loss of profits, of production, of anticipated savings, of business, or goodwill; (ii) any reliance damages, including but not limited to costs or expenditures incurred to evaluate the viability of entering into this Agreement or to prepare for performance under this Agreement; or (iii) for any other indirect or consequential loss, liability, damage, costs, penalty or expense. For the avoidance of doubt this Section 9.5(c) shall not apply to the costs of a [***] resulting from a Patheon Nonconformance.

(d) Nothing in this Agreement shall exclude or limit either Party's liability for (i) personal injury or death caused by the negligence of that Party, or (ii) for fraud or fraudulent misrepresentation.

(e) Sole & Exclusive Remedies. Notwithstanding anything in this Article IX to the contrary Patheon's sole liability and Client's sole and exclusive remedy whether in contract, tort, equity or otherwise for:

(i) Non-Conforming Product based on or caused by a Patheon Nonconformance shall be the rights and remedies set forth in Section 2.2(o), 2.8, 2.9, 3.12, 3.14, 8.2 and 9.2 of this Agreement;

(ii) late or incomplete deliveries of Product specified in a Purchase Order by the Agreed Delivery Date as described in Section 2.3(h) (provided that the late or incomplete delivery is not the result of a breach by Patheon of any other term of this Agreement) shall be the rights and remedies set forth in Section 2.7 and Schedule D of this Agreement.

9.6 Product Liability Claims. As soon as it becomes aware, each Party will give the other prompt written notice of any defect or alleged defect in a Product, any injury alleged to have occurred as a result of the use or application of the Product, and any circumstances that may give rise to litigation or recall of a Product or regulatory action that may affect the sale or Manufacture of a Product, specifying, to the extent the Party has such information, the time, place, and circumstances thereof and the names and addresses of the persons involved. Each Party will also furnish promptly to the other copies of all papers received in respect of any claim, action, or suit arising out of such alleged defect, injury, or regulatory action.

9.7 Allocation of Risk. This Agreement (including, without limitation, this Article IX) is reasonable and creates a reasonable allocation of risk for the relative profits the Parties each expect to derive from the Products.

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ARTICLE X. MISCELLANEOUS

10.1 Notices. Notwithstanding that advance notification of any notices or other communications may be given by electronic mail transmission, all notices or other communications that shall or may be given pursuant to this Agreement shall be in writing (including by confirmed receipt electronic mail) and shall be deemed to be effective (a) when delivered if sent by registered or certified mail, return receipt requested, or (b) on the next business day, if sent by overnight courier, (c) when sent if sent by electronic mail provided that receipt is confirmed, in each case to the Parties at the following addresses (or at such other addresses as shall be specified by like notice) with postage or delivery charges prepaid:

If to Client:

Insmed Incorporated
10 Finderne Avenue, Building 10
Bridgewater, New Jersey 08807, USA
Attn: General Counsel
Email: [***]

If to Patheon:

Patheon UK Limited
Executive Director & General Manager
Kingfisher Drive, Covingham
Swindon, Wiltshire SN3 5BZ
England
Email: [***]

with copy to

Legal Director.

10.2 Force Majeure. Neither Party shall be liable for delay in delivery, performance or nonperformance, in whole or in part, nor shall the other Party have the right to terminate this Agreement except as otherwise specifically provided in this Section 10.2 where such delay in delivery, performance or nonperformance results from acts beyond the reasonable control and without the fault or negligence of such Party including, but not limited to, the following conditions: fires, floods, storms, embargoes, shortages, epidemics, quarantines, war, acts of war (whether war be declared or not), terrorism, insurrections, riots, civil commotion, or acts, omissions, or delays in acting by any governmental authority; provided that the Party affected by such a condition shall, on or before [***] of its occurrence, give notice to the other Party stating the nature of the condition, its anticipated duration, and any action being taken to avoid or minimize its effect. The suspension of performance shall be of no greater scope and no longer duration than is reasonably required, and the nonperforming Party shall use its Commercially Reasonable Efforts to remedy its inability to perform; provided, however, that in the event the suspension of performance continues for [***] days after the date of the occurrence, and such failure to perform would constitute a material breach

of this Agreement in the absence of such force majeure event, the non-affected Party may terminate this Agreement immediately by written notice to the affected Party.

10.3 Independent Contractor. The Parties to this Agreement are independent contractors. Nothing contained in this Agreement shall be construed to place the Parties in the relationship of employer and employee, partners, principal, and agent or a joint venture. Neither Party shall have the power to bind or obligate the other Party nor shall either Party hold itself out as having such authority.

10.4 Waiver. Save where expressly stated to the contrary in this Agreement, including Sections 2.8, 2.9, 3.12, 3.14, 8.2, 8.4 and 9.5, no waiver by either Party of any provision or breach of this Agreement shall constitute a waiver by such Party of any other provision or breach, and no such waiver shall be effective unless made in writing and signed by an authorized representative of the Party against whom waiver is sought. No course of conduct or dealing between the Parties will act as a modification or waiver of any provision of this Agreement. Either Party's consent to or approval of any act of the other Party shall not be deemed to render unnecessary the obtaining of that Party's consent to or approval of any subsequent act by the other Party.

10.5 Entire Agreement. This Agreement (together with all Schedules hereto, which are hereby incorporated by reference), the Quality Agreement, the Confidentiality Agreement, and the Technology Transfer Agreement constitute the final, complete, and exclusive agreement between the Parties relating to the subject matter hereof and supersede all prior conversations, understandings, promises, and agreements relating to the subject matter hereof. Neither Party has relied upon any communications, representations, terms or promises, verbal or written, not set forth herein. No terms, provisions or conditions of any Purchase Order or other business form or written authorization used by Client or Patheon will have any effect on the rights, duties, or obligations of the Parties under or otherwise modify this Agreement, regardless of any failure of Client or Patheon to object to the terms, provisions, or conditions unless the document specifically refers to this Agreement and is signed by both Parties.

10.6 Assignment; Change of Control. This Agreement may not be assigned by Patheon without the prior written consent of Client. Notwithstanding the foregoing, either Party may assign this Agreement to an Affiliate, or to an acquirer or successor in interest in connection with a Change of Control of such Party, without the prior written consent of the other Party, provided that such Party provides the other Party with written notice of any such assignment. This Agreement shall be binding upon and inure to the benefit of Client and Patheon and their respective successors, heirs, executors, administrators, and permitted assigns. "Change of Control" means the earlier of a public announcement of an agreement in principle or the closing of (a) a merger, consolidation or similar transaction providing for the acquisition of the direct or indirect ownership of more than fifty percent (50%) of a Party's shares or similar equity interests or voting power of the outstanding voting securities or that represents the power to direct the management and policies of a Party or (b) the sale of all or substantially all of a Party's assets related to the subject matter of the Agreement.

10.7 Amendment; Modification. This Agreement may not be amended, modified, altered, or supplemented except by a writing signed by both Parties. No modification of any nature to this Agreement and no representation, agreement, arrangement, or other communication shall be binding on the Parties unless such is expressly contained in writing and executed by the Parties as an amendment to this Agreement. This Agreement may not be amended in any respect by any Purchase Order, invoice, acknowledgment, or other similar printed document issued by either Party.

10.8 Governing Law.

(a) This Agreement and any matter, claim or dispute arising out of or in connection with it, whether contractual or non-contractual, shall be construed under and governed by the laws of England without regard to the application of principles of conflicts of law. Both Parties hereby submit to the exclusive jurisdiction of the courts of England.

(b) The Parties expressly exclude the application of the United Nations Convention on Contracts for the International Sale of Goods, if applicable.

(c) The Parties agree that nothing in this Agreement shall (i) grant Client any property ownership rights in the Manufacturing Suite or the Facility or (ii) constitute a lease to the Manufacturing Suite or the Facility and no relationship of landlord and tenant is created between Patheon and Client pursuant to this Agreement. Patheon retains control, possession and management of the Facility and Manufacturing Suite and Client has no right to exclude Patheon from the Facility or Manufacturing Suite.

10.9 Compliance with Applicable Laws. Each Party and its Affiliates, and their respective representatives, shall comply with all Applicable Laws in the performance of their obligations under this Agreement. Without limiting the foregoing, each Party and its Affiliates, and their respective representatives, shall comply with export control laws and regulations of the country of Manufacture and of the United States. Neither Party nor its Affiliates (or representatives) shall, directly or indirectly, without prior U.S. government authorization, export, re-export, or transfer the Product to any country subject to a U.S. trade embargo, to any resident or national of any country subject to a U.S. trade embargo, or to any person or entity listed on the "Entity List" or "Denied Persons List" maintained by the U.S. Department of Commerce or the list of "Specifically Designated Nationals and Blocked Persons" maintained by the U.S. Department of Treasury. In so far as the same applies to a Party or its Affiliates, each Party and its Affiliates and respective representatives shall comply with the requirements of the Foreign Corrupt Practices Act of 1977 (15 U.S.C. § 78dd-1, *et seq.*).

10.10 Dispute Resolution.

(a) The Parties recognize that disputes may arise from time to time during the Term of this Agreement. It is the objective of the Parties to establish procedures to facilitate the resolution of such disputes arising under this Agreement in an expedient manner by mutual cooperation. To accomplish this objective, the Parties agree to follow the procedures set forth in this Section 10.10 if and when a dispute arises under this Agreement.

(b) Unless otherwise specifically recited in the Agreement, disputes between the Parties under this Agreement will be first referred to the Project Manager of each Party as soon as reasonably possible after such dispute has arisen. If the Project Managers are unable to resolve such a dispute within [***] days of being requested by a Party to resolve such dispute, each Party shall have the right, pursuant to written notice, to refer such dispute to the Senior Management of each Party for attempted resolution by negotiations within [***] days after such written notice is received. If the Senior Management are unable to resolve such dispute within [***] days of being requested by a Party to resolve such dispute, each Party shall have the right to pursue any remedies available to it at law or in equity.

10.11 Press Releases; Use of Trademarks. The Parties agree not to disclose in any press release or other public statement any terms or conditions of this Agreement to any Third Party without the prior consent of the other Party, save as permitted pursuant to the Confidentiality Agreement. Neither Party shall (a) issue a press release or make any other public statement that references this Agreement or (b) use the other Party's or the other Party's Affiliates' names or trademarks for publicity or advertising purposes, except with the prior written consent of the other Party, save as permitted pursuant to the Confidentiality Agreement or Securities and Exchange Commission filings which are required by Applicable Law, in which instance both Parties shall work together in good faith to agree the disclosure to be made having due and proper regard to their legal obligations. Each Party agrees that it shall cooperate fully and in a timely manner with the other with respect to all disclosures to the Securities and Exchange Commission or any other governmental or regulatory agencies, including requests for confidential treatment of Confidential Information of either Party included in any such disclosure.

10.12 Severability. If any provision of this Agreement is found by a proper authority to be unenforceable, that provision to the extent it is found to be unenforceable or invalid shall be severed and the remainder of the provision and this Agreement will continue in full force and effect. The Parties shall use their best efforts to agree upon a valid and enforceable provision as a substitute for any invalid or unenforceable provision, taking in to account the Parties' original intent of this Agreement.

10.13 Construction. Unless the context of this Agreement otherwise requires: (a) words of any gender include each other gender; (b) words using the singular or plural number also include the plural or singular number, respectively; (c) the terms "hereof," "herein," "hereby," and derivative or similar words refer to this entire Agreement; (d) the terms "Article," "Section," "Schedule," refer to the specified Article, Section or Schedule of this Agreement; (e) "or" is disjunctive but not necessarily exclusive; and (f) the term "including" or "includes" means "including without limitation" or "includes without limitation." Whenever this Agreement refers to a number of days, such number shall refer to calendar days unless business days are specified. The captions and headings of this Agreement are for convenience of reference only and in no way define, describe, extend, or limit the scope or intent of this Agreement or the intent of any provision contained in this Agreement. The language of this Agreement shall be deemed to be the language mutually chosen by the Parties, and no rule of strict construction shall be applied against either Party hereto.

*** Certain information on this page has been omitted and filed separately with the Securities and Exchange Commission. Confidential treatment has been requested with respect to the omitted portions.

10.14 Third Party Beneficiaries. This Agreement is not intended to confer upon any non-party rights or remedies hereunder, except as may be received or created as part of a valid assignment.

Without prejudice to the previous sentence, any Affiliate of Client may submit Purchase Orders under this Agreement if the quantities of Product ordered are included in the Forecasts given by Client such that Patheon shall receive a single consolidated Forecast pursuant to Section 2.3(a). Patheon shall submit invoices to the Affiliate of Client directly for all applicable fees and charges, which shall be payable by the Affiliate of Client directly in accordance with ARTICLE IV. The Parties agree that Client may delegate (in part) the benefits it receives under this Agreement, and its obligations, to any Affiliate in order that it may benefit from the terms of this Agreement in connection with Purchase Orders, provided that Client shall remain ultimately liable for any act or omission under this Agreement of such Affiliate. This shall not give an Affiliate any right to enforce any term of this Agreement against Patheon.

10.15 The rights of Patheon and Client to terminate, rescind or agree any variation, modification, amendment, waiver or settlement under this Agreement are not subject to the consent of any other person and expressly do not require the consent of any Affiliate.Further Assurances. Each of the Parties agrees to duly execute and deliver, or cause to be duly executed and delivered, such further instruments and do and cause to be done such further acts and things, including the filing of such additional assignments, agreements, documents, and instruments, that may be necessary or as the other Party hereto may at any time and from time to time reasonably request in connection with this Agreement or to carry out more effectively the provisions and purposes of, or to better assure and confirm unto such other Party its rights and remedies under, this Agreement.

10.16 Counterparts. This Agreement may be signed in counterparts, each and every one of which shall be deemed an original. Electronic signatures shall be treated as original signatures.

[The remainder of this page is left blank intentionally.]

IN WITNESS WHEREOF, the Parties have executed this Agreement as of the date first written above.

PATHEON UK LIMITED:	**INSMED INCORPORATED**:
By: /s/ Luca Andretta	By: /s/ William H. Lewis
Name: Luca Andretta	Name: William H. Lewis
Title: Director	Title: President and CEO
Date: 10/20/2018	Date: 10/20/2018

[Signature Page of Manufacturing and Supply Agreement]

Schedule A
Product

Product	Vial Size	Fill Weight	Packaging Configuration
Amikacin Liposome Inhalation Suspension in Vials	[***]	[***]	[***]

*** Certain information on this page has been omitted and filed separately with the Securities and Exchange Commission. Confidential treatment has been requested with respect to the omitted portions.

Schedule B
Fees

I. Base Fee

[***]

Commencement Date	End Date	Fee (per calendar [***])
[***]	[***]	[***]
[***]	[***]	[***]
[***]	[***]	[***]
[***]	[***]	[***]
[***]	[***]	[***]

For the avoidance of doubt, the Base Fees will accrue under this Agreement alone. The fees for the Transfer Services are specified in the Technology Transfer Agreement.

Consequences for the failure to achieve milestones for the Transfer Services or effects of early completion of the Transfer Services are specified in Exhibit H of the Technology Transfer Agreement.

II. Product Fees

[***]

Tier pricing:

	[***]	[***]	[***]	[***]	[***]	[***]	[***]	[***]
Product Conversion Price	[***]	[***]	[***]	[***]	[***]	[***]	[***]	[***]

Notes:

The tier pricing will apply if [***].

In tier pricing, for any given year the first [***]-[***] vials cost £[***], the [***] to [***] vials cost £[***], the [***] to [***] vials cost £[***]. etc.

Tier pricing [***]:

The tier pricing below will apply if [***]

	[***]	[***]	[***]	[***]	[***]	[***]	[***]	[***]
Product Conversion Price	[***]	[***]	[***]	[***]	[***]	[***]	[***]	[***]

Base Fees and Product Fees include:

[***]

Base Fee and Product Fees DO NOT Include:

[***]

Materials:

Cost allocation for the procurement of Materials is set forth in Section 2.2 of this Agreement. A provisional bill of Materials is listed in Schedule C.

Bill Back Items:

During the Transfer Services, Patheon and Client will work together to develop a non-exhaustive list of typical Bill Back Items. Terms for the procurement of Bill Back Items are described in Section 2.2(r).

Additional Services:

The following non-exhaustive list shall be considered Additional Services and will be invoiced to Client at the price agreed according to Section 2.2(s).

[***]

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Schedule C
Materials

Part A: Client-Supplied Materials

Material	**Specification**		**Cost ($/kg)**
[***]	[***]	[***]	[***]
[***]	[***]	[***]	[***]
[***]	[***]	[***]	[***]

Part B: Patheon-Supplied Materials

Material	**Long lead time**
[***]	

The column for items with a long lead time will be completed in the final version of the bill of materials to be established during the Transfer Services.
The above list will form the initial basis of the bill of materials for the Product ("BOM").The BOM will be further developed during the Transfer Services to reflect the possibility of local suppliers and any changes to the equipment /materials needed at the Facility.
[***]
This BOM will be updated and agreed by the Parties prior to commercial launch of the Product.

Schedule D
On Time In Full Delivery Performance

I. Calculation of OTIF delivery

[***]

II. [***] Delivery Target

[***]

III. Shortfall

[***]

IV. Bonus
[***]

Example calculation:

	Actual OTIF [***]	**Amount of Credit** [***]
Bonus Credit due to Patheon	[***]	[***]
	[***]	[***]
	[***]	[***]
	[***]	[***]
	[***]	[***]
	[***]	[***]
	[***]	
	[***]	
	[***]	
	[***]	
Annual Delivery Target (example)	[***]	
Shortfall Credit due to Client	[***]	
	[***]	
	[***]	
	[***]	
	[***]	
	[***]	[***]
	[***]	[***]
	[***]	[***]
	[***]	[***]
	[***]	[***]

*** Certain information on this page has been omitted and filed separately with the Securities and Exchange Commission. Confidential treatment has been requested with respect to the omitted portions.

Schedule E
Client On Site Representatives

The following terms shall apply to any use of on-site office space or other accommodations that is provided by Patheon for the Client On Site Representatives:

(a) Patheon permits only the Client On Site Representatives to use the relevant office space, which use shall be in common with Patheon and all others authorised by Patheon;
(b) the purpose of use of the office space shall be within Use Class B1 of the Town and Country Planning (Use Classes) Order 1987 and only in connection with the exercise of the rights of Client under Section 3.5(a);
(c) the Client On Site Representatives shall use the office space as a licensee and that no relationship of landlord and tenant shall be created between Patheon and Client;
(d) Patheon retains control, possession and management of the office space and Client has no right to exclude Patheon from the office space;
(e) the right to use the office space is personal to Client and is not assignable;
(f) the Client On Site Representatives shall not be entitled to the exclusive use or occupation of the office space;
(g) Patheon shall be entitled at any time on giving not less than [***] notice to require the Client On Site Representatives to transfer to alternative, comparable space elsewhere within the Facility and the Client On Site Representatives shall comply with such requirement.

In relation to use of on-site office space or other accommodations that is provided by Patheon for the Client On Site Representatives, Client agrees:

(a) not to make any alteration or addition to the office space;
(b) not to display any advertisement, signboards, nameplate, inscription, flag, banner, placard, poster, signs or notices in the office space or elsewhere in the Facility without the prior written consent of Patheon;
(c) not to do or permit to be done in the office space anything that is illegal or that may be or become a nuisance, annoyance, inconvenience or disturbance to Patheon or to occupiers of the Facility or any owner or occupier of a neighbouring property;
(d) not to cause or permit to be caused any damage to the office space, any property of Patheon, the Facility or any neighbouring property; or
(e) not to obstruct the common parts of the Facility;
(f) not to apply for any planning permission in respect of the office space or the Facility;
(g) not to do anything that will or might constitute a breach of any planning permissions or similar consents affecting the office space or the Facility or that will or might invalidate in whole or in part any insurance effected by Patheon in respect of the office space or the Facility from time to time;
(h) to comply with all laws and with any recommendations of the relevant suppliers relating to the supply and removal of electricity, gas, water, sewage, telecommunications and data and other services and utilities to or from the office space; and
(i) to observe any reasonable rules and regulations Patheon makes and notifies to Client from time to time governing Client's use of the office space and the common parts.

*** Certain information on this page has been omitted and filed separately with the Securities and Exchange Commission. Confidential treatment has been requested with respect to the omitted portions.

Schedule F
Client [***] Volume Forecast

Product	[***] Volume Forecast (Vials)	
	[***]	[***]
Amikacin Liposome Inhalation Suspension in Vials	[***]	[***]

The Client [***] Volume Forecast for [***] shall be a minimum of [***] unless agreed otherwise (only for the purpose of determining the Product Fee). Any commercial Product manufactured for stock building purposes prior to commercial launch shall count towards the volume of Product purchased.

Schedule G
Example Exchange Rate Fluctuation Mechanism

Option 1 - GBP to USD Contract Pricing

Re-pricing of the following Contract elements:

[***]

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EXHIBIT 10.40

CONFIDENTIAL TREATMENT HAS BEEN REQUESTED AS TO CERTAIN PORTIONS OF THIS DOCUMENT. EACH SUCH PORTION, WHICH HAS BEEN OMITTED HEREIN AND REPLACED WITH ASTERISKS (***), HAS BEEN FILED SEPARATELY WITH THE SECURITIES AND EXCHANGE COMMISSION.

TECHNOLOGY TRANSFER AGREEMENT

TECHNOLOGY TRANSFER AGREEMENT

This **TECHNOLOGY TRANSFER AGREEMENT** (this "Agreement"), dated as of 20 October 2017 (the "Effective Date"), is made by and between Insmed Incorporated, a Virginia corporation having its principal place of business at 10 Finderne Avenue, Building 10, Bridgewater, New Jersey 08807, USA ("Client"), and Patheon UK Limited, a company incorporated in England and Wales having its principal place of business at Kingfisher Drive, Covingham, Swindon, SN35BZ, United Kingdom ("Patheon"). Client and Patheon are sometimes referred to herein individually as a "Party" and collectively as the "Parties."

RECITALS

WHEREAS, Client has a commercial interest in the manufacture and commercialization of Amikacin Liposome Inhalation Suspension (ARIKAYCE®), a sterile, aqueous liposomal suspension designed for inhalation via nebulization which is manufactured using the Client Manufacturing Process (the "Product");

WHEREAS, concurrently herewith, the Parties are executing a manufacturing and supply agreement pursuant to which Patheon would be a manufacturer and supplier of the Product; and

WHEREAS, in anticipation of the manufacturing and supply agreement and the goods and services that Patheon will supply thereunder, the Parties desire to enter into a binding agreement pursuant to which Patheon would undertake certain technology transfer and construction services in order to validate Client's technology package and prepare Patheon's facilities for the manufacture of the Product;

NOW, THEREFORE, in consideration of the foregoing, the mutual promises and covenants of the Parties contained herein, and other good and valuable consideration, the receipt and sufficiency of which are hereby acknowledged, the Parties hereto, intending to be legally bound, do hereby agree as follows:

ARTICLE 1
DEFINITIONS

The following terms will have the meanings set forth below. Unless the context indicates otherwise, the singular will include the plural and the plural will include the singular. Any term not defined hereunder shall have the meaning ascribed to such term in the Manufacturing and Supply Agreement.

"Agreement" has the meaning set forth in the preamble hereto.

"Capital Expenditures" has the meaning set forth in Section 2.4(a).

"Client" has the meaning set forth in the Preamble.

"Client Indemnified Parties" has the meaning set forth in Section 7.2.

"Completion of the Tech Transfer" has the meaning set forth in Section 8.2.

"Effective Date" has the meaning set forth in the Preamble.

"Key Technical Assumptions" means the assumptions set forth in Exhibit D.

"Manufacturing and Supply Agreement" means the Manufacturing and Supply Agreement executed by the Parties on the date hereof as described in more detail in the Preamble.

"Manufacturing Suite" means the manufacturing suite at the Facility, whose footprint and engineering approach shall be in substantially the form attached as Exhibit A.

"Milestones" means the milestones in respect of the Transfer Services set forth in Exhibit H.

"Party" or "Parties" has the meaning set forth in the Preamble.

"Patheon" has the meaning set forth in the Preamble.

"Patheon Indemnified Parties" has the meaning set forth in Section 7.1.

"Steering Committee" has the meaning set forth in Section 2.10(d).

"Technology Transfer Fees" means the monthly fees paid by Client in consideration for the Transfer Services, as more specifically set forth in Part 1 of Exhibit B. Technology Transfer Fees do not include Capital Expenditures, Product Fees, Material Costs, Maintenance Costs, Disposal Costs or charges for Bill Back Items or Additional Services.

"Term" has the meaning set forth in Section 8.1.

"Timeline" has the meaning set forth in Section 2.3.

"Transfer Services" means the services rendered under this Agreement, as described in Section 2.1 and in the Exhibits attached to this Agreement, based on the Key Technical Assumptions stated therein.

"Transfer Services Termination Costs" has the meaning set forth in Section 8.12(f).

ARTICLE 2
TRANSFER SERVICES

2.1 Description of Transfer Services.

Patheon will:

(a) provide engineering and construction services, directly or using approved (as described in Section 2.11) Third Parties, to construct the Manufacturing Suite in accordance with the engineering approach and the footprints set forth in Exhibit A of this Agreement, as it may be amended;

(b) procure and/or validate the Equipment necessary to Manufacture the Product in accordance with Section 2.9 and perform the Transfer Services set forth in Exhibit C in order to validate and implement the Client Manufacturing Process for the Product in compliance with the Quality Agreement, GMP, all other Applicable Law and the Specifications; and

(c) register the Facility to Manufacture the Product,

(collectively, the "Transfer Services").

2.2 Patheon will perform the Transfer Services and facilitate Client obtaining Regulatory Approval of the Manufacturing Suite as the manufacturing, testing, and packaging site for the Product. The Transfer Services will be performed with the aim of ensuring that the Product is Manufactured and tested using the Client Manufacturing Process according to the Specifications and test methods.

2.3 Payments for Transfer Services. The Parties acknowledge and agree that Patheon's consideration for the Transfer Services performed hereunder is the payment of the Technology Transfer Fees. Patheon will use its Commercially Reasonable Efforts to complete the Transfer Services in a timely fashion in accordance with the schedule set forth in Exhibit E (the "Timeline"). In the event of any delays in completion of the Transfer Services, Client's sole remedy whether in contract, tort, equity or otherwise, shall be adjustment of the Technology Transfer Fees (and, where relevant, any Base Fee payable pursuant to the Manufacturing and Supply Agreement) as set out in Exhibit H, together with the remedies expressly set forth in Section 7.5 and ARTICLE 8). The dates on which the Technology Transfer Fees become payable as set out in Exhibit B shall be reviewed and (if necessary, and subject to agreement) updated by the Steering Committee within [***] of the Effective Date.

2.1 Additional Payments. In addition to the Technology Transfer Fees, Client shall also pay:

(a) the capital requirements and the payments associated with the Equipment, Manufacturing Suite construction and related process and support and validation services set forth in Part 2 of Exhibit B (the "Capital Expenditures");

(b) the Material Costs of Patheon-Supplied Materials in accordance with Section 2.2(b) of the Manufacturing and Supply Agreement, except that the handling fee will be [***], save in respect of any Material Costs of Patheon-Supplied Materials for use in the Manufacture of commercial Product (i.e. after the completion of Manufacture of process validation batches), which shall have a handling fee of [***]; and

(c) any Maintenance Costs, Disposal Costs and any charges for Bill Back Items or any Additional Services.

2.1 All fees and costs in this Agreement are shown in British Pounds (GBP) but which shall be adjusted as described in Section 2.6(c) of the Manufacturing and Supply Agreement so that all invoices from Patheon and payments from Client to Patheon hereunder shall be in United States Dollars (USD) and will be due and payable in accordance with ARTICLE IV of the Manufacturing and Supply Agreement (which is incorporated herein). All invoices from Patheon to Client for Capital Expenditures shall include all (if any) applicable invoices from vendors for the supply, transportation, installation, and commissioning of the Equipment that pertain to the Transfer Services invoiced by Patheon. Client acknowledges that the amounts of Capital Expenditures set forth in Part 2 of Exhibit B are estimates and are subject to review by the Steering Committee and agreement by the Parties in writing once manufacturing details and process specification requirements have been confirmed, any necessary machine trials performed and upon receipt of formal quotations from the equipment suppliers to the extent not already obtained as at the Effective Date.

2.2 Modifications. The Parties may modify and agree upon the definitive engineering approach, footprint of the Manufacturing Suite, or the Timeline, taking into account parameters such as the exact design of the space, space classifications, code requirements, Equipment, materials, personnel, waste stream process flows, equipment sizing and utility requirements. For example, feasibility work and/or engineering runs may be executed prior to completion of operational qualification, if mutually agreed upon by both parties. Any such modifications shall be discussed by the Steering Committee but shall not take effect until agreed in writing (including as to any consequential fees and costs or savings relating thereto) and duly executed by the Parties, provided that the selection and use of stability material (including the selection of materials to be used for generation of the stability data to be used in the post approval inspection) shall be agreed by the Parties. By way of example an alternate non-contractual timeline that Client may choose to pursue is set out in Exhibit E and if so the Parties shall work together to achieve this Timeline provided that it is compliant with GMP). The alternate timeline in Exhibit E shall not form part of this Agreement unless the Parties agree to incorporate it by a written amendment that is executed by the Parties (such agreement not to be unreasonably withheld).

*** Certain information on this page has been omitted and filed separately with the Securities and Exchange Commission. Confidential treatment has been requested with respect to the omitted portions.

2.1 Client's Responsibilities.

(a) To assist Patheon in its performance of the Transfer Services under this Agreement, Client shall at its expense:

(i) deliver to Patheon DDP Incoterms 2010 the Facility the Client Manufacturing Equipment;

(ii) provide Patheon with relevant information, documentation, and data relating to (1) the Client Manufacturing Process, (2) the Equipment necessary to Manufacture the Product in accordance with the Client Manufacturing Process, and (3) Product safety and information, documentation, and data, including any applicable NDA numbers, NDC codes, "CMC" sections of NDAs, validation protocols, validation reports, method validation protocols, method validation reports, and other documents necessary or reasonably requested by Patheon for Patheon to Manufacture the Product, provide the Transfer Services or otherwise necessary or appropriate for Patheon's performance hereunder; and

(iii) provide to Patheon Client-Supplied Materials pursuant to Section 2.13,

in each case consistent with the dates set out in the Timeline or within such period as agreed by the Parties.

(b) If Client is to review or approve any information, documentation, data, or samples prepared or supplied by or on behalf of Patheon, it will do so on the dates set out in the Timeline or within such period as agreed by the Parties.

(c) It is understood and acknowledged by the Parties that Client will retain ownership of the Regulatory Approval for the Product including any application therefor, and any supplements thereto. Subject to Section 2.7(d) Client is responsible for all submission of documents and correspondence with the FDA and other competent Regulatory Authorities relating to the Regulatory Approval for the Product . Client shall have the sole responsibility for the filing of the documents with the applicable Regulatory Authorities, and to take any other actions that may be required for the receipt of Regulatory Approval as described in Section 3.17 of the Manufacturing and Supply Agreement, provided, however, that Patheon shall have the right to review and comment on Client's draft submissions to any Regulatory Authorities to the extent they relate to the Facility prior to Client's issuance of the submission in accordance with Section 2.7(f).

(d) Client will use Commercially Reasonable Efforts to pursue Regulatory Approval for the Product. Patheon will use Commercially Reasonable Efforts to support Client in relation to the same, to the extent required in order for Patheon to Manufacture the Product at the Facility. For the avoidance of doubt Patheon shall be responsible at its cost for all Regulatory Filings, and obtaining and maintaining all licences, necessary for or required in connection with the manufacture of pharmaceutical products in general at the Facility including GMP inspections by Regulatory Authorities, including a manufacturing authorisation issued to Patheon by the Medicines and Healthcare products Regulatory Agency in the United Kingdom.

(e) Client shall provide Patheon with a copy of any Regulatory Approval relevant to this Agreement on request including any Regulatory Approval required for the storage, receipt or distribution of the Product by Client or its designee, to the extent reasonably required by Patheon for Regulatory Filings or in order to satisfy its obligations under Applicable Laws.

(f) Where documents or data generated by Patheon in relation to the Transfer Services are to be filed by Client with any Regulatory Authority and such filing includes data or information pertaining to a Patheon Regulatory Obligation (as such term is defined in the Manufacturing and Supply Agreement), prior to filing any such documents and data with the Regulatory Authority, Client shall provide Patheon with a copy of the documents incorporating such data so as to give Patheon the opportunity to review the accuracy of such documents as it relates to the Patheon Regulatory Obligation in accordance with the review and comment procedures set forth in Section 3.17 of the Manufacturing and Supply Agreement (including the process for resolution of inaccuracies set forth in Section 3.17(f) thereto). Notwithstanding anything in Section 3.17 of the Manufacturing and Supply Agreement to the contrary:

(i) at least [***] prior to Client's planned filing date with the Regulatory Authority of any documentation which is or is equivalent to the Quality document portion (Drug Product section) of the U.S. Investigational New Drug application, the EU Clinical Trial application and Investigational Medicinal Product Dossier, the Common Technical Document module 3 (Drug Product section) of the US New Drug Application, U.S. Biological License Application, or the EU Marketing Authorization Application, as the case may be, Client shall provide Patheon with a copy of the Initial Draft (defined in the Manufacturing and Supply Agreement) of such portion so as to permit Patheon to verify that the Initial Draft accurately describes the development and validation work Patheon has performed and the manufacturing and control processes that Patheon will perform pursuant to this Agreement;

(ii) Patheon shall provide comments regarding such Initial Draft no later than [***] prior to the required filing date with the applicable Regulatory Authority (including notifying Client of any identified inaccuracies);

(iii) at least [***] prior to Client's planned filing date with the Regulatory Authority of the above documentation Client shall provide Patheon with a revised copy of the Initial Draft and Patheon shall provide any further comments regarding such Initial Draft no later than [***] prior to the required filing date with the applicable Regulatory Authority; and

(iv) Client shall deliver a copy of the Final Filing to Patheon at least [***] prior to the date it is planned to be submitted to the relevant Regulatory Authority.

2.2 Patheon's Responsibilities.

(a) Patheon will provide to Client all data and documentation necessary to support Client's submissions to the FDA, or any responses to questions raised by the FDA with respect to those Transfer Services, that are necessary for Regulatory Approval of the Facility as the manufacturing, testing, and bulk-packaging site for the Product.

(b) Patheon shall at its own cost ensure that any and all necessary licenses, registrations, and Regulatory Authority approvals have been obtained in connection with the Facility and Equipment used in connection with the Manufacture of the Product by Patheon. Any changes to the Transfer Services shall be subject to the change control procedure set out in Section 2.10(b) of the Manufacturing and Supply Agreement.

(c) Patheon will promptly notify Client in writing and by telephone if an authorized agent of a Regulatory Authority visits the Manufacturing Suite, or any other location in the Facility where the Product is being manufactured, bulk-packaged, stored or quality tested, and the procedures set forth in Section 3.6 of the Manufacturing and Supply Agreement shall apply.

(d) Patheon shall install and validate the Equipment in compliance with the capital requirements set forth in Exhibit B and the technical transfer process set forth in Exhibit C.

2.3 Equipment.

(a) Client shall be responsible for the design of all Client Manufacturing Equipment and for the cost of procurement, installation, commissioning and validation of all Client Manufacturing Equipment and any Patheon Manufacturing Equipment as set out in the Capital Expenditures.

Patheon shall be responsible for the design of all Patheon Manufacturing Equipment in collaboration with Client.

(b) The Client Manufacturing Equipment must be supplied with appropriate cleaning certificates and must comply with the requirements set out in Section 2.10(a)(xiii) of the Manufacturing and Supply Agreement which is incorporated herein.

(c) Maintenance, replacement, insurance ownership and use of the Client Manufacturing Equipment and Patheon Manufacturing Equipment shall be governed by Section 2.10(a) of the Manufacturing and Supply Agreement which is incorporated herein.

(d) With respect to all Equipment, Patheon shall provide engineering project management and process validation, qualification support, installation and commissioning services, in consideration for the payments set forth in Exhibit B. After such Equipment is delivered to the Facility, Patheon shall manage the installation, commissioning and validation activities of such Equipment.

(e) The Parties shall provide their Commercially Reasonable Efforts to minimize the Capital Expenditures and the costs of procurement, transportation, installation and commissioning of the Equipment. Patheon shall provide Client with quotes and copies of all applicable invoices from vendors, for the costs of procurement, transportation, installation, and commissioning of the Equipment. In order to obtain, and prior to obtaining, any payment for the Capital Expenditures hereunder, Patheon must obtain prior written approval from Client and provide Client with quotes and invoices, including copies of all applicable invoices from vendor(s), for the supply, transportation, installation, and commissioning of the Equipment.

2.4 Client On Site Representatives; Reporting of Results; Project Managers; Steering Committee.

(a) Client shall have the right at all times throughout the Term to have [***] Client On Site Representatives present in that portion of the Facility that is being constructed or used to Manufacture the Product or store Materials, to observe the procedures and processes used to Manufacture the Product or to perform the activities associated with the transfer of Client Manufacturing Process hereunder as further described in Section 3.5 of the Manufacturing and Supply Agreement and provided that Client complies with the terms set out in Schedule E of the Manufacturing and Supply Agreement which are incorporated herein.

(b) Patheon will respond to Client's inquiries regarding the status of the Transfer Services on an ongoing basis, and Patheon will endeavor to keep Client informed of interim results of the Transfer Services. Patheon will provide copies of all analytical, cleaning, and process validation protocols, data summaries, reports and all batch records, test methods, and specifications for Client's review, comment, and approval prior to implementation and execution. Once such protocols, data

summaries, reports, records, methods, and specifications have been approved and executed, Patheon will provide copies to Client. Patheon will provide Client with information relating to the Equipment to be used in connection with the Manufacture of the Product, which Equipment will be subject to Client's review and approval (not to be unreasonably withheld or delayed). On or before [***] after Client's request, Patheon will provide to Client documentation that summarizes the implementation efforts of the Transfer Services at the Facility.

(c) Patheon and Client will each appoint a Project Manager, who will meet as needed to resolve any issues or problems associated with the Transfer Services. Client's Project Manager may be one of the Client On Site Representatives.

(d) Within [***] of the Effective Date the Parties shall establish a steering committee (the "Steering Committee") as described in Exhibit G. The Steering Committee shall have the responsibilities and authority allocated to it in Exhibit G.

2.5 Subcontractors. Patheon may arrange for Third Party subcontractors ("Third Party Subcontractors") to perform specific Transfer Services (such as testing or analysis) under this Agreement with Client's consent or at Client's request as further described in Section 3.16 of the Manufacturing and Supply Agreement which is incorporated herein.

2.6 Intellectual Property. The Parties' Intellectual Property rights relating to the subject matter of this Agreement shall be governed by ARTICLE V of the Manufacturing and Supply Agreement.

2.7 Materials. Client-Supplied Materials will be purchased by Client and shipped to Patheon in accordance with this Section 2.13. Client shall purchase all Client-Supplied Materials for the Transfer Services and ship such Client-Supplied Materials to Patheon in accordance with this Section 2.13. All shipments from Client to Patheon will be made DDP (Incoterms 2010) the Facility unless otherwise agreed. All shipments of Client-Supplied Materials will be accompanied by Certificate(s) of Analysis from the Material manufacturer, confirming its compliance with the Material's specifications and the required documentation as specified in the Quality Agreement. Client or Client's designee will be the "Importer of Record". Client-Supplied Materials will be held by Patheon on behalf of Client as set forth in this Agreement. Title to Client-Supplied Materials will at all times remain the property of Client or a Client Affiliate. Any Client-Supplied Materials received by Patheon will only be used by Patheon to perform the Manufacturing Services or the Transfer Services or associated activities necessary to perform the Manufacturing Services or the Transfer Services.

2.8 Compliance Audits. With the exception of "for cause" audits (e.g., audits arising from regulatory issues or material Product conformity issues), Client and its designated representatives shall have the right to audit once per year all applicable non-financial records pertaining to the

Product or Patheon's obligations hereunder and non-financial records of Patheon for the purpose of determining Patheon's compliance with the obligations set forth in this Agreement. The terms of such audit shall be as set out in Section 3.10 of the Manufacturing and Supply Agreement (which is incorporated herein) and an audit may be performed once per year under this Agreement or the Manufacturing and Supply Agreement but not both.

2.9 Patheon shall store, handle, and protect the Materials with a reasonable level of care, which shall include taking all reasonable precautions to ensure that the Materials are not subject to contamination, deterioration, destruction, or theft. Patheon shall keep adequate records of its usage of the Materials during the Term.

2.10 Bill Back Items. Bill Back Items will be charged to Client at Patheon's cost plus a [***] handling fee. Patheon shall invoice Client [***] for any Bill Back Items used in connection with the Transfer Services during the preceding [***] in accordance with ARTICLE IV of the Manufacturing and Supply Agreement (which is incorporated herein). Patheon may only invoice Bill Back Items that have been quoted to and approved in writing by an authorized person of Client in advance. The cost of any Bill Back Items where use is shared between Client and other clients of Patheon will be apportioned in good faith in proportion to their use.

2.11 Additional Services. If Client is interested in having Patheon perform Additional Services, Client will provide Patheon with a written request containing sufficient detail to enable Patheon to provide Client with a quote and proposal to provide such Additional Services. Patheon may only invoice for Additional Services that have been quoted to and approved in writing by an authorized person of Client in advance. Patheon shall invoice Client monthly for any Additional Services performed by Patheon during the preceding month in accordance with ARTICLE IV of the Manufacturing and Supply Agreement (which is incorporated herein).

2.12 Storage. Patheon will provide [***] sufficient storage capacity to support storage of the required quantity of Materials necessary for the Transfer Services.

2.13 Shipping. Except to the extent set forth otherwise in this Agreement or the Manufacturing and Supply Agreement, any shipment from Patheon to Client, whether of Product, Materials or otherwise, shall be made EXW (Incoterms 2010) the Facility unless otherwise mutually agreed. Title and risk of loss shall pass to Client (or a designated Client Affiliate) at the time when Patheon loads the Product onto the carrier's vehicle for shipment at the shipping point at the Facility. Client shall collect shipments promptly from the Facility following notification of availability for delivery from Patheon. Any shipment from Client to Patheon will be made DDP (Incoterms 2010) the Facility. Storage of Product will be provided in accordance with Section 2.2(q) of the Manufacturing and Supply Agreement.

2.14 Payment of Technology Transfer Fees. Patheon will invoice Client monthly in advance for the Technology Transfer Fees. All fees will be due and payable in accordance with ARTICLE IV of the Manufacturing and Supply Agreement (which is incorporated herein). The Technology Transfer Fees stated herein are calculated as at the Effective Date and shall be fixed until [***]. Thereafter, starting on [***] the Technology Transfer Fees shall be adjusted annually to reflect any change in the UK Consumer Price Index: All Items Index published by the Office for National Statistics (as published at www.ons.gov.uk) during the preceding twelve (12) months (based on the average of the monthly changes over the 12-month period), provided that if the increase in the index exceeds [***] it will be implemented but the Parties shall meet and negotiate in good faith measures to mitigate the effect of the fee increase.

2.15 Exchange Rate Fluctuations. The fees and charges under this Agreement will be adjusted in accordance with Section 2.6(c) of the Manufacturing and Supply Agreement.

2.16 Amendment of Product Specifications, Manufacturing Process, Equipment, and Formulation; Changes in Applicable Law. Any changes to the Specifications, Quality Agreement, the Client Manufacturing Process, the Equipment, the Transfer Services to be provided pursuant hereto, the formulation of the Product or changes (required as a result of changes in Applicable Law or otherwise) shall be governed by Section 2.10(b) of the Manufacturing and Supply Agreement which is incorporated herein.

2.17 Commercial supply of Products. The Parties acknowledge that any technical batches, stability batches or validation batches manufactured under this Agreement are intended for validation purposes and are governed by the terms and conditions of this Agreement, and that any supplies of Products that are intended for commercial use shall be subject to, and governed by, the Manufacturing and Supply Agreement. Any commercial Product (i.e. after the completion of Manufacture of process validation batches) that Client wishes to use for a clinical trial shall be governed by the Manufacturing and Supply Agreement.

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ARTICLE 3
CONFIDENTIALITY

ARTICLE VII of the Manufacturing and Supply Agreement shall apply to this Agreement and is incorporated herein.

ARTICLE 4
CLIENT'S REPRESENTATIONS, WARRANTIES, AND COVENANTS

4.1 Commercially Reasonable Efforts. Except where specifically stated to the contrary in this Agreement otherwise, Client will use its Commercially Reasonable Efforts to perform Client's obligations hereunder.

4.2 Additional Representations, Warranties, and Covenants of Client. Client warrants, represents, and covenants that:

(a) to its knowledge, as at the Effective Date (1) it or its Affiliates Control all right, title, and interest in all Intellectual Property in the Client Manufacturing Process, the Client Manufacturing Equipment, the Product and the Specifications necessary for performance of the Transfer Services; and (2) it has the right to authorize Patheon to perform the Transfer Services, in each case in accordance with the terms and conditions hereof;

(b) to its knowledge, as at the Effective Date, the performance of the Transfer Services hereunder, in accordance with the terms and conditions hereof and using the Client Manufacturing Process, or the manufacture, use, supply or other disposition of the Product by Patheon as may be required to perform its obligations under this Agreement or by Client, does not and will not result, in the infringement or misappropriation of any Third Party's Intellectual Property rights; and

(c) Client or its Affiliates Control and have the right to lawfully disclose the Specifications to Patheon and to authorize Patheon to use the Specification to perform the Transfer Services.

ARTICLE 5
PATHEON'S REPRESENTATIONS, WARRANTIES, AND COVENANTS

Patheon represents, warrants, and covenants to Client as follows:

5.1 Commercially Reasonable Efforts. Except where specifically stated to the contrary in this Agreement otherwise, Patheon will use its Commercially Reasonable Efforts to perform its obligations hereunder. If Patheon is not able to meet the Timeline, Patheon will provide written notice to Client of such inability as soon as practical, but in any event on or before [***] of discovering such inability.

5.1 Transfer Services. Patheon warrants that there is no claim, suit, proceeding, or other investigation issued on Patheon, or to the actual knowledge of Patheon, pending or threatened against Patheon, which is likely to prevent or materially adversely affect the rights and interests of Client hereunder or keep Patheon from performing its obligations hereunder.

5.1 Additional Representations, Warranties, and Covenants of Patheon. Section 6.2 of the Manufacturing and Supply Agreement shall apply to this Agreement and the performance of the Transfer Services and is incorporated herein.

5.1 Disclaimer. THE FOREGOING EXPRESS WARRANTIES AND THOSE IN ARTICLE 4 and ARTICLE 6 ARE IN LIEU OF ALL OTHER WARRANTIES, EXPRESS OR IMPLIED, INCLUDING ANY WARRANTY OF MERCHANTABILITY, OR FITNESS FOR A PARTICULAR PURPOSE, OR NON-INFRINGEMENT, AND ALL OTHER WARRANTIES ARE HEREBY DISCLAIMED AND EXCLUDED BY EACH PARTY.

ARTICLE 6
GENERAL REPRESENTATION AND WARRANTIES

Sections 6.1(a) and 6.1(c) of the Manufacturing and Supply Agreement shall apply to this Agreement and are incorporated herein.

ARTICLE 7
INDEMNIFICATION

7.1 Indemnification by Client. Client will indemnify Patheon, its Affiliates, and their respective directors, officers, employees, and agents (the "Patheon Indemnified Parties"), and defend and save each of them harmless from and against:

(a) any Third Party Loss incurred by any of them in connection with, arising from, or occurring as a result of: (i) any claim of personal injury or property damage to the extent that the

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injury or damage arises other than from a breach of this Agreement by Patheon; (ii) a claim that the Transfer Services performed by Patheon hereunder, in accordance with the terms and conditions of this Agreement, infringes or misappropriates a patent or any other Intellectual Property rights, if it is a claim related to the use of Existing Client Intellectual Property, the Client Manufacturing Equipment or the Client Manufacturing Process or the Product; or (iii) a claim that the use of any device, composition, or process provided by Client to Patheon and used in connection with the Transfer Services in accordance with the terms and conditions of this Agreement constitutes infringement or misappropriation of a Third Party's Intellectual Property rights; or

(b) any Loss incurred by any of them in connection with: (i) the negligence or willful misconduct of the Client On Site Representatives at the Facility; or (ii) any damage to Patheon's property or any claims of personal injury to any Patheon employees or Third Party Subcontractors caused as a result of Patheon's use of the Client Manufacturing Equipment in the performance of the Transfer Services provided that Patheon and its employees and Third Party Subcontractors have complied with all applicable Equipment Standard Operating Procedures or the manufacturer's terms of operation and recommended procedures for the Client Manufacturing Equipment, Specifications, and have not otherwise acted in a negligent manner or committed an act of willful misconduct in connection with the use and Maintenance of the Client Manufacturing Equipment;

except, in each case for (a) and (b), for those Losses for which Patheon has an obligation to indemnify the Client Indemnified Parties pursuant to Section 7.2 below, as to which Losses each Party shall indemnify the other to the extent of their respective liability for such Losses; and provided, however, that Client will not be required to indemnify the Patheon Indemnified Parties with respect to any such Loss hereunder to the extent the same is caused by any breach of contract, negligent act or omission, or willful misconduct by Patheon or any or its Affiliates. Client acknowledges that Patheon has not and will not conduct any freedom to operate searches in relation to the Product or the Client Manufacturing Process nor reviewed any Third Party patents in relation thereto and that Patheon's failure or omission to do so will not be considered negligence for the purposes of excluding or limiting a claim under this indemnity.

7.1 Indemnification by Patheon. Patheon will indemnify Client, its Affiliates, and their respective directors, officers, employees, and agents (the "Client Indemnified Parties"), and defend and save each of them harmless from and against any Third Party Loss incurred by any of them in connection with, arising from, or occurring as a result of:

(a) any claim of personal injury or property damage to the extent that the injury or damage is the result of a failure by Patheon to perform the Transfer Services in accordance with the terms of this Agreement; or

(b) a claim that any Existing Patheon Intellectual Property employed in providing the Transfer Services infringes or misappropriates a United States patent or any other Intellectual

Property rights except to the extent such claim is based on the use of Existing Client Intellectual Property in accordance with the terms and conditions of this Agreement;

except, in each case for (a) and (b), for those Losses for which Client has an obligation to indemnify the Patheon Indemnified Parties pursuant to Section 7.1 above, as to which Losses each Party shall indemnify the other to the extent of their respective liability for such Losses; and provided, however, that Patheon will not be required to indemnify the Client Indemnified Parties with respect to any such Loss hereunder to the extent the same is caused by any breach of contract, negligent act or omission, or willful misconduct by Client or any or its Affiliates.

7.1 Indemnification Procedures. Section 9.3 of the Manufacturing and Supply Agreement shall apply to Sections 7.1 and 7.2 of this Agreement and is incorporated herein.

7.2 Limitation of Liability.

(a) Subject to Section 7.4(b), neither Party will be liable to the other in contract, tort, negligence, breach of statutory duty, equity, or otherwise for: (i) any direct or indirect loss of profits, of production, of anticipated savings, of business, or goodwill; (ii) any reliance damages, including but not limited to costs or expenditures incurred to evaluate the viability of entering into this Agreement or to prepare for performance under this Agreement; or (iii) for any other indirect or consequential loss, liability, damage, costs, penalty, or expense.

(b) Nothing in this Agreement is intended to limit either Party's liability for: (i) death or personal injury caused by its negligence; or (ii) fraud or fraudulent misrepresentation.

7.3 Re-performance. If any part of the Transfer Services provided or procured by Patheon is not performed in accordance with the terms of this Agreement, then as Client's sole remedy (whether in contract, tort, equity or otherwise, and subject to the remedies expressly set forth in Section 2.3 and ARTICLE 8) Client may request Patheon to repeat that part of the Transfer Service at Patheon's cost, provided that:

(a) where the Transfer Services to be repeated require Client-Supplied Materials, Client will provide such Client-Supplied Materials;

(b) where the Transfer Services to be repeated require the supply of additional Patheon-Supplied Materials, Patheon will provide any Patheon-Supplied Materials at its cost and at no additional cost to Client;

(c) in the event that any loss of Client-Supplied Materials has arisen from the [***] of Patheon in its performance of this Agreement prior to the Manufacture of process validation batches (having regard to the nature of this Agreement and that at this stage of the Transfer Services, the process for commercial Manufacture will not have been established and errors of judgement and

mistakes may be made in good faith in establishing the same), in each calendar year (or part thereof) Patheon will reimburse Client for losses of Client-Supplied Materials at cost, up to a maximum amount of either (i) [***] in the case of [***], or (ii) [***] in the case of [***], of the total [***] received by or payable to Patheon pursuant to this Agreement in that calendar year or part thereof (for the avoidance of doubt sub-Sections (i) and (ii) shall not be additive); and

(d) in the event that any loss of Client-Supplied Materials has arisen from the [***] of Patheon in its performance of this Agreement during the Manufacture of process validation or subsequent batches, in each calendar year (or part thereof) Patheon will reimburse Client for losses of Client-Supplied Materials at cost, up to a maximum amount of [***] of the total [***] received by or payable to Patheon pursuant to this Agreement in that calendar year (or part thereof).

(e) For the first [***]period after the Effective Date, as Patheon will not have received [***] for a full [***] period, the amount of the [***] for the purpose of the limitation of liability in this Section shall be calculated based on the expected [***] for the first [***] of Transfer Services based on the Timeline in place at the Effective Date.

For the purpose of this Section 7.5, "[***]" means any failure to comply with GMP or any breach (being an act or omission) of obligations provided under this Agreement or any other negligent act or omission of Patheon in connection with this Agreement that either:

[***].

ARTICLE 8
TERM AND TERMINATION

8.1 Term. This Agreement will remain in full force and effect unless and until it expires or is terminated in accordance with the provisions of this ARTICLE 8 (the "Term").

8.2 Expiration. This Agreement will expire when the Parties agree that the Transfer Services have been completed (by Client's acceptance in writing of a written notification from Patheon) (the "Completion of the Tech Transfer").

8.1 Termination by Client. Client may terminate this Agreement in its entirety:

(a) by giving Patheon [***] prior written notice if: (i) Client's application for Marketing Authorization in the United States is rejected, or (ii), or (iii) any Regulatory Authority causes the clinical hold or permanent withdrawal of the Product in the United States;

(b) for convenience, at any time prior to the FDA Approval Date, with [***] written notice to Patheon and subject to payment of the compensation set out in Section 8.13; or

(c) by giving Patheon [***] written notice if Patheon (due solely to its acts or omissions) fails to deliver:

(i) Milestones 1 and 2 as described in Exhibit H on or before [***] after the date stated in the Timeline;

(ii) Milestone 3 as described in Exhibit H on or before [***] after the date stated in the Timeline; or

(iii) Milestone 4 [***] on or before [***] after the date stated in the Timeline.

8.2 Termination by Mutual Agreement. This Agreement may be terminated at any time upon mutual written agreement between the Parties.

8.3 Termination for Default. Each Party will have the right to terminate this Agreement at any time upon written notice to the other Party, if such other Party (a) breaches any of the representations, warranties, covenants, or agreements set forth in this Agreement or (b) otherwise defaults in the performance of any of its duties or obligations under this Agreement, which in either case has a material effect on the other Party, and which breach or default is not cured on or before [***] after written notice is given to the breaching Party specifying the breach or default, or such longer period as the Parties acting reasonably may agree ("Remediation Period"), provided that the Parties shall use Commercially Reasonable Efforts to agree a plan to remedy the breach or default within [***] after written notice is given to the breaching Party. The aggrieved Party's right to terminate this Agreement for a particular breach under this Section 8.5 may only be exercised for a period of [***] following the expiry of the Remediation Period (where the breach has not been remedied) and, if the termination right is not exercised during this period, then the aggrieved Party will be deemed to have waived its right to terminate this Agreement for such breach.

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8.4 Bankruptcy; Insolvency. To the extent permitted by law, each Party will have the right to terminate this Agreement immediately upon notice to the other Party, if the other Party shall file in any court or agency, pursuant to any statute or regulation of any state or country, a petition in bankruptcy or insolvency or for reorganization or for arrangement or for the appointment of a receiver or trustee of the other Party or of its assets, or if the other Party proposes a written agreement of composition or extension of its debts, or if the other Party shall be served with an involuntary petition against it, filed in any insolvency proceeding, and such petition shall not be dismissed on or before [***] after the filing thereof, or if the other Party shall propose or be a party to any dissolution or liquidation, or if the other Party shall make an assignment for the benefit of its creditors.

8.5 Cross Termination. Should either Client or Patheon exercise its right to terminate this Agreement in its entirety prior to the FDA Approval Date (but not in the event of an expiration of this Agreement as set forth in Section 8.2), then the Manufacturing and Supply Agreement and the Quality Agreement will concurrently and automatically terminate.

8.6 No Release. Neither the termination nor expiration of this Agreement will release or operate to discharge either Party from any liability or obligation that may have accrued prior to such termination or expiration, including any obligation to pay to the other Party any amounts accrued under this Agreement with respect to the period prior to the effective date of such expiration or termination. Except as otherwise expressly provided herein, termination of this Agreement in accordance with the provisions hereof will not limit remedies that may otherwise be available in law or equity.

8.7 Obligations. Notwithstanding the giving of any notice of termination pursuant to this ARTICLE 8, each Party will continue to fulfill its obligations under this Agreement at all times until the effective date of any such termination or expiration.

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8.1 Survival. The expiration or termination of this Agreement shall be without prejudice to any rights or obligations of the Parties that may have accrued prior to such termination, and the provisions of Sections 2.3 (as it may relate to any unpaid amounts due and owing), 2.9 (as it may relate to the use to which Patheon may put the Client Manufacturing Equipment), 2.12 and ARTICLE 1, ARTICLE 3, ARTICLE 7, ARTICLE 8, and ARTICLE 9 shall survive the expiration or termination of this Agreement.

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8.2 Rights and Duties Upon Expiration. Upon expiration of this Agreement pursuant to Section 8.2, the terms of the Manufacturing Supply Agreement shall apply to any relevant finished Products, semi-finished Products and Materials held by Patheon as at the Completion of the Tech Transfer. In addition, any outstanding Technology Transfer Fees shall remain payable in accordance with the payment schedule set out in Part 1 of Exhibit B.

8.3 Rights and Duties Upon Termination. Upon termination of this Agreement for any reason:

(a) Patheon will, as promptly as practicable, (i) cease work on the Transfer Services, and (ii) subject to Section 8.12(d), make available for collection by Client at its option, EXW (Incoterms 2010) the Facility, all Products, semi-finished Products, and Materials, that are then in Patheon's possession, and any results and information resulting from the Transfer Services (whether in written or electronic form) that are the property of Client in accordance with Section 2.12 of this Agreement;

(b) each Party shall return to the other all Confidential Information and any licences of Intellectual Property granted pursuant to Section 2.12 shall terminate;

(c) Patheon will dismantle the Client Manufacturing Equipment and prepare and make it available for collection from the Facility according to a procedure agreed by the Parties (acting reasonably), following which Client shall remove all Client Manufacturing Equipment, Product and Materials from the Facility on or before the day [***] days after the completion of said procedure, failing which Client will pay a fee equivalent to the aggregate monthly Base Fee for the Manufacturing Suite for each month or part month the Client Manufacturing Equipment, Product or Materials remain at the Facility after [***] post termination.

(d) Client will, as promptly as practicable, (i) pay all earned but unpaid fees and charges for the Transfer Services, including Technology Transfer Fees, Material Costs, Maintenance Costs, Disposal Costs and Capital Expenditures, to reflect Transfer Services performed as of the date of such termination by Patheon; and (ii) pay all due and outstanding invoices in accordance with ARTICLE IV of the Manufacturing and Supply Agreement (which is incorporated herein);

(e) unless this Agreement has been terminated by [***] pursuant to [***] Client will, as promptly as practicable, pay to Patheon all and any (i) dismantling costs, (ii) removal costs and (iii) Make Good Costs, associated with the cessation of the Manufacturing Services or the removal of the Client Manufacturing Equipment and Materials from the Facility; and

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(f) unless this Agreement has been terminated by [***] pursuant to [***] Client will, as promptly as practicable, pay to Patheon the following costs ("Transfer Services Termination Costs"): (i) all actual costs incurred by Patheon to complete reasonable activities associated with the completion, expiry or termination including, without limitation, disposal fees that may be payable for any Materials and supplies owned by Client to be disposed of by Patheon; (ii) all and any direct costs and expenses, or wasted costs and expenses, or termination or cancellation fees payable by Patheon as a consequence of or arising from the termination of this Agreement, to include but not limited to, all and any redundancy costs of employees employed by Patheon to work solely or mainly in providing the Transfer Services and/or Manufacturing the Product, all and any termination costs in relation to subcontractors and agency staff working solely or mainly in providing the Transfer Services and/or Manufacturing the Product, any termination or cancellation fees payable to Third Party suppliers; and (iii) any additional costs incurred by Patheon in connection with the Transfer Services that are required to fulfill outstanding applicable regulatory and contractual requirements,

in each case subject to Patheon using Commercially Reasonable Efforts to minimise such costs and Patheon providing Client with documentation to substantiate the costs have been properly and reasonably incurred.

8.4 Consequences of termination for convenience. Upon termination of this Agreement by Client pursuant to Section 8.3(b), in addition to any other obligations of Client under Section 8.12. Client shall pay Patheon a compensation payment calculated in accordance with the table below. The Parties confirm that this sum represents a genuine pre-estimate of Patheon's loss in such circumstances and shall be in full and final settlement of all liabilities of Client arising out of any termination of this Agreement pursuant to Section 8.3(b) but shall be without prejudice to any obligation of Client under Sections 7.1, 8.12 or any obligations which survive termination of this Agreement. For the avoidance of doubt no such compensation shall be payable in circumstances where the Products are sold to a Third Party and this Agreement is assigned or novated to such Third Party, unless the Third Party terminates this Agreement pursuant to Section 8.3(b) in which case, this Section 8.13 shall apply as between Patheon and the Third Party.

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Date of termination (number of months after the Effective Date)	**Amount of compensation**
On or before [***]	[***]
After [***] and on or before [***]	[***]
After [***] and on or before [***]	[***]
After [***] and on or before [***]	[***]
After [***] and on or before [***]	[***]
After [***] and on or before [***]	[***]
After [***]	[***]

ARTICLE 9
MISCELLANEOUS

ARTICLE X of the Manufacturing and Supply Agreement shall apply to this Agreement and the performance of the Transfer Services and is incorporated herein (*mutatis mutandis*).

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IN WITNESS WHEREOF, this Technology Transfer Agreement has been executed by the Parties hereto as of the day and year first written above.

PATHEON UK LIMITED:	**INSMED INCORPORATED**:
By: /s/ Luca Andretta	By: /s/ William H. Lewis
Name: Luca Andretta	Name: William H. Lewis
Title: Director	Title: President and CEO

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Signature Page of Technology Transfer Agreement

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Exhibit A

Engineering Approach and Footprint

Engineering Approach

The engineering approach for the Product and project is still to be finalised but would be based on the assumptions built into the Basic Engineering Design.

Manufacturing Suite

[***]

Exhibit B

Part 1: Technology Transfer Fees

Ref	Technology Transfer Fee	Payment structure	First payment due	End date
1	[***]	[***]	[***]	[***]
2	[***]	[***]	[***]	[***]
3	[***]	[***]	[***]	[***]

Consequences for the failure to achieve Milestones or effects of early completion of the Transfer Services are specified in Exhibit H.

Part 2: Capital Expenditures as at the Effective Date

The Capital Expenditures for the Product are still to be finalised but will be based on the following estimate and the assumptions built into the Basic Engineering Design.

[***]

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Exhibit C

Transfer Services

Construction and Validation phase

[***]

Development and Transfer Services phase

[***]

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Exhibit D

Key Technical Assumptions

Manufacturing Parameters

The full manufacturing process for the Product is still to be finalised and but would be based on the assumptions built into the Basic Engineering Design.

[***]

1.1.1

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Exhibit E

[***]

Exhibit F

Equipment

Client Manufacturing Equipment

Details of the Client Manufacturing Equipment are the subject of the Basic Engineering Design and will be finalized between the Parties during the Transfer Services.

Patheon Manufacturing Equipment

Details of the Patheon Manufacturing Equipment are the subject of the Basic Engineering Design and will be finalized between the Parties during the Transfer Services.

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Exhibit G

Steering Committee

1. Generally. The purpose of the Steering Committee shall be to oversee this Agreement and to facilitate communications between the Parties with respect thereto. The Steering Committee shall have the responsibilities and authority allocated to it in this Exhibit G. The Steering Committee shall have the obligation to exercise its authority consistent with the respective purpose for the Steering Committee as stated herein and any such decisions shall be made in good faith.

2 Formation and Purpose. Promptly following the Effective Date, the Parties shall confer and then create a Steering Committee. The Steering Committee shall have authority, subject to Paragraph 5, to oversee the priorities and budgets for the Transfer Services (with all expenditure to be reviewed on not less than a quarterly basis), to oversee manufacturing and controls for the Products, to review and approve all associated regulatory filings and correspondence under this Agreement (including reviewing and approving itemized budgets with respect to the foregoing), to approve the projects and plans of any subcommittee it establishes consistent with this authority and to review any concerns either Party may have concerning key employees employed by the Parties to provide the Transfer Services under this Agreement. The Steering Committee shall also review any potential restrictions on the availability of additional space within the Facility, which shall be notified by Patheon sufficiently far in advance of any proposed agreement with a Third Party in order for Client to be able assess its likely future requirements and for the Parties to have the opportunity to negotiate in good faith any reservation of the same.

3 General Steering Committee Membership and Procedure.

(a) Membership. Each Party shall designate an equal number of representatives (not to exceed three (3) for each Party) to the Steering Committee with appropriate expertise to serve as members of the Steering Committee. The Steering Committee representatives must all be employees of such Party or an Affiliate of such Party, with the caveat that each Party may designate for the Steering Committee up to one (1) representative who is not an employee if : (i) such non-employee representative agrees in writing to be bound to the terms of this Agreement for the treatment and ownership of confidential information of the Parties, and (ii) the other Party consents to the designation of such non-employee representative, which consent shall not be unreasonably withheld. Each Party may replace its Steering Committee representatives at any time upon written notice to the other Party. The Steering Committee shall have a chairperson which shall be appointed by Client. The chairperson of the Steering Committee shall be responsible for calling meetings, preparing and circulating an agenda in advance of each meeting of the Steering Committee, and preparing and issuing minutes of each meeting within fifteen (15) days thereafter.

(b) Meetings. The Steering Committee shall be constituted and the first meeting of the Steering Committee shall be held within [***] following the Effective Date, with the Steering Committee considering finalization and approval of workplans prepared by the Parties for inclusion and commencement under this Agreement. Otherwise, the Steering Committee shall hold meetings at such times as it elects to do so, but in no event shall such meetings be held less frequently than once every three (3) months. Meetings of the Steering Committee may be held in person or by means of telecommunication (telephone, video, or web conferences). To the extent that the Steering Committee holds any meetings in person, the Parties will alternate in designating the location for such in-person meetings, with Client selecting the first meeting location for the Steering Committee. A reasonable number of additional representatives of a Party may attend meetings of the Steering Committee in a non-voting capacity. Each Party shall be responsible for all of its own expenses of participating in the Steering Committee.

(c) Meeting Agendas. Each Party will disclose to the other proposed agenda items along with appropriate information at least three (3) business days in advance of each meeting of the Steering Committee; provided, that a Party may provide its agenda items to the other Party within a lesser period of time in advance of the meeting, or may propose that there not be a specific agenda for a particular meeting, so long as such other Party consents to such later addition of such agenda items or the absence of a specific agenda for the Steering Committee meeting.

(d) Limitations of Steering Committee Powers. The Steering Committee shall have only such powers as are specifically delegated to it hereunder or from time to time as agreed to in writing by the mutual consent of the Parties and shall not be a substitute for the rights of the Parties. Without limiting the generality of the foregoing, the Steering Committee shall not have any power to amend this Agreement. Additionally, no member of the Steering Committee shall be able to vote in the Steering Committee and thereby bind its respective Party on any material matter except as otherwise properly authorized, approved, or delegated by such Party in accord with Paragraph 5.

(e) Quorum and voting. The quorum for meetings of the Steering Committee shall be one (1) representative of each Party, provided that the chairperson, or, if the chairperson is not available then an alternate chairperson agreed by the Parties, must be present at all meetings of the Steering Committee. At any meeting, the Steering Committee members present appointed by Client shall have one (1) vote in aggregate and the Steering Committee members present appointed by Patheon shall have one (1) vote in aggregate, irrespective of the number of representatives actually in attendance at a meeting. In the event of deadlock the matter will be first referred to the Project Manager of each Party as soon as reasonably possible. If the Project Managers are unable to resolve the deadlock within seven (7) days of the referral, the matter shall be referred to the Senior Management of each Party for resolution. If the Senior Management are unable to resolve the matter within seven (7) days each Party shall have the right to pursue any remedies available to it at law or in equity. Each Party may invite additional employees or consultants to attend meetings of the Steering Committee but any such additional attendees shall not have any right to vote.

4 Restrictions. Neither Party shall exercise its right to finally resolve a dispute at the Steering Committee in accordance with this Paragraph 4 in a manner that (i) excuses such Party from any of its obligations specifically enumerated under this Agreement; (ii) expands the obligations of the other Party under this Agreement; (iii) negates any consent rights or other rights specifically allocated to the other Party under this Agreement; (iv) purports to resolve any dispute involving the breach or alleged breach of this Agreement; (v) resolves a matter if the provisions of this Agreement specify that mutual agreement is required for such matter; or (vi) would require the other Party to perform any act that is inconsistent with applicable law.

5 Authorization of Steering Committee Representatives. Each representative serving on the Steering Committee shall be responsible for ensuring that he or she acts only as duly authorized by its respective Party and obtains any advance approvals, delegations, or other authorizations from his or her respective Party in advance of making any Steering Committee votes.

*** Certain information on this page has been omitted and filed separately with the Securities and Exchange Commission. Confidential treatment has been requested with respect to the omitted portions.

Exhibit H

Milestones and consequences of delay

	Milestone	Target completion date	Consequence of on time or early completion	Consequence of completion being delayed solely as result of any Patheon breach, act or omission	Consequence of completion being delayed for any other reason
1.	[***]	[***]	[***]	[***]	[***]
2.	[***]	[***]	[***]	[***]	
3.	[***]	[***]	[***]	[***]	
4.	[***]	[***]	[***]	[***]	

[***]

*** Certain information on this page has been omitted and filed separately with the Securities and Exchange Commission. Confidential treatment has been requested with respect to the omitted portions.

EXHIBIT 21.1

LIST OF SUBSIDIARIES

Name	Jurisdiction of Incorporation
Celtrix Pharmaceuticals, Inc.	Delaware
Insmed Limited	England and Wales
Insmed Holdings Limited	Ireland
Insmed Ireland Limited	Ireland
Insmed Germany GmbH	Germany
Insmed France SAS	France
Insmed Netherlands B.V.	Netherlands
Insmed Godo Kaisha	Japan

EXHIBIT 23.1

Consent of Independent Registered Public Accounting Firm

We consent to the incorporation by reference in the following Registration Statements:

(1) Registration Statement on Form S-3 No. 333-218118 of Insmed Incorporated, and

(2) Registration Statements on Form S-8 Nos. 333-39200, 333-87878, 333-129479, 333-175532, 333-188852, 333-204503, and 33-218668 of Insmed Incorporated;

of our reports dated February 23, 2018, with respect to the consolidated financial statements of Insmed Incorporated and the effectiveness of internal control over financial reporting of Insmed Incorporated included in this Annual Report (Form 10-K) of Insmed Incorporated for the year ended December 31, 2017.

/s/ Ernst & Young LLP

Iselin, New Jersey

February 23, 2018

EXHIBIT 31.1

Section 302 Certification

I, William H. Lewis, Chief Executive Officer of Insmed Incorporated, certify that:

(1) I have reviewed this annual report on Form 10-K of Insmed Incorporated;

(2) Based on my knowledge, this report does not contain any untrue statement of a material fact or omit to state a material fact necessary to make the statements made, in light of the circumstances under which such statements were made, not misleading with respect to the period covered by this report;

(3) Based on my knowledge, the financial statements, and other financial information included in this report, fairly present in all material respects the financial condition, results of operations and cash flows of the registrant as of, and for, the periods presented in this report;

(4) The registrant's other certifying officer and I are responsible for establishing and maintaining disclosure controls and procedures (as defined in Exchange Act Rules 13a-15(e) and 15d-15(e)) and internal control over financial reporting (as defined in Exchange Act Rules 13a-15(f) and 15d-15(f)) for the registrant and have:

(a) Designed such disclosure controls and procedures, or caused such disclosure controls and procedures to be designed under our supervision, to ensure that material information relating to the registrant, including its consolidated subsidiaries, is made known to us by others within those entities, particularly during the period in which this report is being prepared;

(b) Designed such internal control over financial reporting, or caused such internal control over financial reporting to be designed under our supervision, to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles;

(c) Evaluated the effectiveness of the registrant's disclosure controls and procedures and presented in this report our conclusions about the effectiveness of the disclosure controls and procedures, as of the end of the period covered by this report based on such evaluation; and

(d) Disclosed in this report any change in the registrant's internal control over financial reporting that occurred during the registrant's most recent fiscal quarter (the registrant's fourth fiscal quarter in the case of an annual report) that has materially affected, or is reasonably likely to materially affect, the registrant's internal control over financial reporting; and

(5) The registrant's other certifying officer and I have disclosed, based on our most recent evaluation of internal control over financial reporting, to the registrant's auditors and the audit committee of the registrant's board of directors (or persons performing the equivalent functions):

(a) All significant deficiencies and material weaknesses in the design or operation of internal control over financial reporting which are reasonably likely to adversely affect the registrant's ability to record, process, summarize and report financial information; and

(b) Any fraud, whether or not material, that involves management or other employees who have a significant role in the registrant's internal control over financial reporting.

Date: February 23, 2018

By: /s/ William H. Lewis

William H. Lewis

Chief Executive Officer (Principal Executive Officer) and Director

EXHIBIT 31.2

CERTIFICATION PURSUANT TO

18 USC. SECTION 1350,

AS ADOPTED PURSUANT TO

SECTION 906 OF THE SARBANES-OXLEY ACT OF 2003

In connection with this Annual Report on Form 10-K of Insmed Incorporated (the "Company") for the period ended December 31, 2017 as filed with the Securities and Exchange Commission on the date hereof (the "Report"), I, William H. Lewis, Chief Executive Officer of the Company, certify, pursuant to 18 USC. § 1350, as adopted pursuant to § 906 of the Sarbanes-Oxley Act of 2003, that:

(1) the Report fully complies with the requirements of Section 13(a) or 15(d) of the Securities Exchange Act of 1934, as amended; and

(2) the information contained in the Report fairly presents, in all material respects, the financial condition and results of operations of the Company.

By: /s/ William H. Lewis

William H. Lewis

Chief Executive Officer (Principal Executive Officer) and Director

February 23, 2018

This certification accompanies the Form 10-K to which it relates, is not deemed filed with the Securities and Exchange Commission and is not to be incorporated by reference into any filing of Insmed Incorporated under the Securities Act of 1933, as amended, or the Securities Exchange Act of 1934, as amended (whether made before or after the date of the Form 10-K), irrespective of any general incorporation language contained in such filing.

EXHIBIT 32.1

Section 302 Certification

I, Paolo Tombesi, Chief Financial Officer of Insmed Incorporated, certify that:

(1) I have reviewed this annual report on Form 10-K of Insmed Incorporated;

(2) Based on my knowledge, this report does not contain any untrue statement of a material fact or omit to state a material fact necessary to make the statements made, in light of the circumstances under which such statements were made, not misleading with respect to the period covered by this report;

(3) Based on my knowledge, the financial statements, and other financial information included in this report, fairly present in all material respects the financial condition, results of operations and cash flows of the registrant as of, and for, the periods presented in this report;

(4) The registrant's other certifying officer and I are responsible for establishing and maintaining disclosure controls and procedures (as defined in Exchange Act Rules 13a-15(e) and 15d-15(e)) and internal control over financial reporting (as defined in Exchange Act Rules 13a-15(f) and 15d-15(f)) for the registrant and have:

(a) Designed such disclosure controls and procedures, or caused such disclosure controls and procedures to be designed under our supervision, to ensure that material information relating to the registrant, including its consolidated subsidiaries, is made known to us by others within those entities, particularly during the period in which this report is being prepared;

(b) Designed such internal control over financial reporting, or caused such internal control over financial reporting to be designed under our supervision, to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles;

(c) Evaluated the effectiveness of the registrant's disclosure controls and procedures and presented in this report our conclusions about the effectiveness of the disclosure controls and procedures, as of the end of the period covered by this report based on such evaluation; and

(d) Disclosed in this report any change in the registrant's internal control over financial reporting that occurred during the registrant's most recent fiscal quarter (the registrant's fourth fiscal quarter in the case of an annual report) that has materially affected, or is reasonably likely to materially affect, the registrant's internal control over financial reporting; and

(5) The registrant's other certifying officer and I have disclosed, based on our most recent evaluation of internal control over financial reporting, to the registrant's auditors and the audit committee of the registrant's board of directors (or persons performing the equivalent functions):

(a) All significant deficiencies and material weaknesses in the design or operation of internal control over financial reporting which are reasonably likely to adversely affect the registrant's ability to record, process, summarize and report financial information; and

(b) Any fraud, whether or not material, that involves management or other employees who have a significant role in the registrant's internal control over financial reporting.

Date: February 23, 2018

/s/ Paolo Tombesi

Paolo Tombesi
Chief Financial Officer
(Principal Financial and Accounting Officer)

EXHIBIT 32.2

CERTIFICATION PURSUANT TO

18 USC. SECTION 1350,

AS ADOPTED PURSUANT TO

SECTION 906 OF THE SARBANES-OXLEY ACT OF 2003

In connection with this Annual Report on Form 10-K of Insmed Incorporated (the "Company") for the period ended December 31, 2017 as filed with the Securities and Exchange Commission on the date hereof (the "Report"), I, Paolo Tombesi, Chief Financial Officer of the Company, certify, pursuant to 18 USC. § 1350, as adopted pursuant to § 906 of the Sarbanes-Oxley Act of 2003, that:

(1) the Report fully complies with the requirements of Section 13(a) or 15(d) of the Securities Exchange Act of 1934, as amended; and

(2) the information contained in the Report fairly presents, in all material respects, the financial condition and results of operations of the Company.

/s/ Paolo Tombesi

Paolo Tombesi
Chief Financial Officer
(Principal Financial and Accounting Officer)

February 23, 2018

This certification accompanies the Form 10-K to which it relates, is not deemed filed with the Securities and Exchange Commission and is not to be incorporated by reference into any filing of Insmed Incorporated under the Securities Act of 1933, as amended, or the Securities Exchange Act of 1934, as amended (whether made before or after the date of the Form 10-K), irrespective of any general incorporation language contained in such filing.