ACELRX PHARMACEUTICALS INC
Form 10-K
March 07, 2016

UNITED STATES

SECURITIES AND EXCHANGE COMMISSION

WASHINGTON, DC 20549

FORM 10-K

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

or

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

Commission File Number: 001-35068

ACELRX PHARMACEUTICALS, INC.
(Exact name of registrant as specified in its charter)

Delaware	**41-2193603**
(State or other jurisdiction of incorporation or organization)	**(IRS Employer Identification No.)**

351 Galveston Drive

Redwood City, CA 94063

(650) 216-3500

(Address, including zip code, and telephone number, including area code, of registrant's principal executive offices)

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

Title of Each Class	**Name of Each Exchange on Which Registered**
Common Stock, $0.001 par value	The NASDAQ Stock Market LLC

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 (§-229.405) 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, or a smaller reporting company. See the definitions of “large accelerated filer,” “accelerated filer,” and “smaller reporting company” in Rule 12b-2 of the Exchange Act. (Check one):

Large accelerated filer Accelerated filer
Non-accelerated filer (Do not check if a smaller reporting company) Smaller reporting company
Indicate by check mark whether the registrant is a shell company (as defined in Exchange Act Rule 12b-2) Yes No

The aggregate market value of the voting stock held by non-affiliates of the registrant on June 30, 2015 (the last business day of the registrant’s most recently completed second fiscal quarter), based upon the last sale price reported on the NASDAQ Global Market on that date, was approximately $145,535,000. The calculation excludes 10,050,102 shares of the registrant’s common stock held by current executive officers, directors and stockholders that the registrant has concluded are affiliates of the registrant. Exclusion of such shares should not be construed to indicate that any such person possesses the power, direct or indirect, to direct or cause the direction of the management or policies of the registrant or that such person is controlled by or under common control with the registrant.

As of February 24, 2016, the number of outstanding shares of the registrant’s common stock was 45,273,772.

DOCUMENTS INCORPORATED BY REFERENCE

Portions of the Registrant's notice of annual meeting of stockholders and proxy statement to be filed pursuant to Regulation 14A within 120 days after Registrant's fiscal year end of December 31, 2015, are incorporated by reference into Part III of this report.

ACELRX PHARMACEUTICALS, INC.

2015 ANNUAL REPORT ON FORM 10-K

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Unless the context indicates otherwise, the terms "AcelRx," "AcelRx Pharmaceuticals," "we," "us" and "our" refer to AcelRx Pharmaceuticals, Inc.

ACELRX and “ACCELERATE.INNOVATE.ALLEVIATE.” are registered trademarks of AcelRx Pharmaceuticals, Inc. Other trademarks of AcelRx Pharmaceuticals, Inc., including ZALVISO™, appearing in this annual report on Form 10-K are the property of AcelRx Pharmaceuticals, Inc. This report also contains trademarks and trade names that are the property of their respective owners.

Forward-Looking Statements

This Annual Report on Form 10-K, or Form 10-K, contains "forward-looking statements" within the meaning of Section 21E of the Securities Exchange Act of 1934, as amended, or the Exchange Act, which are subject to the "safe harbor" created by that section. The forward-looking statements in this Form 10-K are contained principally under "Item 1. Business," "Item 1A. Risk Factors" and "Item 7. Management's Discussion and Analysis of Financial Condition and Results of Operations." In some cases, you can identify forward-looking statements by the following words: "may," "will," "could," "would," "should," "expect," "intend," "plan," "anticipate," "believe," "estimate," "predict," "project," "potential," "c or the negative of these terms or other comparable terminology, although not all forward-looking statements contain these words. These statements involve risks, uncertainties and other factors that may cause our actual results, levels of activity, performance or achievements to be materially different from the information expressed or implied by these forward-looking statements. Although we believe that we have a reasonable basis for each forward-looking statement contained in this Form 10-K, we caution you that these statements are based on a combination of facts and factors currently known by us and our projections of the future, about which we cannot be certain. Many important factors affect our ability to achieve our objectives, including:

- the success, cost and timing of our product development activities and clinical trials, including the SAP302 and SAP303 studies for ARX-04 (sufentanil sublingual tablet, 30 mcg) and the additional clinical study, IAP312, for Zalviso™ (sufentanil sublingual tablet system);

- our ability to fund the completion of our ARX-04 Phase 3 development with the proceeds from the contract with the Department of Defense, or DoD;

- our ability to resubmit the Zalviso New Drug Application, or NDA, including our ability to satisfactorily conduct the additional clinical study requested by the U.S. Food and Drug Administration, or FDA, and any additional studies that may be required by the FDA in order to resubmit the Zalviso NDA, and the time and resources required to do so;

- our ability to manufacture and supply Zalviso to Grünenthal GmbH, or Grünenthal, in accordance with their forecast and the Manufacture and Supply Agreement with Grünenthal;

- our ability to successfully recruit a full-time Chief Executive Officer and retain our key scientific or management personnel;

- our ability to obtain and maintain regulatory approval of Zalviso and other product candidates, and any related restrictions, limitations, and/or warnings in the label of an approved product candidate;

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the status of the Collaboration and License Agreement with Grünenthal or any other future potential collaborations, including potential milestones and royalty payments under the Grünenthal agreement and obligations under the Purchase and Sale Agreement with PDL BioPharma, Inc., or PDL;

- the outcome of any potential FDA Advisory Committee meetings held for any of our product candidates;

- our plans to research, develop and commercialize our product candidates;

- our ability to attract additional collaborators with development, regulatory and commercialization expertise;

- the size and growth potential of the markets for our product candidates, and our ability to serve those markets;

- our liquidity and capital resources;

- our ability to successfully commercialize our product candidates;

- the rate and degree of market acceptance of our product candidates;

- our ability to develop sales and marketing capabilities, whether alone or with potential future collaborators;

- regulatory developments in the United States and foreign countries;

- the performance of our third party suppliers and manufacturers;

- the success of competing therapies that are or become available;

- the accuracy of our estimates regarding expenses, future revenues, capital requirements and needs for additional financing; and

- our ability to obtain and maintain intellectual property protection for our product candidates.

In addition, you should refer to “Item 1A. Risk Factors” in this Form 10-K for a discussion of these and other important factors that may cause our actual results to differ materially from those expressed or implied by our forward-looking statements. As a result of these factors, we cannot assure you that the forward-looking statements in this Form 10-K will prove to be accurate. Furthermore, if our forward-looking statements prove to be inaccurate, the inaccuracy may be material. In light of the significant uncertainties in these forward-looking statements, you should not regard these statements as a representation or warranty by us or any other person that we will achieve our objectives and plans in any specified time frame, or at all. Also, forward-looking statements represent our estimates and assumptions only as of the date of this Form 10-K. We undertake no obligation to publicly update any forward-looking statements, whether as a result of new information, future events or otherwise, except as required by law.

PART I

Item 1. Business

Overview

We are a specialty pharmaceutical company focused on the development and commercialization of innovative therapies for the treatment of acute pain. Our lead product candidates, ARX-04 and Zalviso, utilize sublingual sufentanil, delivered via a non-invasive route of administration. We intend to commercialize our product candidates in the United States and license the development and commercialization rights to our product candidates for sale outside of the United States through strategic partnerships and collaborations. We may also consider the option to enter into strategic partnerships for our product candidates in the United States.

We have chosen sufentanil as the therapeutic ingredient for all of our product candidates. Opioids have been utilized for pain relief for centuries and are the standard of care for the treatment of moderate-to-severe acute pain. Sufentanil is available as an injectable in several markets around the world and is used by anesthesiologists for induction of sedation or as an epidural; however, the injectable formulation is not suitable for the treatment of acute pain. The Company has created a proprietary sublingual (under the tongue) formulation of sufentanil intended for the treatment of moderate-to-severe acute pain. The sublingual formulation retains the therapeutic value of sufentanil and novel delivery devices provide a non-invasive route of administration. Sufentanil is highly lipophilic which provides for rapid absorption in the mucosal tissue, or fatty cells, found under the tongue, and for rapid transit across the blood-brain barrier to reach the mu-opioid receptors in the brain. The sublingual delivery used by ARX-04 and Zalviso provides a recognized onset of analgesia. The sublingual delivery system also eliminates the risk of intravenous, or IV, complications, such as catheter-related infections. In addition, because patients do not require direct connection to an IV infusion pump, ARX-04 and Zalviso allow for ease of patient mobility.

ARX-04 (sufentanil sublingual tablet, 30 mcg)

ARX-04 is an investigational product candidate consisting of a single 30 mcg sufentanil sublingual tablet delivered via a disposable, pre-filled, single-dose applicator, or SDA. We are developing ARX-04 for the treatment of moderate-to-severe acute pain to be administered by a healthcare professional to a patient in medically supervised settings. If approved, examples of potential patient populations and settings in which ARX-04 could be used include: emergency room patients; patients who are recovering from short-stay or ambulatory surgery and do not require more long-term patient-controlled analgesia; post-operative patients who are transitioning from the operating room to the recovery floor; patients being treated and transported by paramedics; and for battlefield casualties.

In September 2015, we reported that SAP301, a pivotal Phase 3 multi-center, double-blind, placebo-controlled study of ARX-04, met the primary (summed pain intensity, or SPID, over 12 hours, or SPID-12) and secondary endpoints in the short-term treatment of patients with moderate-to-severe acute pain following ambulatory abdominal surgery.

In October 2015, we initiated SAP302, an open-label Phase 3 study of ARX-04 for the treatment of adult patients who present in the emergency room with moderate-to-severe acute pain associated with trauma or injury. Based on discussions with the FDA, we have amended the protocol for SAP302 to allow for multiple dosing of ARX-04. We are planning to enroll up to an additional 60 patients in the extension phase of the SAP302 study. The SAP302 study is expected to be completed by the third quarter of 2016.

In December 2015, we, along with representatives from our partner at the U.S. Department of Defense, or DoD, held a pre-NDA meeting with the FDA to review plans for an NDA for ARX-04. Based on discussions with the FDA, we intend to increase the safety database by expanding the clinical program for ARX-04 by approximately 160 additional patients to include individuals from specific populations and settings. Enrollment in the ongoing SAP302 open-label study in the emergency room will be increased, as described above, and a new study, known as SAP303, was initiated in March 2016 in post-operative patients with moderate-to-severe acute pain. SAP303 will focus on enrolling patients greater than 40 years of age and will allow for administration of ARX-04 for up to 12 hours. With these modifications, assuming successful completion of SAP302 and SAP303 by the third quarter of 2016, we anticipate submitting the NDA for ARX-04 in the fourth quarter of 2016.

The FDA has also agreed to allow us to include as supporting safety information in the NDA for ARX-04, data from approximately 323 patients treated in the Zalviso clinical studies who had administered two 15 mcg tablets 20-to-25 minutes apart. AcelRx had previously completed and analyzed pharmacokinetic and modeling data, which demonstrated the equivalency of one ARX-04 sufentanil sublingual tablet, 30 mcg, to two sufentanil sublingual tablets, 15 mcg, taken 20-to-25 minutes apart.

In the fall of 2015, we had informal scientific advice meetings regarding the planned Marketing Authorization Application, or MAA, filing for ARX-04. Divergent advice was received regarding the need for an additional active comparator clinical study for product registration in the European Union, or EU. Accordingly, we plan to meet with three additional health authorities in April 2016 to further clarify the need for such a study.

On May 11, 2015, we entered into an award contract supported by the United States Army Medical Research and Materiel Command, or USAMRMC, within the DoD, in which the DoD agreed to provide up to $17.0 million to support the development of ARX-04, referred to as the DoD Contract. Under the terms of the contract, the DoD will reimburse us for costs incurred for development, manufacturing, regulatory and clinical costs outlined in the contract in order to submit an NDA to the FDA, including reimbursement for certain personnel and overhead expenses. The period of performance under the DoD Contract began on May 11, 2015. The contract gives the DoD the option to extend the term of the contract and provide additional funding. On March 2, 2016, the DoD Contract was amended to approve enrollment of additional patients in the SAP302 study, approve the addition of the SAP303 study, and extend the contract period of performance by four months from November 10, 2016 to March 9, 2017, to accommodate the increased SAP302 patient enrollment and the SAP303 study. The costs for these changes will be absorbed within the current contract value. If ARX-04 is approved by the FDA, the DoD has the option to purchase a certain number of units of commercial product pursuant to the terms of the contract.

Zalviso™ (sufentanil sublingual tablet system)

Our U.S. product candidate, Zalviso, is intended for the management of moderate-to-severe acute pain in hospitalized adult patients. Zalviso consists of sufentanil sublingual tablets, 15 mcg, delivered by the Zalviso System, a needle-free, handheld, patient-administered, pain management system, or together, Zalviso. While still under development in the U.S., as discussed further below, Zalviso is approved in the EU.

Zalviso is an investigational pre-programmed, non-invasive, secure system to allow hospital patients with moderate-to-severe acute pain to self-dose with sufentanil sublingual tablets, 15 mcg, to manage their pain. Zalviso is designed to help address certain problems associated with post-operative intravenous patient-controlled analgesia, or IV PCA, such as the risk of programming errors and complications associated with IV delivery of pharmaceuticals.

On December 16, 2013, AcelRx and Grünenthal entered into a Collaboration and License Agreement, which was amended effective July 17, 2015, or the Amended License Agreement, which grants Grünenthal rights to commercialize Zalviso in the countries of the EU, Switzerland, Liechtenstein, Iceland, Norway and Australia, or the Territory, for human use in pain treatment within or dispensed by hospitals, hospices, nursing homes and other medically-supervised settings, or the Field. We retain rights with respect to Zalviso in countries outside the Territory, including the United States, Asia and Latin America. In September 2015, the European Commission approved the MAA for Zalviso for the management of acute moderate-to-severe post-operative pain in adult patients. The approval allows Grünenthal to market Zalviso in the 28 EU member states as well as in the European Economic Area countries of Norway, Iceland and Liechtenstein, or EEA.

Under the terms of the Amended License Agreement, we received an upfront cash payment of $30.0 million in December 2013, a milestone payment of $5.0 million related to the MAA submission to the European Medicines Agency, or EMA, in the third quarter of 2014, and an additional milestone payment of $15.0 million related to the EC approval of the MAA for Zalviso in the third quarter of 2015. In addition, we are eligible to receive approximately $194.5 million in additional milestone payments, based upon successful regulatory and product development efforts ($28.5 million) and net sales target achievements ($166.0 million). Grünenthal will also make tiered royalty, supply and trademark fee payments in the mid-teens up to the mid-twenties percent range, depending on the sales level achieved, on net sales of Zalviso in the Territory. A portion of the tiered royalty payment, exclusive of the supply and trademark fee payments, will be paid to PDL in connection with the Royalty Monetization, as discussed below.

Also on December 16, 2013, we entered into the related Manufacture and Supply Agreement with Grünenthal, which was amended effective July 17, 2015, or the Amended MSA, and together with the Amended License Agreement, the Amended Agreements. Under the Amended MSA, we will exclusively manufacture and supply Zalviso to Grünenthal for the Field in the Territory. For additional information on the Amended Agreements, see Note 6 “Collaboration Agreement” in the accompanying notes to the Consolidated Financial Statements.

On September 18, 2015, we sold a portion of the expected royalty stream and commercial milestones from the sales of Zalviso in the EU and EEA by Grünenthal to PDL, or the Royalty Monetization. AcelRx received gross proceeds of $65.0 million in the Royalty Monetization. PDL will receive 75% of the European royalties under the Amended License Agreement with Grünenthal, as well as 80% of the first four commercial milestones worth $35.6 million (or 80% of $44.5 million), subject to the capped amount of $195.0 million. For additional information on the Royalty Monetization with PDL, see Note 8 “Liability Related to Sale of Future Royalties” in the accompanying notes to the Consolidated Financial Statements.

We submitted an NDA for Zalviso in September 2013, which the FDA accepted for filing in December 2013. On July 25, 2014, the FDA issued a Complete Response Letter, or CRL, for the Zalviso NDA. The CRL contains requests for additional information on the Zalviso System to ensure proper use of the device. The requests include submission of data demonstrating a reduction in the incidence of optical system errors, changes to address inadvertent dosing, among other items, and submission of additional data to support the shelf life of the product. Although there were no requests for additional clinical studies in the CRL, in March 2015, we received correspondence from the FDA stating that, in addition to the work we had performed to address the items in the CRL, a clinical study would be required to test the modifications to the Zalviso device.

Our IAP312 study is designed to evaluate the effectiveness of changes made to enhance performance of the Zalviso device and takes into account comments from the FDA on the protocol. The IAP312 study will include approximately 315 post-operative patients and collect information requested by the Division to supplement the three positive Phase 3 trials already completed. AcelRx plans to initiate the study in the first quarter of 2016.

IAP312 is an open-label Phase 3 study and will enroll adult post-operative patients who will self-administer sufentanil sublingual tablets, 15 mcg, using Zalviso for 24-to-72 hours. Patients will self-administer a tablet as often as once every 20 minutes to manage their moderate-to-severe acute pain. The study will measure the rate of device errors, including the failure to dispense medication, as well as the incidence of any misplaced or dropped tablets. Efficacy pain measurements and safety data will also be collected in the study. The results of the study, including the actual device failure rate and the number of misplaced or dropped tablets, will be subject to final review by the FDA. There can be no assurance that the results of the study will be sufficient to address the issues raised by the Division, or that the Zalviso NDA, once resubmitted, will be approved.

The initial 505(b)(2) NDA submission for Zalviso was based on a development program that included data from seven Phase 1 clinical studies, three Phase 2 clinical trials, and three Phase 3 clinical trials. The Phase 3 trial program included two placebo-controlled efficacy and safety trials and one open-label active comparator trial, in which Zalviso was compared to IV PCA with morphine. To date, the Zalviso safety database includes more than 600 patients. Zalviso successfully achieved the primary efficacy endpoints for each of the Phase 2 and Phase 3 trials. A summary of the Phase 3 trials completed to-date, and the results, follows:

- *Active comparator trial (IAP309)*—in November 2012, we reported top-line data demonstrating that Zalviso met its primary endpoint of non-inferiority in a Phase 3 open-label active comparator trial designed to compare the efficacy and safety of Zalviso (15 mcg/dose, 20 minute lock-out) to IV PCA with morphine (1mg/dose, 6 minute lock-out) for the treatment of moderate-to-severe acute post-operative pain immediately following major abdominal or orthopedic surgery.

- *Double-blind, placebo-controlled, abdominal surgery trial (IAP310)*—in March 2013, we reported top-line data demonstrating that Zalviso met its primary endpoint in a pivotal Phase 3 trial designed to compare the efficacy and safety of Zalviso to placebo in the management of moderate-to-severe acute post-operative pain after major open abdominal surgery. Adverse events reported in the trial were generally mild or moderate in nature and similar in both placebo and treatment groups. Utilizing a randomized, double-blind, placebo-controlled design, this pivotal Phase 3 trial enrolled 178 adult patients at 13 U.S. sites.

- *Double-blind, placebo-controlled, orthopedic surgery trial (IAP311)*—in May 2013, we reported top-line data demonstrating that Zalviso met its primary endpoint in a pivotal Phase 3 trial designed to compare the efficacy and safety of Zalviso to placebo in the management of moderate-to-severe acute post-operative pain after major orthopedic surgery. Utilizing a randomized, double-blind, placebo-controlled design, this pivotal Phase 3 trial enrolled 426 adult patients at 34 U.S. sites. Treatment-emergent adverse events were generally mild-to-moderate in nature and similar for the majority of adverse events between Zalviso and placebo-treated patients, despite the shorter duration of exposure in the placebo-treated patients caused by early termination due to inadequate analgesia.

ARX-03

In addition to ARX-04 and Zalviso, our product candidate pipeline consists of another sufentanil-based sublingual product candidate. The sufentanil/triazolam sublingual tablet, or ARX-03, is a single, fixed-dose, combination drug product designed to provide mild sedation, anxiety reduction and pain relief for patients undergoing painful procedures in a physician's office. We have successfully completed Phase 2 clinical trials for ARX-03. Future development of ARX-03 is contingent on funding from a corporate partnership or other external funding source.

ARX-02

We have made a strategic decision to focus our pipeline on products delivered in medically-supervised settings and since ARX-02 (Sufentanil Sublingual Tablet BTP Management System) would be used in a broader setting and was not actively being developed, the Investigational New Drug, or IND, application for ARX-02 was withdrawn.

Sufentanil Sublingual Tablets

Sufentanil, a high therapeutic index opioid, which has no active metabolites, is 5 to 10 times more potent than fentanyl and is used intravenously as a primary anesthetic to produce balanced general anesthesia for surgery, and for epidural administration during labor and delivery. Sufentanil has many pharmacological advantages over other opioids. Published studies demonstrate that sufentanil produces significantly less respiratory depressive effects relative to its analgesic effects compared to other opioids, including morphine and fentanyl. These third-party clinical results correlate well with preclinical trials demonstrating sufentanil's high therapeutic index, or the ratio of the toxic dose to the therapeutic dose of a drug, used as a measure of the relative safety of the drug for a particular treatment. Accordingly, we believe that sufentanil can be developed to provide an effective and well-tolerated treatment for acute pain. The following table illustrates the difference between the therapeutic index of different opioids.

Opioid	**Therapeutic Index**
Meperidine	5
Methadone	12
Morphine	71
Hydromorphone	250
Fentanyl	277
Sufentanil	26,716

In addition, the pharmaceutical attributes of sufentanil, including lipid solubility and ionization, result in rapid cell membrane penetration and onset of action, which we believe make sufentanil an optimal opioid for the treatment of

acute pain.

Although the analgesic efficacy and safety of sufentanil have been well established, the product's use has been historically limited due to its short duration of action when delivered intravenously. Sublingual delivery of sufentanil avoids the high peak plasma levels and short duration of action of IV administration.

Our portfolio of product candidates leverages the above-mentioned advantages of sufentanil delivered via the sublingual route. We believe our non-invasive, proprietary sufentanil tablet sublingual dosage form potentially overcomes many of the limitations of current treatment options available for moderate-to-severe acute pain.

None of our product candidates have been approved by the FDA.

We have not generated any revenue from the sale of any of our product candidates.

Our Product Candidates

The following table summarizes key information about our existing product candidates.

Product Candidate	Description	Target Indication	Status
ARX-04	Sufentanil sublingual tablet, 30 mcg	Moderate-to-severe acute pain in a medically supervised setting, administered by a healthcare professional	Phase 3 development ongoing. Pending successful completion of Phase 3 studies, NDA submission planned for fourth quarter of 2016.
Zalviso	Sufentanil sublingual tablet system, 15 mcg	Moderate-to-severe acute pain in the hospital setting, administered by the patient as needed	Phase 3 development ongoing. Planning to initiate IAP312, open label study in post-operative patients. Pending successful completion of IAP312, NDA resubmission planned for by the end of 2016. European Commission approved MAA in September 2015 and Zalviso device is CE marked. Grünenthal expects to launch Zalviso in the European Union in 2016.
ARX-03	Sufentanil, 15 mcg/ triazolam, 200 mg sublingual tablet	Mild sedation and pain relief during painful procedures in a physician's office	Phase 2 clinical trial and End of Phase 2 meeting completed. Future development contingent upon identification of corporate partnership resources.

ARX-04 (sufentanil sublingual tablet, 30 mcg)

This product candidate has not been approved by the FDA. We have not generated any revenue from the sale of any of our product candidates.

The Market Opportunity for ARX-04

We believe that ARX-04 could be useful in a variety of medically supervised settings, including emergency room patients; patients who are recovering from short-stay or ambulatory surgery and do not require more long-term patient-controlled analgesia; post-operative patients who are transitioning from the operating room to the recovery floor; patients being treated and transported by paramedics; and for battlefield casualties. According to the Nationwide Emergency Department Sample, or NEDS, there were more than 109 million adult emergency room visits in the United States during 2011, of which we estimate more than 51 million were associated with moderate-to-severe acute pain. Based on the National Survey of Ambulatory Surgery, in 2006, an estimated 30 million adult patients underwent outpatient surgical procedures in the United States, of which we estimate more than 12 million patients experienced moderate-to-severe acute pain. According to the National Inpatient Sample, in 2011, more than 16 million adult patients in the United States underwent surgical procedures in an inpatient setting, of which we estimate more than 8 million resulted in moderate-to-severe acute pain. In the EU, we estimate that there were more than 95 million adult emergency room visits, of which more than 36 million were associated with moderate-to-severe acute pain. Also in the EU, we estimate 13 million adult patients underwent outpatient surgical procedures, and of these, nearly 3 million patients experienced moderate-to-severe acute pain, while more than 18 million adult patients underwent surgical procedures in an inpatient setting in the EU, of which we estimate more than 9 million of these procedures resulted in moderate-to-severe acute pain. In the EU, the pricing of prescription drugs is subject to government control. In addition, the EU provides options for its member states to restrict the range of medicinal products for which their national health insurance systems provide reimbursement and to control the prices of medicinal products for human use. If we are unable to achieve premium pricing for ARX-04 in the EU and/or the United States, the profitability of ARX04, if approved, may be negatively impacted.

How ARX-04 Addresses the Unmet Medical Need for Moderate-to-Severe Acute Pain

ARX-04 is a proprietary, non-invasive, investigational product candidate consisting of a single 30 mcg sufentanil sublingual tablet delivered via a disposable, pre-filled SDA. We are developing ARX-04 for the treatment of moderate-to-severe acute pain to be administered by a healthcare professional in medically supervised settings. Our proprietary sufentanil sublingual tablet technology enables rapid sublingual absorption when the tablet is placed under the tongue. As a result, sufentanil sublingual tablets can provide recognized onset of analgesia and display a consistent pharmacokinetic profile due to a high percentage of drug being absorbed sublingually instead of through the gastrointestinal tract. If approved, examples of potential patient populations and settings where ARX-04 could be used include: emergency room patients; patients who are recovering from short-stay or ambulatory surgery and do not require more long-term patient-controlled analgesia; post-operative patients who are transitioning from the operating room to the recovery floor; patients being transported by paramedics; and battlefield casualties. In the emergency room and in ambulatory care environments, patients often do not have immediate IV access available, or maintaining IV access can be an impediment to rapid discharge. Oral pills and liquids generally have slow and erratic onset of analgesia. Moreover, IV dosing results in high peak plasma levels, thereby limiting the opioid dose and requiring frequent redosing intervals to titrate to satisfactory analgesia. Based on internal market research conducted to date, we believe that additional treatment options are needed that can safely and rapidly treat acute trauma pain, in both civilian and military settings.

Phase 3 Clinical Program for ARX-04

In September 2015, we reported that SAP301, a pivotal Phase 3 multi-center, double-blind, placebo-controlled study of ARX-04 that evaluated the efficacy and safety of ARX-04 vs. placebo for the treatment of moderate-to-severe acute pain following ambulatory abdominal surgery, met its primary and secondary endpoints. Results demonstrated that patients receiving ARX-04 administered via a disposable, pre-filled SDA, experienced significantly greater pain reduction compared to placebo, as measured by the SPID-12 ($p<0.001$). Adverse events reported in the study were typical of opioid therapy and were similar for patients treated with ARX-04 and placebo, the most common of which were nausea, headache and vomiting. SAP301 is considered the second of two pivotal placebo-controlled studies required to be included in the NDA submission.

The Phase 3 SAP301 trial enrolled adult patients undergoing outpatient abdominal surgery procedures at four clinical sites in the United States. Following surgery, 163 patients were randomized to receive either ARX-04, or placebo, in a 2:1 active to placebo ratio. ARX-04, or placebo, was administered by site staff as requested by the patient, but not more than once per hour. The intent-to-treat, or ITT, population in this study averaged 40.9 years of age with an average Body Mass Index of 27.5, and had a higher percent of females to males (68%:32%). Eighty-nine percent of patients entering the study completed the 24-hour study period.

The primary endpoint of the study was the difference in the SPID-12 score of patients receiving ARX-04 compared to those receiving placebo. SPID 12 scores were +25.8 for ARX-04-treated patients and +13.1 for placebo-treated patients; the difference between the two groups being highly statistically significant ($p<0.001$). Notably, the difference in pain intensity from baseline was superior for ARX-04 over placebo at the earliest time point measured (15 minutes; $p=0.002$). Secondary efficacy endpoints were also superior for ARX-04 compared to placebo.

There were two SAEs reported during the study period, both of which were in the placebo group and resulted in early termination of the affected patients. No patient in the ARX-04 group dropped out of the study prior to 24 hours due to an adverse event. A lower percent of patients treated with ARX-04 dropped out of the study prior to 24 hours due to lack of efficacy compared to the placebo group (3.7% and 18.5%, respectively; $p=0.002$).

In October 2015, we announced the initiation of an open-label Phase 3 study, SAP302, of ARX-04 for the treatment of adult patients who present in the emergency room with moderate-to-severe acute pain associated with trauma or injury. The primary efficacy endpoint is the summed pain intensity difference, or SPID, over 1-hour, or SPID-1. Safety endpoints, such as adverse events and vital signs will also be assessed, as will the patients' and healthcare providers' satisfaction with the method of pain control. Based on a pre-NDA meeting held with the FDA in December 2015, we have amended the protocol for SAP302 to allow for multiple dosing of ARX-04. We are planning to enroll an additional 60 patients in the extension phase of the SAP302 study. The SAP302 study is expected to be completed by the third quarter of 2016.

As mentioned above, we met with the FDA in December 2015 to review plans for an NDA for ARX-04. Based on feedback from the FDA, we intend to increase the safety database by expanding the clinical program for ARX-04 by approximately 160 additional patients to include individuals from specific populations and settings. Enrollment in the ongoing SAP302 open-label study in the emergency room will continue, and a new study, known as SAP303, was initiated in March 2016 in post-operative patients with moderate-to-severe acute pain. SAP303 will focus on enrolling patients greater than 40 years of age and will allow for administration of ARX-04 for up to 12 hours. With these modifications, assuming successful completion of SAP302 and SAP303 by the third quarter of 2016, AcelRx anticipates submitting the NDA for ARX-04 in the fourth quarter of 2016.

The FDA has also agreed to allow us to include as supporting safety information in the NDA for ARX-04, data from approximately 323 patients treated in the Zalviso clinical studies who had administered two sufentanil sublingual 15 mcg tablets 20-to-25 minutes apart. AcelRx had previously completed and analyzed pharmacokinetic and modeling data, which demonstrated the equivalency of one sufentanil sublingual tablet, 30 mcg, to two sufentanil sublingual tablets, 15 mcg, taken 20-to-25 minutes apart.

In June 2014, we completed a pharmacokinetic study in support of the ARX-04 development program. In this study of healthy volunteers, it was shown that two sublingual administrations of a Zalviso sufentanil sublingual tablet, 15 mcg, dosed 20 minutes apart were comparable, in terms of AUC exposure and peak plasma concentration, to one sublingual administration of sufentanil sublingual tablet, 30 mcg.

Phase 2 Clinical Trial for ARX-04

In April 2013, we announced top-line results demonstrating that a placebo-controlled, dose-finding, Phase 2 trial of our investigational single-dose sufentanil sublingual tablet for acute pain, ARX-04, successfully met its primary endpoint. Results demonstrated that patients receiving ARX-04 administered by a healthcare professional, no more frequently than once per hour, had significantly greater pain reduction as measured by SPID-12 than placebo-treated patients (+6.53 for ARX-04-treated patients and -7.12 for placebo-treated patients; p=0.003). The sufentanil sublingual 20 mcg tablet-treated patients did not achieve SPID-12 scores that differentiated from placebo. Adverse events reported in the study were generally mild-to-moderate in nature, with two serious adverse events of post-surgical infection reported, both of which were determined by the investigator to be unrelated to study drug. This dose-ranging study randomized 101 patients following bunionectomy surgery in a 2:2:1 ratio to sufentanil sublingual tablet, 30 mcg, sufentanil sublingual tablet, 20 mcg, or placebo treatment arms. The intent-to-treat, or ITT, population in this study averaged 42.5 years of age and was evenly balanced for males and females (51%:49%). Ninety-one percent of patients entering the study completed the full 12-hour study period.

A number of secondary endpoints were also achieved, as follows:

For the time-weighted sum of pain relief scores over the 12-hour study period, or TOTPAR12, there was a statistically significant difference in favor of the 30 mcg group over placebo (9.73 vs. 4.37 p = 0.002). Patients treated with the 30 mcg dose of sufentanil sublingual tablet showed a rapid onset of action with a statistically significant beneficial difference in pain relief ($p<0.001$) and pain intensity ($p<0.01$) seen at 30 minutes after dosing compared to placebo. Dosing averaged every 2.4 hours over the duration of the 12-hour study. In addition, patient global assessment of the 30 mcg dose at 12 hours was superior to placebo (p=0.002) with 43.6% vs. 5.0% of the patients responding good or excellent for overall pain control. The 20 mcg dose was not significantly different from placebo for either endpoint.

Two SAEs, both in the 20 mcg-dose group, occurred one week after the study (surgical infections) and were deemed unrelated to study drug. All but two adverse events reported in the study were mild-to-moderate in nature with 58 patients (58%) reporting a total of 135 adverse events. The most frequently reported adverse events for all patients were nausea (30%), vomiting (17%), dizziness (14%) and somnolence (11%). Two patients discontinued treatment, one unrelated to study drug (anxiety/chest pain) and the other probably related to study drug (somnolence/respiratory depression), however both patients recovered without medical intervention.

Zalviso— Sufentanil Sublingual Tablet System

The Market Opportunity for Zalviso

We have not generated any revenue from the sale of any of our product candidates.

According to the 2014 Decision Resources Acute Pain Report, or 2014 DR Report, the acute pain market (represented by treatments for post-operative pain, acute musculoskeletal pain and cancer breakthrough pain) in the United States, Europe and Japan realized 2013 revenues of $12.7 billion, and is expected to reach approximately $13.3 billion by 2023. Opioid analgesic use remains a standard the management of acute pain, representing 44% of the 2013 market, and is projected to grow to 46% of the 2023 market. Post-operative acute pain treatment in the United States is projected to grow significantly in the 2013 to 2023 period, from management of 13.8 million procedures in 2011 to 16.0 million procedures in 2023, a 1.5% CAGR. Despite its size, this market remains underserved. Studies report that up to 75% of patients experience inadequate pain relief after surgery. Inadequate pain relief can lead to decreased mobility, which increases the risks of other medical complications, including deep vein thrombosis and partial lung collapse, and can result in extended hospital stays.

In the United States, we estimate that approximately one third of all procedures conducted are orthopedic in nature, one third are gastrointestinal, obstetric or gynecologic, and the remaining third are a mix of spinal, cardiothoracic and other procedures. Commissioned market research targeting surgeons and anesthesiologists has identified a consistent positive response to the attributes of Zalviso and indicates an interest in using Zalviso in at least 75% of their eligible patients. Additional market research indicated that physicians expressed interest in using Zalviso for patients who stay in the hospital for less than 24 hours and are not traditionally treated with IV PCA. Regardless of size or affiliation of hospitals, the majority of Pharmacy and Therapeutics, or P&T, committees we surveyed were likely to review and approve Zalviso, subject to demonstration of satisfactory pharmacoeconomic value.

How Zalviso Addresses the Unmet Medical Need in Moderate-To-Severe Acute Pain Management in a Hospital Setting

While IV PCA does allow patient control over their pain medication, it suffers from the following:

- side effects associated with the most commonly used opioid, morphine, and its active metabolites;
- infection risk, analgesic gaps and decreased mobility associated with the invasive nature of IV delivery; and
- medication errors, which in some instances may be fatal, due to the complexity of IV PCA pumps, many of which arise from programming errors.

Hospitalized patients in moderate-to-severe acute pain could significantly benefit from the following items:

- recognized onset of analgesia;
- reduction in medication errors, especially relating to the use of opioids, such as wrong drug or wrong drug concentration programmed into PCA pumps which are not possible with Zalviso;
- fewer side effects, including infection and bleeding risks due to invasive routes of delivery such as IV route of administration of opioids;
- enhanced ability for patients to ambulate after surgery and avoid falls; and
- patient control over their pain medication which has been shown to increase patient satisfaction.

For example, epidural catheters delivering local anesthetic are invasive and have a significant risk of lower extremity weakness and tethering the patient to a pump attached to an IV pole, creates multiple mobility impediments and fall risks; nerve blocks of the lower extremities (e.g., femoral nerve blocks) are also invasive and create weakness and fall risks; oral multimodal analgesia is not patient-controlled, is nurse-intensive and suffers from slow onset of action.

In our clinical studies, Zalviso has demonstrated the following attributes:

- a rapid onset of effect in comparison to intravenous delivery of morphine, and an ability to control pain as a monotherapy after moderately to severely painful surgeries such as knee replacement or colectomies;

- a rate of adverse events that is similar to a placebo-treated patient population, with the exception of opioid induced itching;

- a high level of Patient Satisfaction as a result of Zalviso usage under patient control to manage pain after surgery over 48 to 72 hours; and

- a high Nurse Ease of Care rating for ease of set-up and use of Zalviso by the health care professional.

According to published literature, an estimated 407 errors occur per 10,000 people treated with IV PCA each year in the United States. The most common and serious types of errors involve human factors, such as mis-programming the PCA pump or administering the wrong dose. In 2009, approximately 6.5% of errors associated with PCA pumps were due to operator error and that nearly half of these events (~19,000) lead to patient harm. Between 2005 and 2009, errors associated with infusion pumps led to 70 Class II recalls of devices that could cause temporary or reversible adverse effects and 14 Class I recalls of devices that could cause serious injury or death. These issues have resulted in the issuance of new draft guidance by the FDA, significantly increasing the data required to be submitted by manufacturers to address safety problems.

Zalviso has the potential to address many of the key disadvantages of IV PCA, including:

- eliminating the risk of IV PCA related infections, and enhancing mobility; and

- eliminating the risk of IV PCA programming errors.

We believe that Zalviso provides a favorable safety, efficacy and tolerability profile, potentially enabling Zalviso to become a new standard of care for moderate-to-severe acute pain control via patient-controlled analgesia.

Zalviso Description

The benefits of Zalviso are the result of combining the following three elements:

- sufentanil, a high therapeutic index opioid;

- sufentanil sublingual tablets, our proprietary, non-invasive sublingual dosage form; and

- our novel, pre-programmed, handheld PCA device that enables simple patient-controlled delivery of sufentanil sublingual tablets in the hospital setting and eliminates the risk of programming errors.

Zalviso allows patients to self-administer sufentanil sublingual tablets as needed to manage their moderate-to-severe acute pain in the hospital setting, and provides the record-keeping attributes of a conventional IV PCA pump while avoiding some of the key issues, such as programming errors, associated with conventional IV PCA use.

Zalviso utilizes sufentanil, which has one of the highest therapeutic indices of all commercially available opioids, making it an attractive candidate for the management of post-operative pain. Formulated in our proprietary sublingual tablet dosage form, sufentanil provides for relatively high bioavailability, with lower peak drug levels and a longer duration of action compared to IV delivery.

The Zalviso System consists of the following components: a disposable dispenser tip (Figure A); a disposable dispenser cap (Figure B); an adhesive thumb tag (Figure C); a cartridge of 40 sufentanil sublingual 15 mcg tablets (approximately a two-day supply) in a disposable radio frequency identification and bar-coded cartridge (Figure D); a reusable, rechargeable handheld controller (as pictured, nurse-side view) (Figure E); a tether (Figure F); and an authorized access card (Figure G).

This product candidate has not been approved by the FDA. We have not generated any revenue

from the sale of any of our product candidates.

Drugs are classified or scheduled by the Drug Enforcement Agency, or DEA, according to their potential for abuse and addiction. Sufentanil is scheduled as a class II opioid. Scheduled drugs, when they are under patient control in a hospital setting, must be secured and have adequate dose access control and tracking mechanisms. Our novel handheld PCA device has the following safety features:

- an authorized access card, which is a wireless system access key for the healthcare professional;
- a wireless, electronic, adhesive thumb tag that acts as a single-patient identification key;
- pre-programmed 20-minute lock-out to avoid overdosing;
- tablet singulation, or dispensing, motion that eliminates runaway motor delivery risk;
- a security tether that is designed to prevent theft and misuse; and
- fully automated inventory record of sufentanil sublingual tablet usage.

To set up Zalviso, the nurse or healthcare professional turns on the controller and follows the simple step-by-step instructions on the color graphical user interface screen described below:

- retrieve the sufentanil sublingual tablet cartridge from secure drug storage;
- insert the cartridge into the dispenser and lock the cartridge and dispenser into the controller; and
- set up the secure patient access system, which is comprised of a security tether and a wireless, electronic, adhesive thumb tag that acts as a single-patient identification key.

To use Zalviso, the patient would:

- confirm that the green indicator light is illuminated, meaning the device is available to dose;
- place dispenser tip under tongue and push the large button on the controller with the thumb to which the thumb tag has been applied, which in turn dispenses a single sufentanil sublingual tablet;

- remove the device from mouth upon hearing a tone confirming delivery of the sufentanil sublingual tablet; and

- see the blue indicator light illuminate, indicating no new dose can be dispensed for the next 20 minutes.

Zalviso—Development Status

We submitted an NDA for Zalviso in September 2013 and, as mentioned above, the FDA issued a CRL for Zalviso on July 25, 2014. Based on interaction with the FDA we have agreed to complete an additional study, known as IAP312, in post-operative patients. This Phase 3 study is designed to measure the performance of the Zalviso device and to measure any misplaced or dropped tablets. IAP312 is expected to begin in the first quarter of 2016.

The NDA resubmission for Zalviso will be based on a development program that includes data from seven Phase 1 studies, three Phase 2 clinical trials, and four Phase 3 clinical trials. The Phase 3 clinical trial program will have included two placebo-controlled efficacy and safety trials and one open-label active comparator trial, in which Zalviso was compared to IV PCA with morphine, and an additional open-label Phase 3 study in post-operative patients (IAP312), designed to measure the performance of the Zalviso device. To date, the Zalviso safety database includes more than 600 patients, and with the data from IAP312 included in the resubmission, will comprise over 900 total patients. Zalviso has successfully achieved the primary efficacy endpoints for each of the Phase 2 and Phase 3 trials performed to date.

Zalviso—Clinical Program

Summary

The Phase 3 program for Zalviso to date has consisted of three Phase 3 clinical trials. We have reported positive top-line results from each of these three clinical trials. Prior to our Phase 3 program, we completed three successful Phase 2 clinical trials of sufentanil sublingual tablets in the post-operative setting.

As mentioned above, in March 2015, we received correspondence from the FDA stating that an additional clinical study is needed. We have completed the protocol review with the FDA for IAP312 and we plan to initiate the study in the first quarter of 2016. IAP312 will be an open-label Phase 3 study conducted in post-operative patients. In the study, Zalviso will be used in patients requiring at least a one night hospital stay. IAP312 will allow for the utilization

of additional post-operative treatments for moderate-to-severe acute pain and will not be limited to orthopedic or abdominal surgeries. The study is powered to rule out a device failure rate of 5%. Unlike our other Phase 3 clinical studies, IAP312 will not include a primary endpoint of efficacy. Rather, we will collect pain scores, device performance data and any misplaced or dropped tablets. The results of the study, including the actual failure rate and the number of misplaced or dropped tablets, will be subject to final review by the FDA.

Phase 3 Clinical Trials for Zalviso

Active comparator trial (IAP309)

In November 2012, we reported top-line data showing that Zalviso had met its primary endpoint of non-inferiority in the Phase 3 open-label active comparator trial designed to compare the efficacy and safety of Zalviso (15 mcg/dose) to IV PCA with morphine (1mg/dose) for the treatment of moderate-to-severe acute post-operative pain. Utilizing a randomized, open-label, parallel group design, this trial enrolled 359 adult patients at 26 U.S. sites for the treatment of pain immediately following open-abdominal or major orthopedic surgery (hip and knee replacement). Patients were randomized 1:1 to treatment with Zalviso or IV PCA morphine and were treated for a minimum of 48 hours and up to 72 hours.

Double-blind, placebo-controlled, abdominal surgery trial (IAP310)

In March 2013, we reported top-line data results demonstrating that Zalviso met its primary endpoint in a pivotal Phase 3 trial designed to compare the efficacy and safety of Zalviso to placebo in the management of acute post-operative pain after major open abdominal surgery. Adverse events reported in the trial were generally mild or moderate in nature and similar in both placebo and treatment groups. Utilizing a randomized, double-blind, placebo-controlled design, this Phase 3 trial enrolled 178 adult patients at 13 U.S. sites. Patients were treated for post-operative pain for a minimum of 48 hours, and up to 72 hours. Patients were randomized 2:1, with 119 patients randomized to sufentanil sublingual tablet treatment and 59 to placebo treatment. Both treatments were delivered by the patient, as needed, using Zalviso with a 20-minute lock-out period. Patients in both groups could receive up to 2 mg morphine intravenously per hour as a rescue medication, the primary purpose of this rescue medication being to provide placebo-treated patients access to pain medication to enable them to stay in the trial as long as possible. Pre-rescue pain scores were imputed to minimize the impact of this rescue opioid on efficacy evaluations.

The primary endpoint evaluated pain intensity over the 48-hour study period compared to baseline, or Summed Pain Intensity Difference, or SPID-48, in patients following major open abdominal surgery. Patients receiving sufentanil sublingual tablets demonstrated a significantly greater SPID-48 compared to placebo-treated patients during the study period (105.6 and 55.6, respectively; p=0.001).

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Double-blind, placebo-controlled, orthopedic surgery trial (IAP311)

In May 2013, we reported top-line data results demonstrating that Zalviso met its primary endpoint in a pivotal Phase 3 trial designed to compare the efficacy and safety of Zalviso to placebo in the management of acute post-operative pain after major orthopedic surgery. Adverse events reported in the study were generally mild or moderate in nature and were similar in both placebo and treatment groups for the majority of adverse events. Utilizing a randomized, double-blind, placebo-controlled design, this pivotal Phase 3 study enrolled 426 adult patients at 34 U.S. sites for treatment of moderate-to-severe acute pain immediately following major orthopedic surgery. Seven patients did not receive study drug, resulting in 419 patients being included in the ITT population. Patients were treated for a minimum of 48 hours, and up to 72 hours. Patients were randomized 3:1, with 323 patients randomized to sufentanil sublingual tablet treatment and 104 to placebo treatment. Both treatments were delivered by the patient, as needed, using the Zalviso System with a 20-minute lock-out period. Patients in both groups could receive up to 2 mg morphine intravenously per hour as a rescue medication, the primary purpose of this rescue medication being to enable placebo-treated patients to stay in the study. Pain scores recorded just prior to the delivery of rescue medication were gathered and imputed forward to minimize the impact of this rescue opioid on efficacy evaluations.

The primary endpoint evaluated SPID-48 in patients following major orthopedic surgery. Patients receiving Zalviso demonstrated a significantly greater SPID-48 compared to placebo-treated patients during the study period (+76.1 and -11.5, respectively; $p < 0.001$). Two hundred fifteen (68.3%) sufentanil sublingual tablet-treated patients completed the 48-hour study period, compared to 43 (41.3%) placebo-treated patients. Primary reasons for drop-out in the sufentanil sublingual tablet- and placebo-treated groups were adverse events (7.0% and 6.7%, respectively) and lack of efficacy (14.3% and 48.1%, respectively).

Two patients (one each in the sufentanil sublingual tablet group and placebo group) experienced a serious adverse event considered possibly or probably related to the study drug by the investigator.

Combined related adverse events for the two placebo-controlled pivotal studies (IAP310 and IAP311) compared to placebo are shown below. Only pruritus (itching) was statistically different for Zalviso compared to placebo ($p = 0.002$).

Adverse Reactions Occurring in ≥ 2% in Either Group

Possibly or Probably Related Adverse Reactions	**Zalviso n=429**	**Placebo n=162**
At least 2% in either group	**Two Placebo-Controlled**	

	Phase 3 Studies	
Nausea	29.4%	22.2%
Vomiting	8.9%	4.9%
Oxygen Saturation Decreased*	6.1%	2.5%
Pruritus	4.7%	0%
Dizziness	4.4%	1.2%
Constipation	3.7%	0.6%
Headache	3.3%	3.7%
Insomnia	3.3%	1.9%
Hypotension	3.0%	1.2%
Confusional state	2.1%	0.6%

*3 patients (0.7%) in the Zalviso group had treatment-emergent respiratory events that required naloxone reversal.

ARX-03—Sufentanil/Triazolam Sublingual Tablet

The Market Opportunity for ARX-03

Each year in the United States, more than 100 million procedures take place in a physician's office that are known to be anxiety-inducing and painful, according to commissioned market research data that was completed in 2010. These include diagnostic procedures such as breast and prostate biopsies, cosmetic procedures such as liposuction and dermal abrasions, interventional radiology procedures, and therapeutic procedures such as vasectomies and endometrial ablation procedures. IV sedative medications are typically not offered to these patients because of the high cost of the specialized personnel and monitoring equipment. Despite the high potential for pain and anxiety, most patients currently undergo these procedures with only a local anesthetic, resulting in unnecessary discomfort during the procedure. We believe there is significant opportunity for a fast-acting, effective and safe product that can provide mild levels of sedation, anxiety reduction and analgesia for painful procedures conducted in a physician's office without the need for specialized personnel to monitor the patient.

ARX-03 Description

ARX-03 sufentanil/triazolam sublingual tablet is a single, fixed-dose sublingual product candidate designed to be administered by a healthcare professional prior to a painful procedure in a physician's office. An important attribute of sufentanil and triazolam compared to current therapies is the rapid uptake from the sublingual mucosa. Our Phase 2 clinical data showed that administering ARX-03 via sublingual route prior to a procedure results in a rapid onset of mild sedation and reduction in anxiety in 15 to 30 minutes. Sufentanil and triazolam have short half-lives compared to many other agents in the same class of compounds, enabling patients treated with ARX-03 to be discharged immediately following completion of the procedure. The sublingual route of administration avoids the high plasma concentrations associated with IV delivery, thereby obviating the need for specialized personnel and extensive monitoring.

ARX-03 Clinical Program Overview

We have completed a successful Phase 2 clinical trial of ARX-03 demonstrating rapid onset of mild sedation and anxiety reduction, with a low adverse event profile during an abdominal liposuction procedure. In addition, we participated in an End of Phase 2 meeting with the FDA in May 2010 to discuss the Phase 3 clinical program and requirements for an NDA submission. Based on these discussions, two four-arm factorial Phase 3 clinical trials will be required with a minimum of 700 patients exposed to active drug.

Further development of the ARX-03 program is contingent on identification of corporate partnership resources. Currently we have no plans to advance the development of ARX-03.

Our Strategy

Our strategy is to develop and commercialize our sufentanil sublingual tablet-based products in the United States. We have designed and are developing product candidates that meet clearly defined unmet medical needs, have clearly defined clinical development programs, target large commercial market opportunities and require modestly-sized commercial organizations in the United States. We selectively utilize third-party contractors in order to maximize the capital efficiency of our development and commercialization efforts. We plan to enter into partnerships to market our product candidates outside the United States. In December 2013, we announced a commercial collaboration with Grünenthal, covering the territory of the European Union, certain other European countries and Australia for Zalviso for potential use in pain treatment within or dispensed by a hospital, hospice, nursing home or other medically supervised setting. We retain all rights in remaining countries, including the United States. We continue to seek partnerships to market Zalviso in markets outside of the Grünenthal territory and the United States.

ARX-04

ARX-04 is a non-invasive investigational product candidate consisting of a single sufentanil sublingual tablet, 30 mcg, delivered via a disposable, pre-filled, single-dose applicator, or SDA. We are developing ARX-04 for the treatment of moderate-to-severe acute pain to be administered by a healthcare professional to a patient in medically supervised settings of acute pain. If approved, examples of potential patient populations and settings in which ARX-04 could be used include: emergency room patients; patients who are recovering from short-stay or ambulatory surgery and do not require more long-term patient-controlled analgesia; post-operative patients who are transitioning from the operating room to the recovery floor; patients being treated and transported by paramedics; and for battlefield casualties. We plan to complete our Phase 3 development program for ARX-04 by the third quarter of 2016, and, pending successful completion, we anticipate submitting the NDA to the FDA for ARX-04 in the fourth quarter of 2016.

Our specific strategy with respect to ARX-04 is to:

- complete our Phase 3 clinical program and seek regulatory approval in the United States and in the EEA;
- further expand our relationship with our existing contract manufacturing organizations, or CMOs, for the manufacture and packaging of ARX-04;
- build a targeted sales force focused on the emergency room and corporate-owned ambulatory surgery centers in the United States;
- on our own, or with a partner, supply the DoD and other military organizations as requested and appropriate; and
- seek commercial partnerships for ARX-04 in countries outside of the United States.

Zalviso

We are seeking FDA approval for the use of Zalviso to treat moderate-to-severe acute pain in the hospital setting. We submitted an NDA for Zalviso in September 2013 and, as mentioned above, the FDA issued a CRL for Zalviso on July 25, 2014. Based on interaction with the FDA we have agreed to conduct the IAP312 study in post-operative patients. We anticipate the initiation of the IAP312 study in the first quarter of 2016. Pending successful completion of IAP312, we plan to resubmit the NDA for Zalviso by the end of 2016.

Our specific strategy with respect to Zalviso is to:

- collaborate with Grünenthal to support the launch of Zalviso in their licensed territories;
- strengthen our commercial relationships for the manufacturing of the components and assembly of the Zalviso System;
- seek regulatory approval in the United States;
- build a targeted hospital-directed sales force in the United States; and

- seek commercial partnerships for Zalviso in other unlicensed countries outside of the United States.

Sales and Marketing

We anticipate developing a distribution capability and commercial organization in the United States to market and sell our product candidates alone or with partners, while out-licensing commercialization rights outside of the United States. In executing our strategy, our goal is to have significant control over the development process and commercial execution for our product candidates, while retaining meaningful economics.

We plan to progressively build commercial capability to support introduction of ARX-04 and Zalviso to the United States market as we move toward potential NDA approval. We foresee two stages of commercial execution to support successful introduction of ARX-04 and Zalviso in the United States:

Prior to FDA approval of ARX-04 and Zalviso, we plan to:

- create and deploy a focused scientific support team to gather a detailed understanding of individual emergency room, ambulatory surgery center and hospital needs in order to be prepared to present ARX-04 and Zalviso effectively at the time of commercial launch;

- increase awareness of the clinical profile of sublingual administration of sufentanil through publication of our clinical data;

- establish advisory boards with emergency room physicians, anesthesiologists, surgeons, nurses and P&T committees to provide us with input on appropriate commercial positioning for ARX-04 and Zalviso for each of these key audiences;

- build a sales and marketing organization that can define appropriate segmentation and positioning strategies and tactics for ARX-04 and Zalviso; and

- present the clinical and health economic data identifying the limitations of IV PCA and other relevant treatments for moderate-to-severe acute pain in use today.

Assuming FDA approval, we plan to:

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establish ARX-04 and Zalviso on formularies through deployment of an experienced team to explain the clinical and economic attributes of ARX-04 and Zalviso;

- create and progressively deploy a high-quality, customer-focused and experienced sales organization dedicated to bringing innovative, highly-valued healthcare solutions to patients, payors and healthcare providers, including progressively building a targeted sales force of approximately 65 people in the United States;

- conduct post-approval clinical trials for ARX-04 and Zalviso;

- undertake efforts to establish ARX-04 and Zalviso as the products of choice for moderate-to-severe acute pain; and

- expand the market through deployment of ARX-04 in medically-supervised settings outside of the hospital and ambulatory surgery centers and, for Zalviso, for 24-hour stay patients and other in-hospital moderate-to-severe acute pain conditions.

Collaborative Arrangements

Grünenthal Collaboration

On December 16, 2013, we and Grünenthal entered into a Collaboration and License Agreement, or the License Agreement, and related Manufacture and Supply Agreement, or the MSA, and together with the License Agreement, the Agreements. The License Agreement grants Grünenthal rights to commercialize Zalviso, or the Product, in the Territory for human use in pain treatment within or dispensed by hospitals, hospices, nursing homes and other medically-supervised settings, or the Field. The Company retains rights with respect to the Product in countries outside the Territory, including the United States, Asia and Latin America. Under the MSA, we will exclusively manufacture and supply the Product to Grünenthal for the Field in the Territory. On July 22, 2015, we entered into amendments to the License Agreement, or the License Amendment, and together with the License Agreement, the Amended License Agreement, and the MSA, or the MSA Amendment, and together with the MSA, the Amended MSA, between AcelRx and Grünenthal, each effective as of July 17, 2015, and together, the Amended Agreements.

In the Amended Agreements, the parties amended the Product supply configurations and packaging of Product components and accessories, and associated pricing therefor, which we will manufacture and supply to Grünenthal for the Territory. The parties agreed to increase the pricing of the Product components and accessories, while reducing the total milestone payments due from Grünenthal contingent upon achieving specified net sales targets from a total of $171.5 million to $166.0 million. As a result of the Royalty Monetization, PDL will receive 75% of the European royalties under the Amended License Agreement with Grünenthal, as well as 80% of the first four commercial milestones worth $35.6 million (or 80% of $44.5 million), subject to the capped amount of $195.0 million. The parties also updated the development plan for the Product in the Territory, providing for additional near-term development services to be rendered by AcelRx in exchange for payments of approximately $0.7 million, primarily in 2015. Simultaneously, we also received a binding Product forecast from Grünenthal for approximately $3.7 million.

Under the terms of the Amended Agreements with Grünenthal, we received an upfront cash payment of $30.0 million in December 2013, and in the third quarter of 2014, we received a milestone payment of $5.0 million related to the MAA submission to EMA and an additional milestone payment of $15.0 million related to the EC approval of the MAA for Zalviso in the third quarter of 2015. Under the Amended License Agreement, we are eligible to receive approximately $194.5 million in additional milestone payments, based upon successful regulatory and product development efforts ($28.5 million) and net sales target achievements ($166.0 million). Grünenthal will also make tiered royalty, supply and trademark fee payments in the mid-teens up to the mid-twenties percent range, depending on the sales level achieved, on net sales of Zalviso in the Territory. A portion of the tiered royalty payment, exclusive of the supply and trademark fee payments, will be paid to PDL in connection with the Royalty Monetization. For additional information on the Royalty Monetization with PDL, see Note 8 “Liability Related to Sale of Future Royalties” in the accompanying notes to the Consolidated Financial Statements.

Grünenthal will be responsible for all commercial activities for Zalviso, including obtaining and maintaining pharmaceutical product regulatory approval in the Territory. We will be responsible for obtaining and maintaining device regulatory approval in the Territory and manufacturing and supply of Zalviso to Grünenthal for commercial sales.

Intellectual Property

We seek patent protection in the United States and internationally for our product candidates. Our policy is to pursue, maintain and defend patent rights developed internally and to protect the technology, inventions and improvements that are commercially important to the development of our business. We cannot be sure that patents will be granted with respect to any of our pending patent applications or with respect to any patent applications filed by us in the future, nor can we be sure that any of our existing patents or any patents granted to us in the future will be commercially useful in protecting our technology. We also rely on trade secrets to protect our product candidates. Our commercial success also depends in part on our non-infringement of the patents or proprietary rights of third parties. For a more comprehensive discussion of the risks related to our intellectual property, please see “Risk Factors—Risks Related to Our Intellectual Property” appearing elsewhere in this Form 10-K.

Our success will depend significantly on our ability to:

- obtain and maintain patent and other proprietary protection for our product candidates;
- defend our patents;
- preserve the confidentiality of our trade secrets; and
- operate our business without infringing the patents and proprietary rights of third parties.

We have established and continue to build proprietary positions for our product candidates and related technology in the United States and abroad.

As of December 31, 2015, we are the owner of record of 17 issued U.S. patents, which provide coverage for sufentanil sublingual tablets, the device components of Zalviso and the ARX-04 SDA. These patents provide coverage through at least 2027. We also hold four issued European patents, each valid in at least six countries in Europe. In addition, we own five patents in Japan, four in China and six in Korea, and a number of other international patents which provide coverage through at least 2027. We are also pursuing a number of U.S. and foreign patent applications. The patent applications that we have filed and have not yet been granted may fail to result in issued patents in the United States or in foreign countries. Even if the patents do successfully issue, third parties may challenge the patents.

We continue to seek and expand our patent protection for both compositions of matter and delivery devices, as well as methods of treatment related to our product candidates. In particular, we are pursuing additional patent protection for our Zalviso and ARX-04 and formulations, our Zalviso device, the combination of drugs and our Zalviso device, our ARX-04 SDA, as well as to methods of treatment using such drug and device compositions.

We have filed for additional patent coverage in the United States, Europe as well as many other foreign jurisdictions including, Japan, China, India, Canada and Korea. If issued, and if the appropriate maintenance, renewal, annuity or other governmental fees are paid, we expect that these patents will expire between 2027 and 2030, excluding any additional term for patent term adjustments or patent term extensions in the United States. We note that the patent laws of foreign countries differ from those in United States, and the degree of protection afforded by foreign patents may be different from the protection offered by U.S. patents.

Further, we seek trademark protection in the United States and internationally where available and when appropriate. We have registered our ACELRX mark in Class 5, “Pharmaceutical preparations for treating pain; pharmaceutical preparations for treating anxiety,” and Class 10, “Drug delivery systems; medical device, namely, a mechanical and electronic device used to administer medications, perform timed medication delivery, and to provide secure access to and delivery of medications,” in the United States.

Our ACELRX mark is also registered in the European Community, Canada, and India. We have also registered the mark ACCELERATE. INNOVATE. ALLEVIATE. in the United States.

Competition

Our industry is highly competitive and subject to rapid and significant technological change. Our potential competitors include large pharmaceutical and biotechnology companies, specialty pharmaceutical and generic drug companies, and medical technology companies. We believe the key competitive factors that will affect the development and commercial success of our product candidates are the safety, efficacy and tolerability profile, the patient and healthcare professional satisfaction with using our product candidates in relation to available alternatives and the reliability, convenience of dosing, price and reimbursement of our product candidates.

Many of our potential competitors, including many of the organizations named below, have substantially greater financial, technical and human resources than we do and significantly greater experience in the development of product candidates, obtaining FDA and other regulatory approvals of products and the commercialization of those products. Accordingly, our competitors may be more successful than we may be in obtaining FDA approval for drugs and achieving widespread market acceptance. Our competitors’ drugs may be more effective, or may be more effectively marketed and sold, than any drug we may commercialize, which may render our product candidates obsolete or non-competitive before we can recover our losses. We anticipate that we will face intense and increasing competition as new drugs enter the market and advanced technologies become available.

Potential Competition for ARX-04

Within the civilian environment, there are a wide variety of approved injectable and oral opioid products to treat moderate-to-severe acute pain, including IV opioids such as morphine, fentanyl, hydromorphone and meperidine or oral opioids such as oxycodone and hydrocodone. More specifically, competitors for ARX-04 in the emergency department are likely to include generic injectable intravenous opioids such as morphine, hydromorphone and fentanyl. In this environment, ARX-04 may also compete with other branded non-invasive products or product candidates, such as Egalet Corporation's SPRIX, Hospira Inc.'s DYLOJECT (Hospira, Inc. acquired by Pfizer, Inc. in September 2015), Acura Pharmaceuticals, Inc.'s OXAYDO, Depomed, Inc.'s NUCYNTA, Bristol-Myers Squibb Company's COMBUNOX, Purdue Pharma, L.P.'s OXYFAST, Endo Pharmaceuticals, Inc.'s OPANA, Medical Developments International Limited's PENTHROX (methoxyflurane) inhaler, CL-108, a bi-layered tablet, in development by Charleston Laboratories Inc., in collaboration with Daiichi Sankyo, or generic oral opioids which have moderate-to-severe acute pain labeling. In the short-stay or ambulatory surgery segment, ARX-04 will likely compete with these products in addition to generic injectable local anesthetics such as bupivacaine, or branded formulations thereof, including Pacira Pharmaceuticals, Inc.'s EXPAREL. Within the military environment, and in certain civilian settings, ARX-04 competitors may also include intramuscular morphine injections that are marketed by a variety of generic manufacturers.

Potential Competition for Zalviso

We are developing Zalviso for the management of moderate-to-severe acute pain in adult patients during hospitalization. We believe that Zalviso would compete with a number of opioid-based and non-opioid based treatment options that are currently available, as well as some products that are in development. These products can be grouped into three classes – PCA-based systems, most commonly using an opioid as the pain control agent; non PCA-based systems that require nurse delivery of oral or parenteral opioids; and other non-opioid based treatment modalities. Due to the difficulty of managing moderate-to-severe acute pain, healthcare professionals will often use a combination of PCA opioids, parenteral or oral opioids and non-opioid based treatments to manage pain.

The primary competition for Zalviso is the IV PCA pump, which is widely used in the moderate-to-severe acute pain in the hospital setting. Leading manufacturers of IV PCA pumps include Hospira, Inc. (acquired by Pfizer, Inc.), CareFusion Corporation (purchased by Becton, Dickinson and Company), Baxter International, Inc., Curlin Medical, Inc. and Smiths Medical. The most common opioids used to treat moderate-to-severe acute pain are morphine, hydromorphone and fentanyl, all of which are available as generics both from generic product manufacturers as well as from compounding pharmacies. In addition, branded manufacturers (e.g., Hospira, Inc.) sell pre-filled glass syringes of morphine to fit their IV PCA pump systems.

Also available on the market is the Avancen Medication on Demand, or MOD, Oral PCA Device developed by Avancen MOD Corporation. Oral opioids and other agents can be used in this system. In addition, oral and parenteral

opioids administered by the nurse are used to manage moderate-to-severe acute pain in the hospital, available both as branded and generic products. These oral opioids, as well as IV PCA opioids, are often used as part of a multi-modal analgesia approach, which might include, in addition to the opioid, NSAIDs, acetaminophen, gabapentanoids and other pain management modalities, as well as local anesthetic blocks to provide temporary blockage of the pain signal, either as a wound infiltration agent or as a nerve block. These local anesthetic agents such as bupivacaine can also utilize controlled-release formulations such as Pacira Pharmaceuticals, Inc.'s EXPAREL. In addition, Halyard Health, Inc. has developed a medical device, the ON-Q* Pain Relief System, which is a non-narcotic elastomeric pump that automatically and continuously delivers a regulated flow of local anesthetic to a patient's surgical site or in close proximity to nerves, providing targeted pain relief for up to five days.

Additional potential competitors for Zalviso include the fentanyl iontophoretic transdermal system, IONSYS, originally developed by Alza Corporation and Ortho-McNeil Pharmaceutical, Inc., both Johnson & Johnson subsidiaries, and most recently by The Medicines Company. On April 30, 2015, IONSYS was approved for marketing in the U.S. by the FDA, providing a potential first-to-market advantage for IONSYS. Cara Therapeutics, Inc. is developing a kappa opioid agonist, CR845, as an IV agent for the management of post-operative moderate-to-severe pain. Trevena, Inc. is developing TRV130, an intravenous G protein biased ligand that targets the mu opioid receptor for the treatment of moderate-to-severe acute pain where intravenous therapy is preferred, with a clinical development focus in acute post-operative pain. Trevena, Inc. expects to initiate Phase 3 development of TRV130 in the first quarter of 2016. Recro Pharma, Inc. is developing an intranasal form of dexmedetomidine as a potential agent for the management of post-operative pain, for which it announced positive efficacy results in its Phase II clinical trial. Finally, Innocoll AG is developing XARACOLL a controlled-release resorbable implant containing bupivacaine, and Durect Corporation has been developing POSIDUR, a controlled-release bupivacaine product candidate utilizing Durect Corporation's Saber technology.

Potential Competition for ARX-03

We are developing ARX-03, the sufentanil/triazolam sublingual tablet, for use in diagnostic or therapeutic painful procedures of short duration in a physician's office. For these procedures, many practitioners rely primarily on local anesthetics injected to the procedural area to reduce the pain of the procedure, and do not use IV sedatives to manage the anxiety of patients because of the cost of having additional trained staff to monitor the patients. Currently, we are not aware of any products on the market that combine an opioid with a benzodiazepine in a single dosage form to manage the anxiety and pain of procedures in a physician's office. However, an anonymous third party filed an Opposition on October 7, 2015 against European patent EP2182902B1, which claims a dosage form related to ARX-03. Although the Opposition is currently pending, the European Patent Office has neither reviewed nor made any initial comments regarding the validity of the EP2182902B1 patent. We are not aware of any approved or development stage non-IV sedative/analgesic products that would present competition to ARX-03. In the future, there may be products developed or approved for this market that could directly compete with ARX-03.

Pharmaceutical Manufacturing and Supply

We currently rely on contract manufacturers to produce sufentanil sublingual tablets for commercial product and for our clinical trials under current Good Manufacturing Practices, or cGMP, with oversight by our internal managers. Equipment specific to the pharmaceutical manufacturing process was purchased and customized for us and is currently owned by us. We plan to continue to rely on contract manufacturers and, potentially, collaboration partners to manufacture commercial quantities of our product candidates if and when approved for marketing by the FDA. We currently rely on a single manufacturer for the preclinical and clinical supplies of our drug product for each of our product candidates and do not currently have agreements in place for redundant supply or a second source for any of our product candidates. We have identified other manufacturers that could satisfy our commercial supply and packaging requirements and we continue to evaluate those manufacturers.

In January 2013, we entered into a Manufacturing Services Agreement, or the Services Agreement, with Patheon Pharmaceuticals, Inc., or Patheon, relating to the manufacture of sufentanil sublingual tablets for use with the Zalviso device. Under the terms of the Services Agreement, Patheon has agreed to manufacture, supply, and provide certain validation and stability services with respect to Zalviso for sale in the United States, Canada, Mexico and other countries, subject to agreement by the parties to any additional fees for such other countries. The term of the Services Agreement extends until December 31, 2017, or the Initial Term, and will automatically renew thereafter for periods of two years, unless terminated by either party upon eighteen months' prior written notice; provided, however, that the Services Agreement may not be terminated without cause prior to the end of the Initial Term. In addition, we entered into a related Amended and Restated Capital Expenditure and Equipment Agreement, or the Amended Capital Agreement, related to clinical and commercial production of our product candidates. Under the terms of the Amended Capital Agreement, we have made, and may make certain future modifications to Patheon's Cincinnati facility.

Device Manufacturing and Supply

The device components of Zalviso are manufactured by contract manufacturers, component fabricators and secondary service providers. Suppliers of components, subassemblies and other materials are located in Korea, Japan, Germany, China, Taiwan, Canada and the United States. All contract manufacturers and component suppliers have been selected for their specific competencies in the manufacturing processes and materials that make up Zalviso. FDA regulations require that materials be produced under cGMPs or Quality System Regulation, or QSR. We outsource injection molding of all the plastic parts for the cartridge and device and product sub-assemblies; tablet cartridge filling and packaging; and assembly, packaging and labeling of the dispenser and controller.

ARX-04 utilizes an SDA in the delivery of the tablets. FDA regulations require that materials be produced under cGMPs or QSR, as required for the respective unit operation within the manufacturing process. We outsource injection molding of all the plastic parts for the SDA, and product sub-assemblies; and filling, packaging and labeling of SDAs.

Government Regulation

Government authorities in the United States at the federal, state and local level, and in other countries, extensively regulate, among other things, the research, development, testing, manufacture, quality control, approval, labeling, packaging, storage, record-keeping, promotion, advertising, distribution, marketing, export and import of products such as those we are developing. Our product candidates must be approved by the FDA through the NDA process before they may legally be marketed in the United States.

In the United States, the FDA regulates drugs under the Federal Food, Drug, and Cosmetic Act, or FDCA, and its implementing regulations. The process of obtaining regulatory approvals and complying with applicable laws and regulations requires the expenditure of substantial time and financial resources. Failure to comply at any time during the product development and approval process, or after approval, may subject an applicant to administrative or judicial sanctions. These sanctions could include the FDA's refusal to approve pending applications, withdrawal of an approval, a clinical hold, warning letters, product recalls, product seizures, total or partial suspension of production or distribution, injunctions, fines, refusals of government contracts, restitution, disgorgement or civil or criminal penalties. The process required by the FDA before a drug product may be marketed in the United States generally involves the following:

- completion of non-clinical laboratory tests, animal trials and formulation studies according to Good Laboratory Practices regulations;
- submission to the FDA of an investigational new drug, or IND, application which must become effective before human clinical trials may begin;
- performance of adequate and well-controlled human clinical trials according to Good Clinical Practices, or GCP, to establish the clinical safety and efficacy of the proposed drug product for its intended use;
- submission to the FDA of an NDA for a new drug product;
- satisfactory completion of an FDA inspection of the manufacturing facility or facilities at which the drug product and the drug substance(s) are produced to assess compliance with cGMP;
- payment of application, user and facility fees; and
- FDA review and approval of the NDA.

The testing and approval process requires substantial time, effort and financial resources and we cannot be certain that any approvals for our product candidates will be granted on a timely basis, if at all.

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

- *Phase 1.* The product is initially introduced into healthy human subjects and tested for safety, dosage tolerance, absorption, metabolism, distribution and excretion. In the case of some products for severe or life-threatening diseases, especially when the product may be too inherently toxic to ethically administer to healthy volunteers, the initial human testing is often conducted in patients.

- *Phase 2.* Involves trials in a limited patient population to identify possible adverse effects and safety risks, to preliminarily evaluate the efficacy of the product for specific targeted conditions and to determine dosage tolerance and optimal dosage and schedule.

- *Phase 3.* Clinical trials are undertaken to further evaluate dosage, clinical safety and efficacy in an expanded patient population at geographically dispersed clinical trial sites. These trials are intended to establish the overall risk/benefit ratio of the product and provide an adequate basis for product labeling.

Progress reports detailing the results of the clinical trials must be submitted at least annually to the FDA and safety reports must be submitted to the FDA and the investigators for serious and unexpected adverse events. The FDA or the sponsor may suspend or terminate a clinical trial at any time on various grounds, including a finding that the research subjects or patients are being exposed to an unacceptable health risk. Similarly, an institutional review board, or IRB, can suspend or terminate approval of a clinical trial at its institution if the clinical trial is not being conducted in accordance with the IRB's requirements or if the drug or biological product has been associated with unexpected serious harm to patients.

Concurrent with clinical trials, companies usually complete additional animal trials and must also develop additional information about the chemistry and physical characteristics of the product and finalize a process for manufacturing the product in commercial quantities in accordance with cGMP and QSR for medical device requirements. The manufacturing process must be capable of consistently producing quality batches of the product candidate and, among other things, the manufacturer must develop methods for testing the identity, strength, quality and purity of the final product. Additionally, appropriate packaging must be selected and tested and stability studies must be conducted to demonstrate that the product candidate does not undergo unacceptable deterioration over its shelf life.

Our product candidates, Zalviso, ARX-04 and others, are regulated under IND applications for clinical development and in the case of Zalviso, all device related information is filed under the Chemistry, Manufacturing and Controls Section, or CMC, of an IND.

The results of product development, preclinical trials and clinical trials, along with descriptions of the manufacturing process, analytical tests conducted on our drug products, proposed labeling and other relevant information, will be submitted to the FDA as part of an NDA for a new drug product, requesting approval to market the product in the United States. The submission of an NDA is subject to the payment of a substantial user fee; a waiver of such fee may be obtained under certain limited circumstances. During its review of an NDA, FDA may inspect our manufacturers for GMP and QSR compliance, and our pivotal clinical trial sites for GCP compliance.

In addition, under the Pediatric Research Equity Act, an NDA or supplement to an NDA must contain data to assess the safety and effectiveness of the drug product for the claimed indications in all relevant pediatric subpopulations and to support dosing and administration for each pediatric subpopulation for which the product is safe and effective. The FDA may grant deferrals for submission of data or full or partial waivers.

The approval process is lengthy and difficult and the FDA may refuse to approve an NDA if the applicable regulatory criteria are not satisfied or may require additional clinical data or other data and information. Even if such data and information is submitted, the FDA may ultimately decide that the NDA does not satisfy the criteria for approval. Data obtained from clinical trials are not always conclusive and the FDA may interpret data differently than we interpret the same data. The FDA issues a Complete Response Letter at the conclusion of its review if the NDA is not yet deemed ready for approval. A Complete Response Letter generally outlines the deficiencies in the submission and may require substantial additional testing or information for the FDA to reconsider the application. If, or when, those deficiencies have been addressed to the FDA's satisfaction in a resubmission of the NDA, the FDA will issue an approval letter. The FDA has committed to reviewing such resubmissions in two or six months depending on the type of information included.

If one or more of our product candidates receive regulatory approval, the approval may be limited to specific conditions and dosages or the indications for use may otherwise be limited, which could restrict the commercial value of the product. Our product candidates, if approved, will also require Risk Evaluations and Mitigation Strategies, or REMS, which can include a medication guide, patient package insert, a communication plan, elements to assure safe use and implementation system, and must include a timetable for assessment of the REMS. Further, the FDA may require that certain contraindications, warnings or precautions be included in the product labeling and may require testing and surveillance programs to monitor the safety of approved products that have been commercialized. In addition, the FDA may require post-approval testing which involves clinical trials designed to further assess a drug product's safety and effectiveness after the NDA.

Post-Approval Requirements

Any drug products for which we receive FDA approvals are subject to continuing regulation by the FDA, including, among other things, record-keeping requirements, reporting of adverse experiences with the product, providing the FDA with updated clinical safety and efficacy information, product sampling and distribution requirements, complying with certain electronic records and signature requirements and complying with FDA promotion and advertising requirements. Phase 4 clinical trials are conducted after approval to gain additional experience from the treatment of patients in the intended therapeutic indication or when otherwise requested by the FDA in the form of postmarketing requirements or commitments. Failure to promptly conduct any required Phase 4 clinical trials could result in withdrawal of NDA approval. The FDA strictly regulates labeling, advertising, promotion and other types of information on products that are placed on the market. Drug products may be promoted only for the approved indications and in accordance with the provisions of the approved label. Further, manufacturers of drug products must continue to comply with cGMP requirements, which are extensive and require considerable time, resources and ongoing investment to ensure compliance. In addition, changes to the manufacturing process generally require prior FDA approval before being implemented and other types of changes to the approved product, such as adding new indications and additional labeling claims, are also subject to further FDA review and approval.

Drug product manufacturers and other entities involved in the manufacturing and distribution of approved drug products are required to register their establishments with the FDA and certain state agencies, and are subject to periodic unannounced inspections by the FDA and certain state agencies for compliance with cGMP and other laws. The cGMP requirements apply to all stages of the manufacturing process, including the production, processing, packaging, labeling, storage and shipment of the drug product. Manufacturers must establish validated systems to ensure that products meet specifications and regulatory standards, and test each product batch or lot prior to its release. In the case of Zalviso, the device component must comply with FDA’s Quality Systems Regulation.

We rely, and expect to continue to rely, on third parties for the production of clinical and commercial quantities of our products. Future FDA and state inspections may identify compliance issues at the facilities of our contract manufacturers that may disrupt production or distribution or may require substantial resources to correct.

The FDA may withdraw a product approval if compliance with regulatory standards is not maintained or if problems occur after the product reaches the market. Later discovery of previously unknown problems with a product may result in restrictions on the product or even complete withdrawal of the product from the market. Further, the failure to maintain compliance with regulatory requirements may result in administrative or judicial actions, such as fines, warning letters, holds on clinical trials, product recalls or seizures, product detention or refusal to permit the import or export of products, refusal to approve pending applications or supplements, restrictions on marketing or manufacturing, injunctions or civil or criminal penalties.

Foreign Regulation

In addition to regulations in the United States, we will be subject to a variety of foreign regulations governing clinical trials and commercial sales and distribution of our products to the extent we choose to sell any products outside of the United States.

In December 2015, the Committee for Medicinal Products for Human Use, or CHMP, at the European Medicines Agency, or EMA, confirmed that an MAA for ARX-04 may be submitted in the EU under the EMA's centralized procedure. This regulatory procedure, reserved for novel products, biotechnology products and new chemical entities, allows for commercialization across 31 EU and EFTA countries based on approval by EMA.

We are responsible for maintaining Zalviso device regulatory approval in the EU in order to support the manufacturing and supply of Zalviso to Grünenthal for commercial sales. We completed the Conformite Europeenne approval process for the Zalviso device, more commonly known as a CE Mark approval. We received CE Mark approval in December 2014, which permits the commercial sale of the Zalviso device in the European Union. In connection with the CE Mark approval, we were also granted International Standards Organization, or ISO, 13485:2003 certification of our quality management system. This is an internationally recognized quality standard for medical devices. Certification of our quality management system was issued by the British Standards Institution, or BSI, a Notified Body. ISO 13485:2003 certification recognizes that consistent quality policies and procedures are in place for the development, design and manufacturing of medical devices. The certification indicates that we have successfully implemented a quality system that conforms to ISO 13485 standards for medical devices. Certification to this standard is one of the key regulatory requirements for a CE Mark in the EU and EEA, as well as to meet equivalent requirements in other international markets. The certification applies to the Redwood City, California location which designs, manufactures and distributes finished medical devices, and includes critical suppliers. In November 2015, we underwent a successful surveillance audit by the Notified Body for the Zalviso CE mark and for our status as an ISO 13485 certified device manufacturer.

Controlled Substances Regulations

Sufentanil, a Schedule II controlled substance, is the active pharmaceutical ingredient in Zalviso and ARX-04. Controlled substances are governed by the Drug Enforcement Administration, or DEA, of the U.S. Department of Justice. The handling of controlled substances and/or drug product by us, our contract manufacturers, analytical laboratories, packagers and distributors, are regulated by the Controlled Substances Act and regulations thereunder.

As sufentanil is a controlled substance, until Zalviso is approved in the U.S., we are limited as to the countries we can export sufentanil cartridges to Europe, Japan, Australia, Israel, Switzerland, Canada and South Africa. Grünenthal has the commercial rights to the European Union and Australia. As a result, we do not anticipate additional collaborations for Zalviso outside of the Grünenthal territories until Zalviso is approved in the U.S.

The Drug Supply Chain Security Act imposes obligations on manufacturers of pharmaceutical products, among others, related to product tracking and tracing. Among the requirements are that manufacturers will be required to provide certain information regarding the drug product to individuals and entities to which product ownership is transferred, label drug product with a product identifier, and keep certain records regarding the drug product. Further, manufacturers will have drug product investigation, quarantine, disposition, and notification responsibilities related to counterfeit, diverted, stolen, and intentionally adulterated products, as well as products that are the subject of fraudulent transactions or which are otherwise unfit for distribution such that they would be reasonably likely to result in serious health consequences or death.

Unforeseen delays to the drug substance and drug product manufacture and supply chain may occur due to delays, errors or other unforeseen problems with the permitting and quota process. Also, any one of our suppliers, contract manufacturers, laboratories, packagers and/or distributors could be the subject of DEA violations and enforcement could lead to delays or even loss of DEA license by the contractors.

Federal and State Fraud and Abuse and Data Privacy and Security and Transparency Laws and Regulations

In addition to FDA restrictions on marketing of pharmaceutical products, federal and state healthcare laws restrict certain business practices in the pharmaceutical industry. These laws include, but are not limited to, anti-kickback, false claims, data privacy and security, and transparency statutes and regulations.

The federal Anti-Kickback Statute prohibits, among other things, knowingly and willfully offering, paying, soliciting or receiving remuneration, directly or indirectly, to induce, or in return for, purchasing, leasing, ordering or arranging for the purchase, lease or order of any good, facility, item or service reimbursable under Medicare, Medicaid or other federal healthcare programs. The term "remuneration" has been broadly interpreted to include anything of value, including for example, gifts, discounts, the furnishing of supplies or equipment, credit arrangements, payments of cash, waivers of payment, ownership interests and providing anything at less than its fair market value. The Anti-Kickback Statute has been interpreted to apply to arrangements between pharmaceutical manufacturers on one hand and prescribers, purchasers and/or formulary managers on the other. Although there are a number of statutory exemptions and regulatory safe harbors protecting certain common activities from prosecution, the exemptions and safe harbors are drawn narrowly, and our practices may not in all cases meet all of the criteria for a statutory exception or safe harbor protection. Practices that involve remuneration that may be alleged to be intended to induce prescribing, purchases or recommendations may be subject to scrutiny if they do not qualify for an exception or safe harbor. A claim including items or services resulting from a violation of the federal Anti-Kickback Statute constitutes a false or fraudulent claim for purposes of the civil False Claims Act (discussed below).

The False Claims Act and related laws prohibit, among other things, any person or entity from knowingly presenting, or causing to be presented, a false or fraudulent claim for payment or approval to the federal government or knowingly making, using or causing to be made or used a false record or statement material to a false or fraudulent claim to the federal government. Pharmaceutical and other healthcare companies have been prosecuted under these laws for, among other things, allegedly providing free product to customers with the expectation that the customers would bill federal programs for the product. Other companies have been prosecuted for causing false claims to be submitted because of the companies' marketing of the product for unapproved, and thus non-reimbursable, uses. Further, the Civil Monetary Penalties Law imposes penalties against any person or entity who, among other things, is determined to have presented or caused to be presented a claim to a federal health program that the person knows or should know is for an item or service that was not provided as claimed or is false or fraudulent.

In addition, we may be subject to data privacy and security regulation by both the federal government and the states in which we conduct our business. HIPAA, as amended by the Health Information Technology for Economic and Clinical Health Act, or HITECH, and its implementing regulations, imposes certain requirements relating to the privacy, security and transmission of individually identifiable health information. Among other things, HITECH makes HIPAA's privacy and security standards directly applicable to business associates—independent contractors or agents of covered entities that receive or obtain protected health information in connection with providing a service on behalf of a covered entity. HITECH also created four new tiers of civil monetary penalties, amended HIPAA to make civil and criminal penalties directly applicable to business associates, and gave state attorneys general new authority to

file civil actions for damages or injunctions in federal courts to enforce the federal HIPAA laws and seek attorney's fees and costs associated with pursuing federal civil actions. In addition, state laws govern the privacy and security of health information in certain circumstances, many of which differ from each other in significant ways and may not have the same effect, thus complicating compliance efforts.

Additionally, the federal Physician Payments Sunshine Act within the Patient Protection and Affordable Care Act, or PPACA, and its implementing regulations, require that certain manufacturers of drugs, devices, biologicals and medical supplies, for which federal healthcare program payment is available, report information related to certain payments or other transfers of value made or distributed to physicians and teaching hospitals, or to entities or individuals at the request of, or designated on behalf of, the physicians and teaching hospitals and to report annually certain ownership and investment interests held by physicians and their immediate family members.

Also, many states have similar healthcare statutes or regulations that apply to items and services reimbursed under Medicaid and other state programs, or, in several states, apply regardless of the payer. FDA and some states require the posting of information relating to clinical studies. In addition, California requires pharmaceutical companies to implement a comprehensive compliance program that includes a limit on expenditures for, or payments to, individual medical or health professionals. If our operations are found to be in violation of any of the health regulatory laws described above or any other laws that apply to us, we may be subject to penalties, including potentially significant criminal, civil and/or administrative penalties, damages, fines, disgorgement, individual imprisonment, exclusion of products from reimbursement under government programs, contractual damages, reputational harm, administrative burdens, diminished profits and future earnings and the curtailment or restructuring of our operations, any of which could adversely affect our ability to operate our business and our results of operations. To the extent that any of our products will be sold in a foreign country, we may be subject to similar foreign laws and regulations, which may include, for instance, applicable post-marketing requirements, including safety surveillance, anti-fraud and abuse laws and implementation of corporate compliance programs and reporting of payments or transfers of value to healthcare professionals.

Pharmaceutical Coverage, Pricing and Reimbursement

In both domestic and foreign markets, our sales of any approved products will depend in part on the availability of coverage and adequate reimbursement from third-party payers. Third-party payers include government health administrative authorities, managed care providers, private health insurers and other organizations. Sales of our products will depend substantially, both domestically and abroad, on the extent to which the costs of our products will be paid by third-party payers. These third-party payers are increasingly focused on containing healthcare costs by challenging the price and examining the cost-effectiveness of medical products and services. In addition, significant uncertainty exists as to the coverage and reimbursement status of newly approved healthcare product candidates. Third-party payers may refuse to include a particular branded drug in their formularies or otherwise restrict patient access to a branded drug when a less costly generic equivalent or other alternative is available. Because each third-party payer individually approves coverage and reimbursement levels, obtaining coverage and adequate reimbursement is a time-consuming, costly and sometimes unpredictable process. We may be required to provide scientific and clinical support for the use of any product to each third-party payer separately with no assurance that approval would be obtained, and we may need to conduct expensive pharmacoeconomic studies in order to demonstrate the cost-effectiveness of our products. This process could delay the market acceptance of any product and could have a negative effect on our future revenues and operating results. We cannot be certain that our products and our product candidates will be considered cost-effective. Because coverage and reimbursement determinations are made on a payer-by-payer basis, obtaining acceptable coverage and reimbursement from one payer does not guarantee that we will obtain similar acceptable coverage or reimbursement from another payer. If we are unable to obtain coverage of, and adequate reimbursement and payment levels for, our product candidates from third-party payers, physicians may limit how much or under what circumstances they will prescribe or administer them. This in turn could affect our ability to successfully commercialize our products and impact our profitability, results of operations, financial condition and future success.

In addition, in many foreign countries, particularly the countries of the European Union, the pricing of prescription drugs is subject to government control. In some non-U.S. jurisdictions, the proposed pricing for a drug must be approved before it may be lawfully marketed. The requirements governing drug pricing vary widely from country to country. For example, the EU provides options for its member states to restrict the range of medicinal products for which their national health insurance systems provide reimbursement and to control the prices of medicinal products for human use. A member state may approve a specific price for the medicinal product or it may instead adopt a system of direct or indirect controls on the profitability of the company placing the medicinal product on the market. We may face competition for our product candidates from lower-priced products in foreign countries that have placed price controls on pharmaceutical products. In addition, there may be importation of foreign products that compete with our own products, which could negatively impact our profitability.

Healthcare Reform

In the United States and foreign jurisdictions, there have been, and we expect there will continue to be, a number of legislative and regulatory changes to the healthcare system that could affect our future results of operations as we

begin to commercialize our products. In particular, there have been and continue to be a number of initiatives at the United States federal and state level that seek to reduce healthcare costs. Government payment for some of the costs of prescription drugs may increase demand for our products for which we receive marketing approval. However, any negotiated prices for our future products will likely be lower than the prices we might otherwise obtain from non-governmental payers. Moreover, private payers often follow federal healthcare coverage policy and payment limitations in setting their own payment rates.

Furthermore, political, economic and regulatory influences are subjecting the healthcare industry in the United States to fundamental change. Initiatives to reduce the federal deficit and to reform healthcare delivery are increasing cost-containment efforts. We anticipate that Congress, state legislatures and the private sector will continue to review and assess alternative benefits, controls on healthcare spending through limitations on the growth of private health insurance premiums and Medicare and Medicaid spending, the creation of large insurance purchasing groups, price controls on pharmaceuticals and other fundamental changes to the healthcare delivery system. Any proposed or actual changes could limit or eliminate our spending on development projects and affect our ultimate profitability. In March 2010, PPACA was signed into law. Among other cost containment measures, PPACA established an annual, nondeductible fee on any entity that manufactures or imports certain branded prescription drugs and biologic agents. In the future, there may continue to be additional proposals relating to the reform of the U.S. healthcare system, some of which could further limit the prices we are able to charge for our products, or the amounts of reimbursement available for our products. If future legislation were to impose direct governmental price controls and access restrictions, it could have a significant adverse impact on our business. Managed care organizations, as well as Medicaid and other government agencies, continue to seek price discounts. Some states have implemented, and other states are considering, price controls or patient access constraints under the Medicaid program, and some states are considering price-control regimes that would apply to broader segments of their populations that are not Medicaid-eligible. Due to the volatility in the current economic and market dynamics, we are unable to predict the impact of any unforeseen or unknown legislative, regulatory, payer or policy actions, which may include cost containment and healthcare reform measures. Such policy actions could have a material adverse impact on our profitability.

Reimbursement and Health Reform

Significant uncertainty exists as to the coverage and reimbursement status of any product candidate that receives regulatory approval. In the United States and markets in other countries, sales of our product candidates, if approved for commercial sale, will depend, in part, on the extent to which third-party payors provide coverage and establish adequate reimbursement levels for product candidates.

In the United States, third-party payors include federal and state healthcare programs, government authorities, private managed care providers, private health insurers and other organizations. There has been increasing legislative and enforcement interest in the United States with respect to specialty drug pricing practices. Specifically, there have been several recent U.S. Congressional inquiries and proposed bills designed to, among other things, bring more transparency to drug pricing, review the relationship between pricing and manufacturer patient programs, and reform government program reimbursement methodologies for drugs. Further, third-party payors are increasingly challenging the price, examining the medical necessity and reviewing the cost-effectiveness of medical drug products and medical services, in addition to questioning their safety and efficacy. Such payors may limit coverage to specific drug products on an approved list, also known as a formulary, which might not include all of the FDA-approved drugs for a particular indication. We may need to conduct expensive pharmacoeconomic studies in order to demonstrate the medical necessity and cost-effectiveness of our product candidates, in addition to the costs required to obtain the FDA approvals. Nonetheless, our product candidates may not be considered medically necessary or cost-effective.

Moreover, the process for determining whether a third-party payor will provide coverage for a drug product may be separate from the process for setting the price of a drug product or for establishing the reimbursement rate that such a payor will pay for the drug product. A payor's decision to provide coverage for a drug product does not imply that an adequate reimbursement rate will be approved. Further, one payor's determination to provide coverage for a drug product does not assure that other payors will also provide coverage for the drug product. Adequate third-party reimbursement may not be available to maintain price levels sufficient to realize an appropriate return on our investment.

In the United States, the PPACA, as amended by the Health Care and Education Reconciliation Act of 2010, collectively, the Health Care Reform Law, was enacted in an effort to, among other things, broaden access to health insurance, reduce or constrain the growth of healthcare spending, enhance remedies against fraud and abuse, impose new taxes and fees on the health industry and impose additional health policy reforms. Aspects of the Health Care Reform Law that may impact our business include:

- extension of manufacturers' Medicaid rebate liability to covered drugs dispensed to individuals who are enrolled in Medicaid managed care organizations;

- expansion of the entities eligible for discounts under the Public Health Service pharmaceutical pricing program;

- expansion of eligibility criteria for Medicaid programs, thereby potentially increasing manufacturers' Medicaid rebate liability;

- expansion of healthcare fraud and abuse laws, including the federal False Claims Act and the federal Anti-Kickback Statute, new government investigative powers and enhanced penalties for non-compliance;

- a requirement to annually report drug samples that manufacturers and distributors provide to physicians;

- a Patient-Centered Outcomes Research Institute to oversee, identify priorities in, and conduct comparative clinical effectiveness research, along with funding for such research; and

- creation of the Independent Payment Advisory Board which has authority to recommend certain changes to the Medicare program that could result in reduced payments for prescription drugs.

The Health Care Reform Law has the potential to substantially change health care financing and delivery by both governmental and private insurers, and may also increase our regulatory burdens and operating costs.

In addition, other legislative changes have been proposed and adopted in the United States since the Health Care Reform Law was enacted. Aggregate reductions of Medicare payments to providers of 2% per fiscal year went into effect on April 1, 2013 and will stay in effect through 2024 unless Congressional action is taken. The American Tax Payer Relief Act further reduced Medicare payments to several providers, including hospitals.

Moreover, the Drug Supply Chain Security Act of 2013 imposes new obligations on manufacturers of pharmaceutical products, among others, related to product tracking and tracing. Among the requirements of this new legislation, manufacturers will be required to provide certain information regarding the drug product to individuals and entities to which product ownership is transferred, label drug product with a product identifier, and keep certain records regarding the drug product.

Legislative and regulatory proposals have been made to expand post-approval requirements and further restrict sales and promotional activities for pharmaceutical products. We are not sure whether additional legislative changes will be enacted, or whether the FDA regulations, guidance or interpretations will be changed, or what the impact of such changes on the marketing approvals of our product candidates, if any, may be.

Research and Development

Conducting research and development is central to our business model. We have invested and expect to continue to invest significant time and capital in our research and development operations. Our research and development expenses were $22.5 million, $24.5 million and $26.3 million during the years ended December 31, 2015, 2014 and 2013, respectively. We plan to incur significant expenditures for the foreseeable future as we seek to continue the development of ARX-04 and Zalviso and begin commercial preparations for ARX-04 and Zalviso.

Employees

As of December 31, 2015, we employed 36 full-time employees. None of our employees are subject to a collective bargaining agreement. We consider our relationship with our employees to be good.

Corporate Information

We were originally incorporated as SuRx, Inc. in Delaware on July 13, 2005. We subsequently changed our name to AcelRx Pharmaceuticals, Inc. on August 13, 2006. We file electronically with the U.S. Securities and Exchange Commission, or 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, as amended, or the Exchange Act. We make available on our website at www.acelrx.com, free of charge, copies of these reports as soon as reasonably practicable after filing these reports with, or furnishing them to, the SEC.

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Item 1A. Risk Factors

This Form 10-K contains forward-looking information based on our current expectations. Because our actual results may differ materially from any forward-looking statements made by or on behalf of us, this section includes a discussion of important factors that could affect our actual future results, including, but not limited to, our revenues, expenses, net loss and loss per share. We believe the risks described below are the risks that are material to us as of the date of this Form 10-K. If any of the following risks comes to fruition, our business, financial condition, results of operations and future growth prospects would likely be materially and adversely affected.

Risks Related to Clinical Development and Regulatory Approval

We depend substantially on the success of ARX-04, which may not receive regulatory approval in the United States.

Since our inception in 2005, we have focused primarily on development of our product candidate, Zalviso™; however, given the delay in the potential approval of Zalviso in the United States, we believe the importance of ARX-04 (sufentanil sublingual tablet, 30 mcg) to our future success has increased. ARX-04 is a non-invasive investigational product candidate consisting of a single tablet delivered sublingually via a disposable, pre-filled, single-dose applicator, or SDA.

As part of our development program, we met with the United States Food and Drug Administration, or FDA, in December 2015 to review plans for a New Drug Application, or NDA, for ARX-04. Based on feedback from the FDA, we intend to expand the clinical program for ARX-04 by approximately 160 additional patients to include individuals from specific populations and settings. Enrollment in the ongoing SAP302 open-label study in the emergency room will be increased, and a new study, known as SAP303, was initiated in March 2016 in post-operative patients with moderate-to-severe acute pain. SAP303 will focus on enrolling patients greater than 40 years of age and will allow for administration of ARX-04 for up to 12 hours. With these modifications, assuming successful completion of SAP302 and SAP303 by the third quarter of 2016, we anticipate submitting the NDA for ARX-04 in the fourth quarter of 2016. However, while we have announced positive top-line results from SAP301, SAP302 and SAP303 may not achieve positive results, or may not be completed by the third quarter of 2016 as anticipated. Even if we believe the results from SAP301, SAP302 and SAP303 support an NDA submission for ARX-04, the FDA may not agree, or may interpret the study results differently, which would delay the timing of our commercialization of ARX-04 and adversely affect our business operations. If ARX-04 is not approved for sale in the United States, it could have a significant impact on our ability to generate cash flows from product sales or to enter into a collaboration agreement. If we are not able to receive approval to commercialize ARX-04 in the United States, we would be required to find alternative sources of capital to continue operations. If ARX-04 is not approved for sale in the United States, and we are unsuccessful in finding alternative sources of capital, it will be difficult for us to continue under our current operating plan.

Any disagreement with the FDA as to the results from SAP301, SAP302, and SAP303, and therefore any additional requirements imposed by the FDA prior to our ability to submit an NDA, as well as any delay in approval by the FDA of the ARX-04 NDA, if and when it is submitted, may negatively impact our stock price and harm our business operations. If and when the ARX-04 NDA is submitted, the FDA may hold an Advisory Committee meeting to obtain committee input on the safety and efficacy of ARX-04. Typically, Advisory Committees will provide responses to specific questions asked by the FDA, including the Committee's view on the approvability of the drug under review. Advisory Committee decisions are not binding but an adverse decision at the Advisory Committee may have a negative impact on the regulatory review of ARX-04. Any delay in obtaining, or inability to obtain, regulatory approval would prevent us from commercializing ARX-04 in the United States, generating revenues and potentially achieving profitability. If any of these events occur, we may be forced to delay or abandon our development efforts for ARX-04, which would have a material adverse effect on our business and could potentially cause us to cease operations.

We depend substantially on the success of Zalviso, which may not receive regulatory approval in the United States.

Since our inception in 2005, we have focused primarily on development of our product candidate, Zalviso. While ARX-04's importance has increased for our future success, Zalviso remains an important product candidate for us. Zalviso consists of sufentanil sublingual tablets, 15 mcg, delivered by the Zalviso System, a needle-free, handheld, patient-administered, pain management system, or together, Zalviso. The success of our business depends primarily upon our ability to develop, receive regulatory approval in the United States for, and commercialize Zalviso for the management of moderate-to-severe acute pain in adult patients in the hospital setting. We have not marketed, distributed or sold any products to date anywhere in the world.

To date, our Phase 3 program for Zalviso has consisted of three Phase 3 clinical trials. We reported positive top-line data from each of these trials and submitted an NDA for Zalviso to the FDA in September 2013, which the FDA then accepted for filing in December 2013. On July 25, 2014, the FDA issued a Complete Response Letter, or CRL, for our NDA for Zalviso. The CRL contained requests for additional information on the Zalviso System to ensure proper use of the device. The requests included submission of data demonstrating a reduction in the incidence of optical system errors, changes to address inadvertent dosing, among other items, and submission of additional data to support the shelf life of the product. In the third quarter of 2014, we held a Type A meeting with the FDA to discuss the Zalviso CRL. During the meeting, we discussed the resubmission of the Zalviso NDA and the steps necessary for the resubmission. In advance of resubmitting our Zalviso NDA, we agreed with the FDA to submit protocols for the bench testing and Human Factors, or HF, studies for their review and comment. In addition, the FDA requested in the minutes of the meeting, that we provide a risk assessment that analyzes the risks associated with inadvertent dosing and the rationale that bench testing and HF studies would be sufficient to address the specific items included in the CRL. We submitted the protocols and this rationale in the fourth quarter of 2014. In January 2015, we received feedback from the FDA on the protocol and planned analysis of the results of the bench test. Based on the FDA feedback, no modifications to the conduct of the bench test were necessary; however, in response to the FDA's request, we refined the planned analysis of the bench test results. In February 2015, we received feedback from the FDA on the HF protocols. In this feedback, the FDA confirmed that the HF studies as proposed were acceptable to evaluate the design changes related to inadvertent dispensing of tablets. In March 2015, we received additional correspondence from the FDA stating that in addition to the bench testing and two HF studies we had performed in response to the issues identified in the CRL, a clinical trial is needed to assess the risk of inadvertent dispensing and overall risk of dispensing failures. On April 21, 2015, we submitted a request to the Division of Anesthesia, Analgesia, and Addiction Products, or the Division, of the FDA for a Type B meeting. On May 1, 2015, the Division notified us that the request for a meeting was denied and restated the Division's view that a clinical study is required. Subsequently, we were granted a Type C meeting (previously identified as a General Advice meeting) with the FDA, which took place in early September 2015, to discuss their request for an additional clinical trial and our planned response to the CRL. In the Type C meeting minutes, the FDA provided some additional details about the type of clinical data they would like us to provide, as a complement to the other data we already have provided, to assess the overall performance of the Zalviso device. We have also received comments from the FDA on the protocol for the study, known as IAP312. In response to the comments, the protocol has been amended and will include approximately 315 post-operative patients and will collect information requested by the Division to supplement the three positive Phase 3 trials already completed. We expect to initiate the study in the first quarter of 2016.There is no guarantee that the additional work we perform related to Zalviso, including the IAP312 trial, will be supportive of, or guarantee, an NDA resubmission, or result in our successfully obtaining FDA approval of Zalviso in a timely fashion, if at all. For example, the trial might not meet its objectives or the FDA could still have concerns regarding the performance of the device, inadvertent dosing (dropped tablets), or other issues. At any future point in time, the FDA could require us to complete further clinical, Human Factors, pharmaceutical, reprocessing or other studies, which could delay or preclude any NDA submission or approval of the NDA and could require us to obtain significant additional funding. There is no guarantee such funding would be available to us on favorable terms, if at all. If the Zalviso NDA is resubmitted, the FDA may hold an Advisory Committee meeting to obtain committee input on the safety and efficacy of Zalviso. Typically, Advisory Committees will provide responses to specific questions asked by the FDA, including the Committee's view on the approvability of the drug under review. Advisory Committee decisions are not binding but an adverse decision at the Advisory Committee may have a negative impact on the regulatory review of Zalviso. If the Zalviso NDA resubmission receives a second CRL, we may choose to engage in the dispute resolution process with the FDA.

Our proposed trade name of Zalviso has been approved by the FDA, which must approve all drug trade names to avoid medication errors and misbranding. However, the FDA may withdraw this approval in which case any brand recognition or goodwill that we establish with the name Zalviso prior to commercialization may be worthless.

Any delay in approval by the FDA of the Zalviso NDA, if, and when, it is resubmitted, may negatively impact our stock price and harm our business operations. Any delay in obtaining, or inability to obtain, regulatory approval would prevent us from commercializing Zalviso in the United States, generating revenues and potentially achieving profitability. If any of these events occur, we may be forced to delay or abandon our development efforts for Zalviso, which would have a material adverse effect on our business and could potentially cause us to cease operations.

Positive clinical results obtained to date for our product candidates may be disputed in FDA review, do not guarantee regulatory approval and may not be obtained from future clinical trials.

We have reported positive top-line data from our first Phase 3 clinical trial for ARX-04, or SAP301, each of our three Zalviso Phase 3 clinical trials completed to date, in addition to all of our Phase 2 clinical trials for ARX-04 and Zalviso. However, even if we believe that the data from clinical trials is positive, the FDA has and in the future could determine that the data from our trials was negative or inconclusive or could reach a different conclusion than we did on that same data. Negative or inconclusive results of a clinical trial or difference of opinion could cause the FDA to require us to repeat the trial or conduct additional clinical trials prior to obtaining approval for commercialization, and there is no guarantee that additional trials would achieve positive results or that the FDA will agree with our interpretation of the results. Any such determination by the FDA would delay the timing of our commercialization plan for ARX-04 and Zalviso, or further development of our other product candidates, and adversely affect our business operations. For example, although we had achieved the primary endpoints in each of our three Phase 3 clinical trials for Zalviso which were included in our NDA filed in 2013, in March 2015, we received correspondence from the FDA stating that in addition to the bench testing and two Human Factors studies we had performed in response to the issues identified in the CRL, a clinical trial is needed to assess the risk of inadvertent dispensing and overall risk of dispensing failures.

Delays in clinical trials are common and have many causes, and any delay could result in increased costs to us and jeopardize or delay our ability to obtain regulatory approval and commence product sales.

We have experienced and may in the future experience delays in clinical trials of our product candidates. While we have completed one Phase 3 clinical trial for ARX-04, three Phase 3 clinical trials for Zalviso, and several Phase 2 clinical trials both for ARX-04 and Zalviso, current and potential future clinical trials may not begin on time, have an effective design, enroll a sufficient number of patients or be completed on schedule, if at all. For example, in June 2014, we completed a pharmacokinetic study in support of the ARX-04 development program. In this study of healthy volunteers, it was shown that two sublingual administrations of a Zalviso sufentanil sublingual tablet, 15 mcg, dosed 20 minutes apart were equivalent to one sublingual administration of a sufentanil sublingual tablet, 30 mcg. Based on the pharmacokinetic equivalency of two Zalviso tablets to one ARX-04 tablet, the FDA has agreed to accept 323 Zalviso patients into the ARX-04 safety database, however, the FDA also required that the ARX-04 safety database comprise 350 patients dosed with at least one dose of ARX-04. Based on this feedback from the FDA, we intend to increase the safety database by expanding the clinical program for ARX-04 by approximately 160 additional patients to include individuals from specific populations and settings. Enrollment in the ongoing SAP302 open-label study in the emergency room will be increased, and a new study, known as SAP303, was initiated in March 2016 in post-operative patients with moderate-to-severe acute pain. Accordingly, the completion of the Phase 3 clinical program for ARX-04 has been extended and our clinical trial expenses will increase.

Our clinical trials for any of our product candidates could be delayed for a variety of reasons, including:

- inability to raise funding necessary to initiate or continue a trial;
- delays in obtaining regulatory approval to commence a trial;
- delays in reaching agreement with the FDA on final trial design;
- imposition of a clinical hold by the FDA, IRBs or other regulatory authorities;
- delays in reaching agreement on acceptable terms with prospective contract research organizations, or CROs, and clinical trial sites;
- delays in obtaining required institutional review board approval at each site;
- delays in recruiting suitable patients to participate in a trial;

- delays in the testing, validation, manufacturing and delivery of the tablets and device components of our product candidates;

- delays in having patients complete participation in a trial or return for post-treatment follow-up;

- clinical sites dropping out of a trial to the detriment of enrollment or being delayed in entering data to allow for clinical trial database closure;

- time required to add new clinical sites; or

- delays by our contract manufacturers to produce and deliver sufficient supply of clinical trial materials.

If any future clinical trials are delayed for any of the above reasons, our development costs may increase, our approval process could be delayed and our ability to commercialize and commence sales of our product candidates could be materially harmed, which could have a material adverse effect on our business.

We have not yet responded to the Zalviso Complete Response Letter nor resubmitted the Zalviso NDA. Activities that we undertake to address issues raised in the CRL may be deemed insufficient by the FDA.

We completed bench testing and additional Human Factors studies that we believed addressed certain items contained in the CRL. However, before the results from these studies were submitted as a part of the proposed NDA resubmission, the FDA, in March 2015, notified us of the need for a clinical trial prior to the resubmission of the Zalviso NDA. In early September 2015, we had a Type C meeting with the FDA to discuss the FDA's request for an additional clinical trial and our planned response to the CRL. In response to discussions with the FDA, we have agreed to complete an additional open label study with Zalviso in post-operative patients, known as IAP312. We have completed the protocol review for IAP312 and plan to initiate the study in the first quarter of 2016. There is no guarantee that the trial results, even if successful, will address the issues raised by the FDA. Any delay in obtaining, or inability to obtain, regulatory approval would prevent us from commercializing Zalviso in the United States, generating revenues and achieving profitability. If any of these events occur, we may be forced to delay or abandon our development and commercialization efforts for Zalviso in the United States, which would have a material adverse effect on our business and could potentially cause us to cease operations.

If we are able to resubmit an NDA for Zalviso with new clinical data, there is no guarantee that such data will be deemed sufficient by the FDA. While we designed the protocols for bench testing and the Human Factors studies to address the issues raised in the CRL, and designed the protocol for the additional Zalviso clinical trial to further address these issues, there is no guarantee that the FDA will deem such protocols and results sufficient to address those issues when they are formally reviewed as a part of an NDA resubmission.

Lastly, even if we believe that the test results from our bench testing and Human Factors studies are positive, and we are able to conduct and achieve positive results from the IAP312 study, the FDA may hold a different opinion and deem the results insufficient. The FDA may provide review commentary at any time during the resubmission and review process which could adversely affect or even prevent the approval of Zalviso, which would adversely affect our business. We may not be able to identify appropriate remediations to issues that the FDA may raise, and we may not have sufficient time or financial resources to conduct future activities to remediate issues raised by the FDA.

Our product candidates may cause adverse effects or have other properties that could delay or prevent their regulatory approval or limit the scope of any approved label or market acceptance.

Adverse events, or AEs, caused by our product candidates could cause us, other reviewing entities, clinical trial sites or regulatory authorities to interrupt, delay or halt clinical trials and could result in the denial of regulatory approval. In our Phase 3 active comparator clinical trial (IAP309), 7.9% of Zalviso-treated patients dropped out of the trial prematurely due to an AE, and we observed one serious adverse event, or SAE, that was assessed as possibly or probably related to Zalviso. In our Phase 3, double-blind, placebo-controlled, abdominal surgery trial (IAP310), adverse events reported in the trial were generally mild or moderate in nature and similar in both placebo and treatment groups. In addition, one patient in the trial, who was in the sufentanil sublingual tablet group, experienced an SAE, which was determined to be unrelated to the trial drug. In our Phase 3, double-blind, placebo-controlled, orthopedic surgery trial (IAP311), treatment-emergent adverse events were generally mild-to-moderate in nature and similar for the majority of adverse events between sufentanil sublingual tablet- and placebo-treated patients. Two patients (one each in the sufentanil sublingual tablet group and placebo group) experienced a serious adverse event considered possibly or probably related to the trial drug by the investigator.

In our Phase 2 ARX-04 trial, two serious adverse events (SAEs), both in the 20 mcg dose group, occurred one week after the study (surgical infections) and were deemed unrelated to study drug. All but two adverse events reported in the study were mild-to-moderate in nature with 58 patients (58%) reporting a total of 135 adverse events. The most frequently reported adverse events for all patients were nausea (30%), vomiting (17%), dizziness (14%) and somnolence (11%). Two patients discontinued treatment, one unrelated to study drug (anxiety/chest pain) and the other probably related to study drug (somnolence/respiratory depression); however, both patients recovered without medical intervention.

Phase 2 clinical trials we have conducted with Zalviso did generate some AEs, but no SAEs, related to the trial drug.

Further, if any of our future products, including Zalviso or ARX-04 cause serious or unexpected side effects after receiving marketing approval, a number of potentially significant negative consequences could result, including:

- regulatory authorities may withdraw their approval of the product or impose restrictions on its distribution in the form of a modified Risk Evaluation and Mitigation Strategy, or REMS;
- regulatory authorities may require the addition of labeling statements, such as warnings or contraindications;
- we may be required to change the way the product is administered or conduct additional clinical trials;
- we could be sued and held liable for harm caused to patients; or
- our reputation may suffer.

Any of these events could prevent us from achieving or maintaining market acceptance of the affected product candidate and could substantially increase the costs of commercializing our product candidates.

Additional time may be required to obtain U.S. regulatory approval for ARX-04 and Zalviso because they are drug/device combination.

ARX-04 and Zalviso are combination product candidates with both drug and device components. The FDA requires both the drug and device components of combination product candidates to be reviewed as part of an NDA submission. There are very few examples of the FDA approval process for drug/device combination products such as ARX-04 and Zalviso. As a result, we have in the past, and may in the future, experience delays in the development and commercialization of Zalviso due to regulatory uncertainties in the product development and approval process, in particular as it relates to a drug/device combination product approval under an NDA, and we may experience similar delays and regulatory uncertainties when, and if, we submit the NDA for ARX-04. For example, the Zalviso CRL received from the FDA in July 2014 contains requests for additional information on the Zalviso System to ensure proper use of the device. The requests include submission of data demonstrating a reduction in the incidence of optical system errors, changes to address inadvertent dosing, among other items, and submission of additional data to support the shelf life of the product. Furthermore, in March 2015, we received correspondence from the FDA stating that in addition to the bench testing and two Human Factors studies we had performed in response to the issues identified in the CRL, a clinical trial is needed to assess the risk of inadvertent dispensing and overall risk of dispensing failures. Based on the results of the Type C meeting with FDA, which took place in September 2015, we submitted a protocol to the FDA for a clinical study in post-operative patients designed to evaluate the effectiveness of changes made to enhance Zalviso device performance. We have completed the protocol review with the FDA and plan to initiate the study, IAP312, in the first quarter of 2016. Even if we are able to successfully complete IAP312, the FDA may deem the results of IAP312, as well as bench testing and/or the Human Factors studies inadequate, which could delay or

preclude any approval of Zalviso.

We cannot predict when we will obtain regulatory approval to commercialize any of our product candidates, if at all, and we cannot, therefore, predict the timing of any future revenue.

We cannot commercialize any of our product candidates, including ARX-04 or Zalviso, until the appropriate regulatory authorities, such as the FDA or the European Medicines Agency, or EMA, have reviewed and approved the product candidate. The regulatory agencies may not complete their review processes in a timely manner, or we may be unable to obtain regulatory approval for our product candidates. In September 2015, the European Commission approved Grünenthal GmbH, or Grünenthal's, Marketing Authorization Application, or MAA, for Zalviso for post-operative pain; however, we cannot predict the commercial success of Zalviso and thus its impact on us because commercial sales in Europe have not yet begun. We received a CRL for Zalviso on July 25, 2014, which contains requests for additional information on the Zalviso System. In addition, in March 2015, we received correspondence from the FDA stating that in addition to the bench testing and two Human Factors studies we had performed in response to the issues identified in the CRL, a clinical trial is needed to assess the risk of inadvertent dispensing and overall risk of dispensing failures. Based on our Type C meeting with the FDA in early September 2015 to discuss the FDA's request for an additional clinical trial and our planned response to the CRL, we submitted a protocol to the FDA for a clinical study in post-operative patients designed to evaluate the effectiveness of changes made to enhance the Zalviso device. We have completed the protocol review and plan to initiate IAP312 in the first quarter of 2016. There is no guarantee that the IAP312 trial results will address the issues raised by the FDA. Additional delays may result if any of our product candidates is taken before an FDA Advisory Committee which may recommend restrictions on approval or recommend non-approval. In addition, we may experience delays or rejections based upon additional government regulation from future legislation or administrative action, or changes in regulatory agency policy during the period of product development, clinical trials and the review process.

The FDA and other foreign regulatory agencies, such as EMA, can delay, limit or deny marketing approval for many reasons, including:

- a product candidate may not be considered safe or effective;
- the manufacturing processes or facilities we have selected may not meet the applicable requirements; and
- changes in their approval policies or adoption of new regulations may require additional work on our part.

Part of the regulatory approval process includes compliance inspections of manufacturing facilities to ensure adherence to applicable regulations and guidelines. The regulatory agency may delay, limit or deny marketing approval of our product candidates as a result of such inspections. In June 2014, the FDA completed an inspection at our corporate offices. We received a single observation on a Form 483 as a result of the inspection. In addition, in January 2015, EMA conducted a pre-approval inspection of our Zalviso contract manufacturer's manufacturing and packaging site, and provided its observations. Although we believe we have adequately addressed these observations in revised standard operating procedures, we, our contract manufacturers, and their vendors, are all subject to

preapproval and post-approval inspections at any time. The results of these inspections could impact our ability to obtain FDA approval for Zalviso and, if approved, our ability to launch and successfully commercialize Zalviso in the United States. In addition, results of EMA inspections could impact our ability to maintain EC approval of Zalviso, and Grünenthal's ability to commercially launch and sustain sales of Zalviso in the EU.

Any delay in, or failure to receive or maintain, approval for any of our product candidates could prevent us from generating meaningful revenues or achieving profitability. Our product candidates may not be approved even if they achieve their endpoints in clinical trials. Regulatory agencies, including the FDA or EMA, or their advisors, may disagree with our trial design and our interpretations of data from preclinical studies and clinical trials. Regulatory agencies may change requirements for approval even after a clinical trial design has been approved. The FDA exercises significant discretion over the regulation of combination products, including the discretion to require separate marketing applications for the drug and device components in a combination product. To date, our product candidates are being regulated as drug products under the NDA process administered by the FDA. The FDA could in the future require additional regulation of our product candidates under the medical device provisions of the FDCA. We must comply with the Quality Systems Regulation, or QSR, which sets forth the FDA's current good manufacturing practice, or cGMP, requirements for medical devices, and other applicable government regulations and corresponding foreign standards for drug cGMPs. If we fail to comply with these regulations, it could have a material adverse effect on our business and financial condition.

Regulatory agencies also may approve a product candidate for fewer or more limited indications than requested or may grant approval subject to the performance of post-marketing trials. In addition, regulatory agencies may not approve the labeling claims that are necessary or desirable for the successful commercialization of our product candidates. For example, we intend to resubmit our NDA seeking approval of Zalviso for the management of moderate-to-severe acute pain in adult patients in the hospital setting; however, our clinical trial data was generated exclusively from the post-operative segment of this population, and the FDA may restrict any approval to post-operative patients only, which would reduce our commercial opportunity.

The process for obtaining approval of an NDA is time consuming, subject to unanticipated delays and costs, and requires the commitment of substantial resources.

If the FDA determines that any of the clinical work submitted, including the clinical trials, Human Factors studies and bench testing submitted for a product candidate in support of an NDA were not conducted in full compliance with the applicable protocols for these trials, studies and testing as well as with applicable regulations and standards, or if the FDA does not agree with our interpretation of the results of such trials, studies and testing, the FDA may reject the data and results. The FDA may audit some or all of our clinical trial sites to determine the integrity of our clinical data. The FDA may audit some or all of our Human Factors study sites to determine the integrity of our data and may audit the data and results of bench testing. Any rejection of any of our data would negatively impact our ability to obtain marketing authorization for a product candidate and would have a material adverse effect on our business and financial condition. In addition, an NDA may not be approved, or approval may be delayed, as a result of changes in FDA policies for drug approval during the review period. For example, although many products have been approved by the FDA in recent years under Section 505(b)(2) of the Federal Food, Drug and Cosmetic Act, or FDCA, objections have been raised to the FDA's interpretation of Section 505(b)(2). If challenges to the FDA's interpretation of Section 505(b)(2) are successful, the FDA may be required to change its interpretation, which could delay or prevent the approval of such an NDA. Any significant delay in the acceptance, review or approval of an NDA that we have submitted would have a material adverse effect on our business and financial condition and would require us to obtain significant additional funding.

Even if we obtain regulatory approval for ARX-04, Zalviso and our other product candidates in the United States, we and our collaborators face extensive regulatory requirements and our products may face future development and regulatory difficulties.

Even if we obtain regulatory approval in the United States, the FDA may impose significant restrictions on the indicated uses or marketing of our product candidates, or impose ongoing requirements for potentially costly post-approval trials or post-market surveillance. Additionally, the labeling ultimately approved for ARX-04, Zalviso and our other product candidates, if approved, will likely include restrictions on use due to the opioid nature of sufentanil.

ARX-04, Zalviso and our other product candidates, if approved in the future, will also be subject to ongoing FDA requirements governing the labeling, packaging, storage, distribution, safety surveillance, advertising, promotion, record-keeping and reporting of safety and other post-market information. The holder of an approved NDA is obligated to monitor and report AEs and any failure of a product to meet the specifications in the NDA. The holder of an approved NDA must also submit new or supplemental applications and obtain FDA approval for certain changes to the approved product, product labeling or manufacturing process. Advertising and promotional materials must comply with FDA rules and are subject to FDA review, in addition to other potentially applicable federal and state laws.

We must also register and obtain various state prescription drug distribution licenses and controlled substance permits, and any delay or failure to obtain or maintain these licenses or permits may limit our market and materially impact our business. In addition, manufacturers of drug products and their facilities are subject to payment of user fees and continual review and periodic inspections by the FDA and other regulatory authorities for compliance with cGMPs and adherence to commitments made in the NDA. If we, or a regulatory agency, discover previously unknown problems with a product, such as AEs of unanticipated severity or frequency, or problems with the facilities where the product is manufactured, a regulatory agency may impose restrictions relative to that product or the manufacturing facilities, including requiring recall or withdrawal of the product from the market or suspension of manufacturing.

If we fail to comply with applicable regulatory requirements following approval of our product candidates, a regulatory agency may:

- issue a warning letter asserting that we are in violation of the law;
- seek an injunction or impose civil or criminal penalties or monetary fines;
- suspend or withdraw regulatory approval;
- suspend any ongoing clinical trials;

- refuse to approve a pending NDA or supplements to an NDA submitted by us;
- seize product; 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 any future approved products and generate revenues.

Even if we obtain FDA approval for ARX-04, Zalviso or any of our product candidates in the United States, we may never obtain approval for or commercialize our products outside of the United States, which would limit our ability to realize their full market potential.

In order to market any products outside of the United States, we or our commercial partners, including Grünenthal in Europe, must establish and comply with numerous and varying regulatory requirements of other countries regarding safety and efficacy. On September 22, 2015, we announced that the European Commission had approved Grünenthal's MAA for Zalviso for the management of acute moderate-to-severe post-operative pain in adult patients.

Outside of Europe, clinical trials conducted in one country may not be accepted by regulatory authorities in other countries, and regulatory approval in one country does not mean that regulatory approval will be obtained in any other country. Approval processes vary among countries and can involve additional product testing and validation and additional administrative review periods. Seeking foreign regulatory approval could result in difficulties and costs for us and require additional non-clinical trials or clinical trials, which could be costly and time consuming. Regulatory requirements can vary widely from country-to-country and could delay or prevent the introduction of our products in those countries. Our current clinical trial data may not be sufficient to support marketing approval in all territories. In addition, we lack the personnel, expertise and capabilities to gain regulatory approval of our product candidates on a global basis without a commercial partner. With Zalviso's approval for sale in Europe, we will rely on Grünenthal to commercialize it. While Grünenthal does have products approved in international markets, we do not have any product candidates approved for sales in any jurisdiction, including international markets, and we do not have experience in obtaining regulatory approval in international markets. Grünenthal's experience in international markets does not guarantee regulatory approval or compliance with regulatory requirements in international markets. If we fail to comply with regulatory requirements in international markets or to obtain and maintain required approvals, or if regulatory approvals in international markets are delayed, our target market will be reduced and our ability to realize the full market potential of our products will be harmed.

ARX-04, Zalviso and our other product candidates will require Risk Evaluation and Mitigation Strategies.

Our product candidates, if approved in the United States, will require REMS. The REMS may include requirements for special labeling or medication guides for patients, special communication plans to health care professionals and restrictions on distribution and use. While we have received pre-clearance from the FDA regarding certain aspects of the proposed required REMS for Zalviso, we cannot predict the final REMS to be required as part of any FDA approval of Zalviso. Depending on the extent of the REMS requirements, any United States launch may be delayed, the costs to commercialize Zalviso may increase substantially and the potential commercial market could be restricted. ARX-04, if approved, will also require REMS programs that may significantly increase our costs to commercialize these product candidates. Furthermore, risks of sufentanil that are not adequately addressed through proposed REMS for our future product candidates, if approved, may also prevent or delay their approval for commercialization.

Existing and future legislation may increase the difficulty and cost for us to commercialize ARX-04, Zalviso and any of our product candidates that may obtain commercial approval in the future, and affect the prices we may obtain.

In the United States and some foreign jurisdictions, the legislative landscape continues to evolve. There have been a number of legislative and regulatory changes and proposed changes regarding healthcare systems that could prevent or delay marketing approval of Zalviso outside the EU, or our other product candidates, including ARX-04, restrict or regulate post-approval activities for ARX-04 and Zalviso, and affect our ability to profitably sell any products for which we obtain marketing approval.

In the EU, the pricing of prescription drugs is subject to government control. In addition, the EU provides options for its member states to restrict the range of medicinal products for which their national health insurance systems provide reimbursement and to control the prices of medicinal products for human use.

In the United States, the Health Care Reform Law (as defined below) was enacted in an effort to, among other things, broaden access to health insurance, reduce or constrain the growth of healthcare spending, enhance remedies against fraud and abuse, impose new taxes and fees on the health industry and impose additional health policy reforms. Aspects of the Health Care Reform Law that may impact our business include:

- extension of manufacturers' Medicaid rebate liability to covered drugs dispensed to individuals who are enrolled in Medicaid managed care organizations;
- expansion of the entities eligible for discounts under the Public Health Service pharmaceutical pricing program;

- expansion of eligibility criteria for Medicaid programs, thereby potentially increasing manufacturers' Medicaid rebate liability;

- expansion of healthcare fraud and abuse laws, including the federal False Claims Act and the federal Anti-Kickback Statute, new government investigative powers and enhanced penalties for non-compliance;

- a requirement to annually report drug samples that manufacturers and distributors provide to physicians;

- a Patient-Centered Outcomes Research Institute to oversee, identify priorities in, and conduct comparative clinical effectiveness research, along with funding for such research; and

- creation of the Independent Payment Advisory Board which has authority to recommend certain changes to the Medicare program that could result in reduced payments for prescription drugs.

The Health Care Reform Law has the potential to substantially change health care financing and delivery by both governmental and private insurers, and may also increase our regulatory burdens and operating costs.

In addition, other legislative changes have been proposed and adopted in the United States since the Health Care Reform Law was enacted. Aggregate reductions of Medicare payments to providers of 2% per fiscal year went into effect on April 1, 2013 and will stay in effect through 2024 unless Congressional action is taken. The American Tax Payer Relief Act further reduced Medicare payments to several providers, including hospitals.

Moreover, the Drug Supply Chain Security Act of 2013 imposes new obligations on manufacturers of pharmaceutical products, among others, related to product tracking and tracing. Among the requirements of this new legislation, manufacturers will be required to provide certain information regarding the drug product to individuals and entities to which product ownership is transferred, label drug product with a product identifier, and keep certain records regarding the drug product.

Legislative and regulatory proposals have been made to expand post-approval requirements and further restrict sales and promotional activities for pharmaceutical products. We are not sure whether additional legislative changes will be enacted, or whether the FDA regulations, guidance or interpretations will be changed, or what the impact of such changes on the marketing approvals of our product candidates, if any, may be.

We expect that additional healthcare reform measures will be adopted within and outside the United States in the future, any of which could negatively impact our business. The continuing efforts of the government, insurance

companies, managed care organizations and other payors of healthcare services to contain or reduce costs of healthcare may adversely affect the demand for any drug products for which we may obtain regulatory approval, our ability to set a price that we believe is fair for our products, our ability to obtain coverage and reimbursement approval for a product, our ability to generate revenues and achieve or maintain profitability, and the level of taxes that we are required to pay.

Risks Related to Our Financial Condition and Need for Additional Capital

We have incurred significant losses since our inception, anticipate that we will continue to incur significant losses in 2016 and may continue to incur losses for the foreseeable future.

Since our inception in 2005, we have focused primarily on development of our product candidate, Zalviso. In September 2015, we announced that a pivotal Phase 3 study of ARX-04, SAP301, met all primary and secondary endpoints and in October 2015, we announced the initiation of SAP302, a Phase 3 study of ARX-04 in the emergency room, intended to complete the safety database requirements previously agreed to with the FDA. We have incurred significant net losses in each year since our inception in July 2005, and as of December 31, 2015, we had an accumulated deficit of $203.2 million.

We have devoted most of our financial resources to research and development, including our non-clinical development activities and clinical trials. To date, we have financed our operations primarily through the sale of equity securities, debt, government contract funding, sale of royalty and milestones, and proceeds from our commercial partner, Grünenthal. The size of our future net losses will depend, in part, on the rate of future expenditures and our ability to generate revenues. We expect to continue to incur substantial expenses as we continue our research and development activities for our product candidates, including addressing issues raised by the FDA related to regulatory review of Zalviso, as well as to support manufacturing and supply of Zalviso in Europe for Grünenthal. To date, none of our product candidates have been commercialized, and if ARX-04, Zalviso, or our other product candidates are not successfully developed or commercialized, or if revenues are insufficient following marketing approval, we will not achieve profitability and our business may fail. Our success is also dependent on obtaining regulatory approval to market our product candidates outside of the United States through current and future collaborations which may not materialize or prove to be successful.

We are substantially dependent on our commercial partner, Grünenthal, to successfully commercialize Zalviso in Europe.

On December 16, 2013, we entered into a Collaboration and License Agreement, or the License Agreement, and related Manufacture and Supply Agreement, or the MSA, and together with the License Agreement, the Agreements, with Grünenthal. On July 22, 2015, we entered into amendments to the License Agreement, or the License Amendment, and the MSA, or the MSA Amendment, with Grünenthal, each effective as of July 17, 2015, and together with the License Agreement, and the MSA, the Amended Agreements. The Amended Agreements grant rights to commercialize Zalviso in the European Union, or EU, Switzerland, Liechtenstein, Iceland, Norway and Australia, or the Territory, for human use in pain treatment within or dispensed by hospitals, hospices, nursing homes and other medically-supervised settings. In September 2015, the European Commission approved Grünenthal's MAA for Zalviso for post-operative pain. Grünenthal has stated that it expects to initiate commercialization of Zalviso in Western Europe in the first half of 2016. In September 2015, we consummated a monetization transaction with PDL BioPharma, Inc., or PDL, pursuant to which we sold to PDL for $65.0 million 75% of the European royalties from sales of Zalviso and 80% of the first four commercial milestones under the License Agreement, subject to a capped amount, referred to as the Royalty Monetization. Even if Grünenthal is successful in the commercialization of Zalviso in the EU, we will receive only 25% of the royalties and 20% of the first four commercial milestones under the License Agreement, and 100% of the royalties after the capped amount is reached. Any failures in commercialization of Zalviso outside the United States could have a material adverse impact on our business, including an adverse impact on the development of ARX-04 or Zalviso in the United States, if related to issues underlying the sufentanil sublingual tablet technology, safety or efficacy. Additionally, we agreed to certain representations and covenants relating to the Amended Agreements under our agreements with PDL, and, if we breach those representations or covenants, we may become subject to indemnification claims by PDL and liable to PDL for its indemnifiable losses relating to such breaches. The amount of such losses could be material and could have a material adverse impact on our business.

We have never generated product revenue and may never be profitable.

Our ability to generate revenue from commercial sales and achieve profitability depends on our ability, alone or with collaborators, to successfully complete the development of, obtain the necessary regulatory approvals for, and commercialize our product candidates. We may never generate revenues from sales of ARX-04, Zalviso or our other product candidates in the United States. While we have a collaboration with Grünenthal for commercialization of Zalviso in Europe and Australia, we may not achieve all of the development milestones associated with the collaboration, and Grünenthal may not recognize commercial sales of Zalviso, for which we would receive sales milestone payments and product royalties. Even if Grünenthal is successful in commercialization of Zalviso, as a result of our sale to PDL of certain expected royalties from the sales of Zalviso by Grünenthal and a portion of our first four commercial sales milestones, we will receive only 25% of the sales royalties and 20% of the first four commercial milestones under the Amended License Agreement. In addition, we do not anticipate generating revenues from our other product candidates for the foreseeable future, if ever. Our ability to generate future revenues from product sales depends heavily on our success in:

- obtaining and maintaining regulatory approval for ARX-04 and/or Zalviso in the United States and/or in Europe;

- launching and commercializing ARX-04 and/or Zalviso, including building internally or through entering a collaboration, a hospital-directed sales force in the United States and with third parties internationally, including Grünenthal, which may require additional funding; and

- completing the clinical development of, obtaining regulatory approval for, and launching and commercializing ARX-04 and Zalviso, which may require additional funding or corporate partnership resources.

Because of the numerous risks and uncertainties associated with pharmaceutical product development and the regulatory environment, we are unable to predict the timing or amount of increased expenses, or when, or if, we will be able to achieve or maintain profitability. Our expenses could increase beyond expectations if we are delayed in receiving regulatory approval, or in launching ARX-04 and/or Zalviso in the United States, or if we are required by the FDA to complete activities in addition to those we currently anticipate or have already completed.

Even if one or more of our product candidates is approved for commercial sale, we anticipate incurring significant costs associated with commercializing any approved product candidate. Even if we are able to generate revenues from the sale of any future approved products, we may not become profitable and may need to obtain additional funding to continue operations.

We have a limited operating history that may make it difficult to predict our future performance or evaluate our business and prospects.

We were incorporated in 2005. Since inception, our operations have been primarily limited to organizing and staffing our company, developing our technology and undertaking pharmaceutical development and clinical trials for our product candidates, understanding the market potential for our product candidates and preparing for the potential commercialization of ARX-04 and Zalviso in the United States. We have not yet obtained regulatory approval of any of our product candidates in the United States. Consequently, any predictions that are made about our future success, or viability, or evaluation of our business and prospects, may not be accurate.

We will require additional capital and may be unable to raise capital, which would force us to delay, reduce or eliminate our product development programs and could cause us to cease operations.

Developing pharmaceutical products, including conducting preclinical studies and clinical trials, is expensive. We expect to incur significant expenditures in connection with our ongoing activities, including conducting ARX-04 Phase 3 clinical trials, development activities associated with ARX-04, including regulatory costs in support of the potential NDA submission, and the remaining development activities associated with Zalviso, to respond to issues raised by the FDA. While we believe we have sufficient capital resources to continue planned operations through at least the first half of 2017, we may need additional capital to continue development and commercialization of ARX-04, and Zalviso will need additional capital to potentially pursue commercialization of any of our product candidates.

Future events and circumstances, including those beyond our control, may cause us to consume capital more rapidly than we currently anticipate. For example, in March 2015, we received correspondence from the FDA stating that we needed to complete an additional clinical trial of Zalviso. Any further development activities can be time consuming and costly. We submitted a protocol to the FDA for a clinical study in post-operative patients designed to evaluate the effectiveness of changes made to enhance Zalviso device performance. We received comments from the FDA on the protocol for the study, known as IAP312, and we plan to initiate IAP312 in the first quarter of 2016. Clinical trials, regulatory reviews, and a potential launch of a commercial product are expensive activities. In addition, commercialization costs for ARX-04 and Zalviso in the United States may be significantly higher than estimated. We may experience technical difficulties in our commercialization efforts or otherwise, which could substantially increase the costs of commercialization. Revenues may be lower than expected and accordingly costs to produce such revenues may exceed those revenues. We will need to seek additional capital to continue operations. Such capital demands could be substantial. To raise capital, we may seek to sell additional equity or debt securities, monetize or securitize certain assets including future royalty streams and milestones, obtain a credit facility, or enter into product development, license or distribution agreements with third parties, or divest one or more of our product candidates. Such arrangements may not be available on favorable terms, if at all. Furthermore, any product development, licensing, distribution or sale agreements that we enter into may require us to relinquish valuable rights. We may not be able to obtain sufficient additional funding or enter into a strategic transaction in a timely manner. If adequate funds are not available, we would be required to reduce our workforce, delay, reduce the scope of, or eliminate, one or more of our research and development programs in advance of the date on which we exhaust our cash resources to ensure that we have sufficient capital to meet our obligations and continue on a path designed to preserve stockholder value.

Securing additional financing may divert our management from our day-to-day activities, which may adversely affect our ability to develop and commercialize our product candidates. In addition, we cannot guarantee that future financing will be available in sufficient amounts or on terms acceptable to us, if at all. If we are unable to raise additional capital when required or on acceptable terms, we may be required to:

- significantly delay, scale back or discontinue the development or commercialization of our product candidates;

- seek additional corporate partners for Zalviso on terms that might be less favorable than might otherwise be available; or

- relinquish, or license on unfavorable terms, our rights to technologies or product candidates that we otherwise would seek to develop or commercialize ourselves.

We may sell additional equity or debt securities to fund our operations, which may result in dilution to our stockholders and impose restrictions on our business.

In order to raise additional funds to support our operations, we may sell additional equity or debt securities which would result in dilution to our stockholders or impose restrictive covenants that may adversely impact our business. The sale of additional equity or convertible debt securities would result in the issuance of additional shares of our capital stock and dilution to all of our stockholders. The incurrence of indebtedness would result in increased fixed payment obligations and could also result in certain restrictive covenants, such as limitations on our ability to incur additional debt, limitations on our ability to acquire, sell or license intellectual property rights and other operating restrictions, such as minimum cash balances, that could adversely impact our ability to conduct our business. If we are unable to expand our operations or otherwise capitalize on our business opportunities, our business, financial condition and results of operations could be materially adversely affected and we may not be able to meet our debt service obligations.

We might be unable to service our existing debt due to a lack of cash flow and might be subject to default.

In December 2013, we entered into an amended loan and security agreement, or the Amended Loan Agreement, with Hercules Technology II, L.P. and Hercules Technology Growth Capital, Inc., collectively referred to as Hercules, under which we could have borrowed up to $40.0 million in three tranches, represented by secured convertible promissory notes. We drew the first tranche of $15.0 million at the closing of the new credit facility and the second tranche of $10.0 million on June 16, 2014. We did not have access to the third tranche of up to $15.0 million, as it was conditioned upon FDA approval to market Zalviso in the United States by August 1, 2015, which we did not obtain. We began making principal payments in April 2015. On September 18, 2015, we amended the Amended Loan Agreement with Hercules to extend an interest only period from October 1, 2015 through March 31, 2016, with the potential for further extension to September 30, 2016 upon satisfaction of certain conditions, which have since been satisfied. The scheduled maturity date is October 31, 2017.

We granted Hercules a first priority security interest in substantially all of our assets, with the exception of our intellectual property and those assets sold under the Royalty Monetization, where the security interest is limited to proceeds of intellectual property if it is licensed or sold.

If we do not make the required payments when due, either at maturity, or at applicable installment payment dates, or if we breach the agreement or become insolvent, Hercules could elect to declare all amounts outstanding, together with accrued and unpaid interest and penalty, to be immediately due and payable. Additional capital may not be available on terms acceptable to us, or at all. In addition, we recently sold a portion of the royalties and first four commercial sales milestone payments we are entitled to receive under the Amended Agreements with Grünenthal to PDL, which will decrease future cash flows available to us to repay the Hercules debt. Even if we were able to repay the full amount in cash, any such repayment could leave us with little or no working capital for our business. If we are unable to repay those amounts, Hercules will have a first claim on our assets pledged under the Amended Loan Agreement. If Hercules should attempt to foreclose on the collateral, it is unlikely that there would be any assets remaining after repayment in full of such secured indebtedness. Any default under the Amended Loan Agreement and resulting foreclosure would have a material adverse effect on our financial condition and our ability to continue our operations.

We may not receive all of the funding from the Department of Defense for the advancement of ARX-04.

On May 11, 2015, we entered into an award contract supported by the United States Army Medical Research and Materiel Command, or USAMRMC, within the U.S. Department of Defense, or the DoD, in which the DoD agreed to provide up to $17.0 million to support the development of ARX-04, referred to as the DoD Contract. Under the terms of the contract, the DoD will reimburse us for costs incurred for development, manufacturing, regulatory and clinical costs outlined in the contract in order to submit an NDA to the FDA, including reimbursement for certain personnel and overhead expenses. The period of performance under the contract began on May 11, 2015. The contract gives the DoD the option to extend the term of the contract and provide additional funding for the research. On March 2, 2016,

the DoD Contract was amended to approve enrollment of additional patients in the SAP302 study, approve the addition of the SAP303 study, and extend the contract period of performance by four months from November 10, 2016 to March 9, 2017, to accommodate the increased SAP302 patient enrollment and the SAP303 study. The costs for these changes will be absorbed within the current contract value. Funding under this contract will be subject to audit by the DoD to ensure adherence to specific guidance, policies and procedures. The DoD may find deficiencies during the course of an audit which could jeopardize, or even eliminate, continued funding from the DoD, as well as require repayment of any funds they had provided us since inception of the contract. The lack of ARX-04 supportive funding, may adversely affect our ability to continue to advance the development of ARX-04.

Risks Related to Our Reliance on Third Parties

We rely on third party manufacturers to produce our preclinical and clinical drug supplies and intend to rely on third parties to produce commercial supplies of any approved product candidates.

Reliance on third party manufacturers entails many risks including:

- the inability to meet our product specifications and quality requirements consistently;
- a delay or inability to procure or expand sufficient manufacturing capacity;
- manufacturing and product quality issues related to scale-up of manufacturing;
- costs and validation of new equipment and facilities required for scale-up;
- a failure to maintain in good order our production and manufacturing equipment for our products;
- a failure to comply with cGMP and similar foreign standards;
- the inability to negotiate manufacturing agreements with third parties under commercially reasonable terms;
- termination or nonrenewal of manufacturing agreements with third parties in a manner or at a time that is costly or damaging to us;
- the reliance on a limited number of sources, and in some cases, single sources for product components, such that if we are unable to secure a sufficient supply of these product components, we will be unable to manufacture and sell

our product candidates in a timely fashion, in sufficient quantities or under acceptable terms;

- the lack of qualified backup suppliers for those components that are currently purchased from a sole or single source supplier;

- operations of our third party manufacturers or suppliers could be disrupted by conditions unrelated to our business or operations, including the bankruptcy of the manufacturer or supplier;

- carrier disruptions or increased costs that are beyond our control; and

- the failure to deliver our products under specified storage conditions and in a timely manner.

Any of these events could lead to stock outs, inability to successfully commercialize our products, clinical trial delays, or failure to obtain regulatory approval. Some of these events could be the basis for FDA action, including injunction, recall, seizure, or total or partial suspension of production.

As mentioned above, we have entered into the Amended Agreements with Grünenthal under which we are obligated to manufacture and supply Zalviso for use in the EU and their other licensed territories. If we are unable to establish a reliable commercial supply of Zalviso for Grünenthal's Territory, we may be unable to satisfy our obligations under the Amended Agreements in a timely manner or at all, and we may, as a result, be in breach of the Amended Agreements.

We rely on limited sources of supply for the drug component of our product candidates and any disruption in the chain of supply may cause delay in developing and commercializing our product candidates.

Currently, we use two established suppliers of sufentanil citrate for our tablets. We only have one supplier qualified for our manufacture of Zalviso. For each product candidate, only one of the two suppliers will be qualified as a vendor with the FDA. If supply from the approved vendor is interrupted, there could be a significant disruption in commercial supply. The alternative vendor would need to be qualified through an NDA supplement which could result in further delay. The FDA or other regulatory agencies outside of the United States may also require additional trials if a new sufentanil supplier is relied upon for commercial production.

Manufacture of sufentanil sublingual tablets requires specialized equipment and expertise.

Ethanol, which is used in the manufacturing process for our sufentanil sublingual tablets, is flammable, and sufentanil is a highly potent, Schedule II compound. These factors necessitate the use of specialized equipment and facilities for manufacture of sufentanil sublingual tablets. There are a limited number of facilities that can accommodate our manufacturing process and we need to use dedicated equipment throughout development and commercial manufacturing to avoid the possibility of cross-contamination. If our equipment breaks down or needs to be repaired or replaced, it may cause significant disruption in clinical or commercial supply, which could result in delay in the

process of obtaining approval for or sale of our products. Furthermore, we are using one manufacturer to produce our sufentanil sublingual tablets and have not identified a back-up commercial facility to date. Any problems with our existing facility or equipment, including ongoing expansion, may delay or impair our ability to complete our clinical trials or commercialize our product candidates and increase our cost.

Manufacturing issues may arise that could delay or increase costs related to product and regulatory approval, and commercialization.

As we scale up manufacturing of our product candidates and conduct required stability testing, product, packaging, equipment and process-related issues may require refinement or resolution in order to obtain regulatory approval for commercial marketing. In the past we have identified impurities in our product candidates. In the future we may identify significant impurities, which could result in increased scrutiny by the regulatory agencies, delays in clinical program and regulatory approval, increases in our operating expenses, or failure to obtain or maintain approval for our products.

Early development and clinical trial manufacturing of Zalviso was conducted at Patheon in Toronto, Canada. Because the DEA requires that sufentanil be manufactured in the United States if our product candidates are marketed in the United States, we transferred our manufacturing capability in the third quarter of 2011 from Patheon in Toronto, Canada to Patheon's production facility in Cincinnati, Ohio, where we have built out a suite within their existing buildings that will serve as a manufacturing facility for clinical and commercial supplies of sufentanil sublingual tablets. Late stage development and manufacture of registration stability lots, which were utilized in clinical trials, were manufactured at Patheon, Cincinnati. While we have successfully manufactured validation lots, we have not yet produced commercial supplies at this facility and we may encounter difficulties in production at the new facility, which may adversely affect our clinical and commercial plans and our ability to deliver product to Grünenthal.

In January 2013, we entered into a Manufacturing Services Agreement, or the Services Agreement, with Patheon under which Patheon has agreed to manufacture, supply, and provide certain validation and stability services with respect to Zalviso for potential sales in the United States, Canada, Mexico and other countries, subject to agreement by the parties to any additional fees for such other countries. There is no guarantee that Patheon's services will be satisfactory or that they will continue to meet the strict regulatory guidelines of the FDA or other foreign regulatory agencies. In addition, in January 2013, we entered into an Amended and Restated Capital Expenditure and Equipment Agreement, or the Amended Capital Agreement, with Patheon, relating to the manufacture of sufentanil sublingual tablets. Under the terms of the Amended Capital Agreement, we have made and may make certain future modifications to Patheon's Cincinnati facility.

If Patheon cannot provide us with an adequate supply of sufentanil sublingual tablets, we may be required to pursue alternative sources of manufacturing capacity. Switching or adding commercial manufacturing capability can involve substantial cost and require extensive management time and focus, as well as additional regulatory filings which may result in significant delays. In addition, there is a natural transition period when a new manufacturing facility commences work. As a result, delays may occur, which can materially impact our ability to meet our desired commercial timelines, thereby increasing our costs and reducing our ability to generate revenue.

The facilities of any of our future manufacturers of sufentanil-containing sublingual tablets must be approved by the FDA or the relevant foreign regulatory agency, such as EMA, before commercial distribution from such manufacturers occurs. We do not fully control the manufacturing process of sufentanil sublingual tablets and are completely dependent on these third party manufacturing partners for compliance with the FDA or other foreign regulatory agency's requirements for manufacture. In addition, although our third party manufacturers are well-established commercial manufacturers, we are dependent on their continued adherence to cGMP manufacturing and acceptable changes to their process. If our manufacturers do not meet the FDA or other foreign regulatory agency's strict regulatory requirements, they will not be able to secure FDA or other foreign regulatory agency approval for their manufacturing facilities. Although European inspectors have approved our tablet manufacturing site, our third party manufacturing partner is responsible for maintaining compliance with the relevant foreign regulatory agency's requirements. If the FDA or the relevant foreign regulatory agency does not approve these facilities for the commercial manufacture of sufentanil sublingual tablets, we will need to find alternative suppliers, which would result in significant delays in obtaining FDA or other foreign regulatory agency approval for ARX-04 and Zalviso outside the EU. These challenges may have a material adverse impact on our business, results of operations, financial condition and prospects.

Related to the Zalviso device, we have conducted multiple Design Validation, Software Verification and Validation, Reprocessing and Human Factors studies, and have manufactured for and completed Phase 3 clinical trials using the intended commercial device. As mentioned above, the CRL from the FDA contains a request for additional information on the Zalviso System to ensure proper use of the device. In March 2015, we received correspondence from the FDA stating that in addition to the bench testing and two Human Factors studies we had performed in response to the issues identified in the CRL, a clinical trial is needed to assess the risk of inadvertent dispensing and overall risk of dispensing failures. We have made modifications to the design of the Zalviso device subsequent to the original submission of the Zalviso NDA, which we plan to include as a part of any resubmitted NDA. In early September 2015, we met with the FDA to discuss their request for an additional clinical trial and our planned response to the CRL. In the Type C meeting minutes, the FDA provided some additional details about the type of clinical data they would like us to provide, as a complement to the other data we already have provided, to assess the overall performance of Zalviso. We submitted a protocol to the FDA for a clinical study in post-operative patients designed to evaluate the effectiveness of changes made to enhance Zalviso device performance. We received comments from the FDA on the protocol for the study, known as IAP312, and plan to initiate IAP312 in the first quarter of 2016. Furthermore, if any additional changes to the device are substantial, the FDA may require us to perform further clinical trials or studies in order to approve the device for commercial use.

We have manufactured Zalviso devices and supplies on a small scale, including those needed for our Phase 3 clinical trials, and process validation for some of the device components has been completed. We, however, have not yet

manufactured Zalviso devices and supplies on a large scale, for commercial purposes. We are completing the process validation for the device components and beginning to manufacture Zalviso devices and supplies for delivery to Grünenthal. We will continue to rely on contract manufacturers, component fabricators and third party service providers to produce the necessary Zalviso devices for the commercial marketplace. We currently outsource manufacturing and packaging of the controller, dispenser and cartridge components of the Zalviso device to third parties and intend to continue to do so. Some of these purchases and components were made and will continue to be made utilizing short-term purchase agreements and we may not be able to enter into long-term agreements for commercial supply of ARX-04 or Zalviso devices with third-party manufacturers, or may be unable to do so on acceptable terms. In addition, we have encountered and may continue to encounter production issues with our current or future contract manufacturers and other third party service providers, including the reliability of the production equipment, quality of the components produced, their inability to meet demand or other unanticipated delays including the scale-up and automation process, which would adversely impact our ability to supply our customers with ARX-04, if approved, and Zalviso, in the EU, and if approved, in the U.S. and any other foreign territories.

We may not be able to establish additional sources of supply for sufentanil-containing sublingual tablets or device manufacture. Such suppliers are subject to FDA and other foreign regulatory agency's regulations requiring that materials be produced under cGMPs or Quality System Regulations, or QSR, or in ISO 13485 accredited manufacturers, and subject to ongoing inspections by regulatory agencies. Failure by any of our suppliers to comply with applicable regulations may result in delays and interruptions to our product candidate supply while we seek to secure another supplier that meets all regulatory requirements. In addition, if we are unable to establish a reliable commercial supply of Zalviso for Grünenthal's Territory, we may be unable to satisfy our obligations under the Amended Agreements in a timely manner or at all, and we may, as a result, be in breach of the Amended Agreements.

For ARX-04, we currently package the finished goods under a manual process at the Patheon facility. The capacity and cost to package the ARX-04 units under this manual process is not sufficient to support successful future sales of ARX-04. We will need to purchase, install and validate new equipment and processes to automate the ARX-04 manufacturing process. The purchase and subsequent installation of this equipment to automate the ARX-04 packaging process will require substantial resources and take several years. There is no assurance that we will be able to successfully purchase, install or validate the equipment necessary to automate the ARX-04 packaging process. If we are successful in the purchase, installation and validation of this equipment and process, there can be no assurance that we will be able to obtain the necessary regulatory approvals to manufacture product.

Reliance on third party manufacturers entails risks to which we would not be subject if we manufactured the product candidates ourselves, including the possible breach of the manufacturing agreements by the third parties because of factors beyond our control; and the possibility of termination or nonrenewal of the agreements by the third parties because of our breach of the manufacturing agreement or based on their own business priorities.

We rely on third parties to conduct, supervise and monitor our clinical trials, and if those third parties perform in an unsatisfactory manner, it may harm our business.

We utilized contract research organizations, or CROs, for the conduct of our Phase 3 clinical trials of Zalviso, the Phase 2 clinical trial of ARX-04, and our ongoing Phase 3 clinical program for ARX-04. We rely on CROs, as well as clinical trial sites, to ensure the proper and timely conduct of our clinical trials and document preparation. While we have agreements governing their activities, we have limited influence over their actual performance. We have relied and plan to continue to rely upon CROs to monitor and manage data for our clinical programs for ARX-04, Zalviso, and our other product candidates, as well as the execution of nonclinical and clinical trials. We control only certain aspects of our CROs' activities. Nevertheless, we are responsible for ensuring that each of our trials is conducted in accordance with the applicable protocol, legal, regulatory and scientific standards and our reliance on the CROs does not relieve us of our regulatory responsibilities.

We, and our CROs, are required to comply with the FDA's current good clinical practices, or cGCPs, which are regulations and guidelines enforced by the FDA for all of our product candidates in clinical development. The FDA enforces these cGCPs through periodic inspections of trial sponsors, principal investigators and clinical trial sites. If we or our CROs fail to comply with applicable cGCPs, the clinical data generated in our clinical trials may be deemed unreliable and the FDA may require us to perform additional clinical trials before approving our marketing applications. Upon inspection, the FDA may determine that our clinical trials do not comply with cGCPs. Accordingly, if our CROs or clinical trial sites fail to comply with these regulations, we may be required to repeat clinical trials, which would delay the regulatory process.

Our CROs are not our employees, and we cannot control whether or not they devote sufficient time and resources to our ongoing clinical and nonclinical programs. These CROs may also have relationships with other commercial

entities, including our competitors, for whom they may also be conducting clinical trials, or other drug development activities which could harm our competitive position. We face the risk of potential unauthorized disclosure or misappropriation of our intellectual property by CROs, which may allow our potential competitors to access our proprietary technology. If our CROs do not successfully carry out their contractual duties or obligations, fail to meet expected deadlines, or if the quality or accuracy of the clinical data they obtain is compromised due to the failure to adhere to our clinical protocols or regulatory requirements, or for any other reasons, our clinical trials may be extended, delayed or terminated, and we may not be able to obtain regulatory approval for, or successfully commercialize ARX-04 and Zalviso, or our other product candidates. As a result, our financial results and the commercial prospects for ARX-04, Zalviso or any future product candidates for which we may obtain approval would be harmed, our costs could increase, and our ability to generate revenues could be delayed.

Risks Related to Commercialization of Our Product Candidates

The commercial success of ARX-04, and Zalviso outside the EU, if approved, as well as Zalviso in the EU, will depend upon the acceptance of these products by the medical community, including physicians, nurses, patients, and pharmacy and therapeutics committees.

The degree of market acceptance of ARX-04, and Zalviso outside the EU, if approved, as well as Zalviso in the EU, will depend on a number of factors, including:

- demonstration of clinical safety and efficacy compared to other products;
- the relative convenience, ease of administration and acceptance by physicians, patients and health care payors;

- the use of ARX-04 for the management of moderate-to-severe acute pain by a healthcare professional for patient types that were not specifically studied in our Phase 3 trials;

- the use of Zalviso for the management of moderate-to-severe acute pain in the hospital setting for patient types that were not specifically studied in our Phase 3 trials;

- the prevalence and severity of any AEs or SAEs;

- overcoming the perception of sufentanil as a potentially unsafe drug due to its high potency;

- limitations or warnings contained in the FDA-approved label for ARX-04 or Zalviso;

- restrictions or limitations placed on ARX-04 or Zalviso due to the REMS;

- availability of alternative treatments;

- existing capital investment by hospitals in IV PCA technology;

- pricing and cost-effectiveness;

- the effectiveness of our or any future collaborators' sales and marketing strategies;

- our ability to obtain formulary approval; and

- our ability to obtain and maintain sufficient third party coverage or reimbursement.

If our product candidates are approved, but do not achieve an adequate level of acceptance by physicians, nurses, patients and pharmacy and therapeutics committees, or P&T Committees, we may not generate sufficient revenue and we may not become or remain profitable.

If we are unable to establish sales and marketing capabilities or enter into agreements with third parties to market and sell our product candidates, we may be unable to generate any revenue.

In order to commercialize any products that may be approved in the United States, including ARX-04 and Zalviso, we must build our internal sales, marketing, distribution, managerial and other capabilities or make arrangements with third parties to perform these services. In addition, we plan to enter into agreements with third parties for the distribution of approved product candidates, including ARX-04 and Zalviso; however, if there are delays in establishing such relationships or those third parties do not perform as expected, our ability to effectively distribute products would suffer.

As a result of delays in the resubmission of the Zalviso NDA and obtaining FDA approval, our Board of Directors implemented a cost reduction plan that reduced our workforce by 19 employees, approximately 36% of total headcount, in the first quarter of 2015. As a result, the build out of our commercial capabilities, including internal sales, marketing, supply chain and medical affairs departments is currently on hold. This delay in recruiting and hiring the appropriate individuals could adversely affect the potential success of any future approved product candidates, including ARX-04 and Zalviso in the United States.

We have entered into a collaboration with Grünenthal for the commercialization of Zalviso in Europe and Australia and intend to enter into additional strategic partnerships with third parties to commercialize our product candidates outside of the United States. We may also consider the option to enter into strategic partnerships for our product candidates in the United States. We face significant competition in seeking appropriate strategic partners, and these strategic partnerships can be intricate and time consuming to negotiate and document.

We may not be able to negotiate future strategic partnerships on acceptable terms, or at all. We are unable to predict when, if ever, we will enter into any strategic partnerships because of the numerous risks and uncertainties associated with establishing strategic partnerships. Our current or future collaboration partners, if any, may not dedicate sufficient resources to the commercialization of Zalviso or our other product candidates, if approved, or may otherwise fail in their commercialization due to factors beyond our control. If we are unable to establish effective collaborations to enable the sale of our product candidates, if approved, to healthcare professionals and in geographical regions, including the United States, that will not be covered by our own marketing and sales force, or if our potential future collaboration partners do not successfully commercialize our product candidates, if approved, our ability to generate revenues from product sales will be adversely affected.

If we are unable to establish adequate sales, marketing and distribution capabilities, whether independently or with third parties, we may not be able to generate sufficient product revenue and may not become profitable. We will be competing with many companies that currently have extensive and well-funded marketing and sales operations. Without an internal team or the support of a third party to perform marketing and sales functions, we may be unable to compete successfully against these more established companies.

A key part of our business strategy is to establish collaborative relationships to commercialize and fund development and approval of our product candidates, particularly outside of the United States. We may not succeed in establishing and maintaining collaborative relationships, which may significantly limit our ability to develop and commercialize our products successfully, if at all.

We will need to establish and maintain successful collaborative relationships to obtain international sales, marketing and distribution capabilities for our product candidates. The process of establishing and maintaining collaborative relationships is difficult, time-consuming and involves significant uncertainty, including:

- our partners may seek to renegotiate or terminate their relationships with us due to unsatisfactory clinical or regulatory results, manufacturing issues, a change in business strategy, a change of control or other reasons;
- our contracts for collaborative arrangements are terminable at will on written notice and may otherwise expire or terminate and we may not have alternatives available to achieve the potential for our products in those territories or markets;
- our partners may choose to pursue alternative technologies, including those of our competitors;
- we may have disputes with a partner that could lead to litigation or arbitration;
- we have limited control over the decisions of our partners and they may change the priority of our programs in a manner that would result in termination of the agreement or add significant delays to the partnered program;
- our ability to generate future payments and royalties from our partners depends upon the abilities of our partners to establish the safety and efficacy of our drug candidates, obtain regulatory approvals and our ability to successfully manufacture and achieve market acceptance of products developed from our product candidates;
- we or our partners may fail to properly initiate, maintain or defend our intellectual property rights, where applicable, or a party may use our proprietary information in such a way as to invite litigation that could jeopardize or potentially invalidate our proprietary information or expose us to potential liability;
- our partners may not devote sufficient capital or resources towards our product candidates; and
- our partners may not comply with applicable government regulatory requirements necessary to successfully market and sell our products.

If any collaborator fails to fulfill its responsibilities in a timely manner, or at all, any research, clinical development, manufacturing or commercialization efforts pursuant to that collaboration could be delayed or terminated, or it may be necessary for us to assume responsibility for expenses or activities that would otherwise have been the responsibility of our collaborator. If we are unable to establish and maintain collaborative relationships on acceptable terms or to successfully and timely transition terminated collaborative agreements, we may have to delay or discontinue further development of one or more of our product candidates, undertake development and commercialization activities at our own expense or find alternative sources of capital.

Approval of Zalviso in the EU, and any future approvals of our product candidates outside of the United States, will result in a variety of risks associated with international operations and could materially adversely affect our business.

Our existing collaboration with Grünenthal for marketing Zalviso in European countries and Australia requires us to supply product to support the EU commercialization of Zalviso. In addition, if any of our currently unapproved product candidates are approved for commercialization outside the United States, we intend to enter into agreements with third parties to market our product candidates in those countries, which may also require us to supply products to the third party. We may be subject to additional risks related to entering into international business relationships, including:

- different regulatory requirements for drug approvals in foreign countries;
- reduced protection for intellectual property rights;
- unexpected changes in tariffs, trade barriers and regulatory requirements;
- economic weakness, including inflation, or political instability in particular foreign economies and markets;
- compliance with tax, employment, immigration and labor laws for employees living or traveling abroad;
- foreign taxes, including withholding of payroll taxes;
- foreign currency fluctuations, which could result in increased operating expenses and reduced revenues, and other obligations incident to doing business in another country;
- workforce uncertainty in countries where labor unrest is more common than in the United States;

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- production shortages resulting from any events affecting raw material supply or manufacturing capabilities abroad; and

- business interruptions resulting from geopolitical actions, including war and terrorism, or natural disasters including earthquakes, typhoons, floods and fires.

If we, or current and potential partners, are unable to compete effectively, our product candidates may not reach their commercial potential.

The U.S. market for ARX-04, Zalviso, and our other product candidates is characterized by intense competition and cost pressure. If our product candidates obtain FDA approval, they will compete with a number of existing and future pharmaceuticals and drug delivery devices developed, manufactured and marketed by others. We or our current and potential partners will compete against fully integrated pharmaceutical companies and smaller companies that are collaborating with larger pharmaceutical companies.

There are a wide variety of approved injectable and oral opioid products to treat moderate-to-severe acute pain, including IV opioids such as morphine, fentanyl, hydromorphone and meperidine or oral opioids such as oxycodone and hydrocodone. More specifically, competitors for ARX-04 in the emergency department are likely to include generic injectable intravenous opioids such as morphine, hydromorphone and fentanyl. In this environment, ARX-04 may also compete with other branded non-invasive products or product candidates, such as Egalet Corporation's SPRIX, Hospira, Inc.'s DYLOJECT (Hospira, Inc. acquired by Pfizer, Inc. in September 2015), Acura Pharmaceuticals, Inc.'s OXAYDO, Depomed, Inc.'s NUCYNTA, Bristol-Myers Squibb Company's COMBUNOX, Purdue Pharma, L.P.'s OXYFAST, Endo Pharmaceuticals, Inc.'s OPANA, Medical Developments International Limited's PENTHROX (methoxyflurane) inhaler, CL-108, a bi-layered tablet, in development by Charleston Laboratories Inc., in collaboration with Daiichi Sankyo, or generic oral opioids which have moderate-to-severe acute pain labeling. In the short-stay or ambulatory surgery segment, ARX-04 will likely compete with these products in addition to generic injectable local anesthetics such as bupivacaine, or branded formulations thereof, including Pacira Pharmaceuticals, Inc.'s EXPAREL. Within the military environment, and in certain civilian settings, ARX-04 competitors may also include intramuscular morphine injections which are marketed by a variety of generic manufacturers.

We believe that Zalviso would compete with a number of opioid-based and non-opioid based treatment options that are currently available, as well as some products that are in development. The hospital market for opioids for moderate-to-severe acute pain is large and competitive. The primary competition for Zalviso is the IV PCA pump, which is widely used in the moderate-to-severe acute pain in the hospital setting. Leading manufacturers of IV PCA pumps include Hospira, Inc. (acquired by Pfizer, Inc.), CareFusion Corporation (purchased by Becton, Dickinson and Company), Baxter International, Inc., Curlin Medical, Inc. and Smiths Medical. The most common opioids used to treat moderate-to-severe acute pain are morphine, hydromorphone and fentanyl, all of which are available as generics both from generic product manufacturers as well as from compounding pharmacies. In addition, branded manufacturers (e.g., Hospira, Inc.) sell pre-filled glass syringes of morphine to fit their IV PCA pump systems.

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Also available on the market is the Avancen Medication on Demand, or MOD, Oral PCA Device developed by Avancen MOD Corporation. Oral opioids and other agents can be used in this system. In addition, oral and parenteral opioids administered by the nurse are used to manage moderate-to-severe acute pain in the hospital, available both as branded and generic products. These oral opioids, as well as IV PCA opioids, are often used as part of a multi-modal analgesia approach, which might include, in addition to the opioid, NSAIDs, acetaminophen, gabapentanoids and other pain management modalities, as well as local anesthetic blocks to provide temporary blockage of the pain signal, either as a wound infiltration agent or as a nerve block. These local anesthetic agents such as bupivacaine can also utilize controlled-release formulations such as Pacira Pharmaceuticals, Inc.'s EXPAREL. In addition, Halyard Health, Inc. has developed a medical device, the ON-Q* Pain Relief System, which is a non-narcotic elastomeric pump that automatically and continuously delivers a regulated flow of local anesthetic to a patient's surgical site or in close proximity to nerves, providing targeted pain relief for up to five days.

Additional potential competitors for Zalviso include the fentanyl iontophoretic transdermal system, IONSYS, originally developed by Alza Corporation and Ortho-McNeil Pharmaceutical, Inc., both Johnson & Johnson subsidiaries, and most recently by The Medicines Company. On April 30, 2015, IONSYS was approved for marketing in the U.S. by the FDA, providing a potential first-to-market advantage for IONSYS. Cara Therapeutics, Inc. is developing a kappa opioid agonist, CR845, as an IV agent for the management of post-operative moderate-to-severe pain. Trevena, Inc. is developing TRV130, an intravenous G protein biased ligand that targets the mu opioid receptor for the treatment of moderate-to-severe acute pain where intravenous therapy is preferred, with a clinical development focus in acute post-operative pain. Trevena, Inc. expects to initiate Phase 3 development of TRV130 in the first quarter of 2016. Recro Pharma, Inc. is developing an intranasal form of dexmedetomidine as a potential agent for the management of post-operative pain, for which it announced positive efficacy results in its Phase II clinical trial. Finally, Innocoll AG is developing XARACOLL a controlled-release resorbable implant containing bupivacaine, and Durect Corporation has been developing POSIDUR, a controlled-release bupivacaine product candidate utilizing Durect Corporation's Saber technology.

It is possible that any of these competitors could develop or improve technologies or products that would render our product candidates obsolete or non-competitive, which could adversely affect our revenue potential. Key competitive factors affecting the commercial success of our product candidates are likely to be efficacy, safety profile, reliability, convenience of dosing, price and reimbursement.

Many of our potential competitors have substantially greater financial, technical and human resources than we do and significantly greater experience in the discovery and development of drug candidates, obtaining FDA and other regulatory approval of products and the commercialization of those products. Accordingly, our competitors may be more successful than we are in obtaining FDA approval for drugs and achieving widespread market acceptance. Our competitors' drugs or drug delivery systems may be more effective, have fewer adverse effects, be less expensive to develop and manufacture, or be more effectively marketed and sold than any product candidate we may commercialize. This may render our product candidates obsolete or non-competitive before we can recover our losses. We anticipate that we will face intense and increasing competition as new drugs enter the market and additional technologies become available. These entities may also establish collaborative or licensing relationships with our competitors, which may adversely affect our competitive position. Finally, the development of different methods for the treatment of moderate-to-severe acute pain (ARX-04 and Zalviso) could render our products non-competitive or

obsolete. These and other risks may materially adversely affect our ability to attain or sustain profitable operations.

Formulary approval may not be available, or could be subject to certain restrictions for ARX-04 or Zalviso in the United States and our other product candidates, which could make it difficult for us to sell our products profitably.

Obtaining formulary approval can be an expensive and time-consuming process. We cannot be certain if and when we will obtain formulary approval to allow us to sell our products into our target markets. Failure to obtain timely formulary approval will limit our commercial success. If we are successful in obtaining formulary approval, we may need to complete evaluation programs whereby ARX-04 or Zalviso is used on a limited basis for certain patient types. Hospitals may seek to obtain ARX-04 or Zalviso devices at little or no cost during this evaluation period. Revenue generated from these hospitals during the evaluation period would be minimal. The evaluation period may last several months and there can be no assurance that use during the evaluation period will lead to formulary approval of ARX-04 or Zalviso. Further, even successful formulary approval may be subject to certain restrictions based on patient type or hospital protocol. Failure to obtain timely formulary approval for ARX-04 and/or Zalviso would materially adversely affect our ability to attain or sustain profitable operations.

Coverage and adequate reimbursement may not be available for ARX-04 or Zalviso, if approved in the United States, or ARX-04 in the EU, if approved, or Zalviso in the EU, which could make it difficult for us, or our partners, to sell our products profitably.

Our ability to commercialize ARX-04 or Zalviso, if approved in the United States, or ARX-04 in the EU, if approved, or Zalviso in the EU successfully will depend, in part, on the extent to which coverage and adequate reimbursement will be available from government payor programs at the federal and state levels, authorities, including Medicare and Medicaid, private health insurers, managed care plans and other third-party payors.

No uniform policy requirement for coverage and reimbursement for drug products exists among third-party payors in the United States or the EU. Therefore, coverage and reimbursement can differ significantly from payor to payor. As a result, the coverage determination process is often a time-consuming and costly process that will require us to provide scientific and clinical support for the use of our products to each payor separately, with no assurance that coverage and adequate reimbursement will be applied consistently or obtained in the first instance. Our inability to promptly obtain coverage and adequate reimbursement rates from third party payors could significantly harm our operating results, our ability to raise capital needed to commercialize any future approved drugs and our overall financial condition.

A primary trend in the U.S. healthcare industry and elsewhere is cost containment. Government authorities and other third-party payors have attempted to control costs by limiting coverage and the amount of reimbursement for particular medical products. There have been a number of legislative and regulatory proposals to change the healthcare system in the United States and in some foreign jurisdictions that could affect our ability to sell our products profitably. These legislative and/or regulatory changes may negatively impact the reimbursement for our products, following approval. The availability of numerous generic pain medications may also substantially reduce the likelihood of reimbursement for ARX-04, Zalviso or any of our other product candidates, if approved in the United States, and ARX-04 or any of our other product candidates, if approved outside the United States, as well as Zalviso in the EU and elsewhere. The application of user fees to generic drug products may expedite the approval of additional pain medication generic drugs. We expect to experience pricing pressures in connection with the sale of Zalviso in the EU, and ARX-04, Zalviso outside of the EU and any of our other product candidates, if approved, due to the trend toward managed healthcare, the increasing influence of health maintenance organizations and additional legislative changes. If we fail to successfully secure and maintain reimbursement coverage for our products or are significantly delayed in doing so, we will have difficulty achieving market acceptance of our products and our business will be harmed.

Furthermore, market acceptance and sales of our product candidates, if approved, will depend on reimbursement policies and may be affected by future healthcare reform measures. Government authorities and third party payors, such as private health insurers, hospitals and health maintenance organizations, decide which drugs they will pay for and establish reimbursement levels. We cannot be sure that reimbursement will be available for ARX-04, Zalviso, or any of our other product candidates, if approved in the United States or ARX-04, or any of our other product candidates, if approved in the EU, or Zalviso in the EU. Also, reimbursement amounts may reduce the demand for, or the price of, our products. If reimbursement is not available, or is available only to limited levels, we may not be able to successfully commercialize ARX-04, Zalviso, or any of product candidates, if approved in the United States, or ARX-04, or any of our other product candidates, if approved in the EU, or Zalviso in the EU.

Additionally, the regulations that govern marketing approvals, pricing, coverage and reimbursement for new drugs vary widely from country to country. Current and future legislation may significantly change the approval requirements in ways that could involve additional costs and cause delays in obtaining approvals. Some countries require approval of the sale price of a product before it can be marketed. In many countries, the pricing review period begins after marketing or product licensing approval is granted. In some foreign markets, prescription pharmaceutical pricing remains subject to continuing governmental control even after initial approval is granted. As a result, we might obtain marketing approval for a product in a particular country, but then be subject to price regulations that delay commercial launch of the product, possibly for lengthy time periods, and negatively impact the revenues able to be

generated from the sale of the product in that country. For example, although in September 2015 the European Commission approved the MAA for Grünenthal to market Zalviso in the 28 European Union member states as well as for the European Economic Area countries, Norway, Iceland and Liechtenstein, separate pricing and reimbursement approvals may delay or prevent their ability to successfully launch Zalviso. Adverse pricing limitations may hinder our ability to recoup our investment in ARX-04, Zalviso and/or our other drug candidates, even if/when those drug candidates obtain marketing approval.

Furthermore, even after initial price and reimbursement approvals, reductions in prices and changes in reimbursement levels can be triggered by multiple factors, including reference pricing systems and publication of discounts by third party payors or authorities in other countries. In the EU, prices can be reduced further by parallel distribution and parallel trade, i.e. arbitrage between low-priced and high-priced countries. If any of these events occur, Zalviso, and any future approved product candidates would be negatively affected.

The FDA and other regulatory agencies actively enforce the laws and regulations prohibiting the promotion of off-label uses.

If we are found to have improperly promoted off-label uses of our product candidates, including ARX-04 and/or Zalviso, if approved in the United States, we may become subject to significant liability. Such enforcement has become more common in the industry. The FDA and other regulatory agencies strictly regulate the promotional claims that may be made about prescription drug products. In particular, a product may not be promoted for uses that are not approved by the FDA or such other regulatory agencies as reflected in the product's approved labeling. If we receive marketing approval for our product candidates for our proposed indications, physicians may nevertheless use our products for their patients in a manner that is inconsistent with the approved label, if the physicians personally believe in their professional medical judgment it could be used in such manner. However, if the FDA determines that our promotional materials or training constitutes promotion of an off-label use, it could request that we modify our training or promotional materials or subject us to regulatory or enforcement actions, including the issuance of an untitled letter, a warning letter, injunction, seizure, civil fine or criminal penalties. It is also possible that other federal, state or foreign enforcement authorities might take action if they consider our promotional or training materials to constitute promotion of an off-label use, which could result in significant civil, criminal and/or administrative penalties, damages, fines, disgorgement, individual imprisonment, exclusion from government-funded healthcare programs, such as Medicare and Medicaid, contractual damages, reputational harm, increased losses and diminished profits and the curtailment or restructuring of our operations, any of which could adversely affect our ability to operate our business and our financial results. The FDA or other regulatory authorities could also request that we enter into a consent decree or a corporate integrity agreement, or seek a permanent injunction against us under which specified promotional conduct is monitored, changed or curtailed. If we cannot successfully manage the promotion of our product candidates, including ARX-04 and Zalviso in the United States, if approved, we could become subject to significant liability, which would materially adversely affect our business and financial condition.

Guidelines and recommendations published by government agencies can reduce the use of our product candidates, including ARX-04 and Zalviso, if/when approved.

Government agencies promulgate regulations and guidelines applicable to certain drug classes that may include the product candidates that we are developing. Recommendations of government agencies may relate to such matters as usage, dosage, route of administration and use of concomitant therapies. Regulations or guidelines suggesting the reduced use of certain drug classes that may include the product candidates that we are developing or the use of competitive or alternative products as the standard of care to be followed by patients and healthcare providers could result in decreased use of our product candidates, or negatively impact our ability to gain market acceptance and market share.

If we are unable to establish relationships with group purchasing organizations any future revenues or future profitability could be jeopardized.

Many end-users of pharmaceutical products have relationships with group purchasing organizations, or GPOs, whereby such GPOs provide such end-users access to a broad range of pharmaceutical products from multiple suppliers at competitive prices and, in certain cases, exercise considerable influence over the drug purchasing decisions of such end-users. Hospitals and other end-users contract with the GPO of their choice for their purchasing needs. We expect to derive revenue from end-user customers that are members of GPOs, if ARX-04 or Zalviso is approved by the FDA. Establishing and maintaining strong relationships with these GPOs will require us to be a reliable supplier, remain price competitive and comply with FDA regulations. The GPOs with whom we have relationships may have relationships with manufacturers that sell competing products, and such GPOs may earn higher margins from these products or combinations of competing products or may prefer products other than ours for other reasons. If we are unable to establish or maintain our GPO relationships, sales of our products and revenue could be negatively impacted.

We intend to rely on a limited number of pharmaceutical wholesalers to distribute our product candidates, including ARX-04 and Zalviso in the United States, if approved.

We intend to rely primarily upon pharmaceutical wholesalers in connection with the distribution of our product candidates, including ARX-04 and Zalviso in the United States, if approved. If we are unable to establish or maintain our business relationships with these pharmaceutical wholesalers on commercially acceptable terms, it could have a material adverse effect on our sales and may prevent us from achieving profitability.

Risks Related to Our Business Operations and Industry

Failure to receive required quotas of controlled substances or comply with the Drug Enforcement Administration regulations, or the cost of compliance with these regulations, may adversely affect our business.

Our sufentanil-based products are subject to extensive regulation by the DEA, due to their status as scheduled drugs. Sufentanil is a Schedule II opioid, considered to present a high risk of abuse. The manufacture, shipment, storage, sale and use of controlled substances are subject to a high degree of regulation, including security, record-keeping and reporting obligations enforced by the DEA and also by comparable state agencies. This high degree of regulation can result in significant costs in order to comply with the required regulations, which may have an adverse effect on the development and commercialization of our product candidates.

The DEA limits the availability and production of all Schedule II substances, including sufentanil, through a quota system. The DEA requires substantial evidence and documentation of expected legitimate medical and scientific needs before assigning quotas to manufacturers. Our contract manufacturers have applied annually for a quota on our behalf. We will need significantly greater amounts of sufentanil to implement our commercialization plans for Zalviso in the EU, and any of our products that may be approved by the FDA in the future, including ARX-04 and Zalviso. Any delay or refusal by the DEA in establishing the procurement quota or a reduction in our quota for sufentanil or a failure to increase it over time to meet anticipated increases in demand could delay or stop the clinical development of any of our product candidates or the commercial sale of any approved products. This, in turn, could have a material adverse effect on our business, results of operations, financial condition and prospects.

Our relationships with investigators, health care professionals, consultants, commercial partners, third-party payors, hospitals, and other customers are subject to applicable anti-kickback, fraud and abuse and other healthcare laws, which could expose us to penalties.

Healthcare providers, physicians and others play a primary role in the recommendation and prescribing of any products for which we may obtain marketing approval. Our business operations and arrangements with investigators, healthcare professionals, consultants, commercial partners, hospitals, third-party payors and customers may expose us to broadly applicable fraud and abuse and other healthcare laws. These laws may constrain the business or financial arrangements and relationships through which we research, market, sell and distribute the products for which we obtain marketing approval. Restrictions under applicable federal and state healthcare laws, include, but are not limited to, the following:

- the federal healthcare Anti-Kickback Statute prohibits, among other things, persons or entities from knowingly and willfully soliciting, offering, receiving or paying any remuneration (including any kickback, bribe, or rebate), directly or indirectly, overtly or covertly, in cash or in kind, to induce or reward either the referral of an individual for, or the purchase, lease, order or recommendation of, any good, facility, item or service, for which payment may be made, in whole or in part, under federal healthcare programs such as Medicare and Medicaid;

- the federal civil and criminal false claims laws and civil monetary penalties, including civil whistleblower or qui tam actions, which prohibit, among other things, individuals or entities from knowingly presenting, or causing to be presented, to the federal government, claims for payment or approval that are false or fraudulent or from knowingly making a false statement to improperly avoid, decrease or conceal an obligation to pay money to the federal government;

- the federal Health Insurance Portability and Accountability Act of 1996, or HIPAA, which, among other things, imposes criminal liability for knowingly and willfully executing, or attempting to execute, a scheme to defraud any healthcare benefit program or to obtain, by means of false or fraudulent pretenses, representations, or promises, any of the money or property owned by, or under the custody or control of, any healthcare benefit program, regardless of the payor (e.g., public or private) and knowingly or willfully falsifying, concealing, or covering up by any trick or device a material fact or making any materially false statement in connection with the delivery of, or payment for,

healthcare benefits, items or services relating to healthcare matters;

- HIPAA, as amended by the Health Information Technology for Economic and Clinical Health Act, or HITECH, and their implementing regulations, impose certain obligations, including mandatory contractual terms, on covered healthcare providers, health plans and clearinghouses, as well as their respective business associates that perform services for them that involve the use, or disclosure of, individually identifiable health information, with respect to safeguarding the privacy, security and transmission of individually identifiable health information;

- the federal transparency law, enacted as part of the Patient Protection and Affordable Care Act, as amended by the Health Care and Education Reconciliation Act of 2010 (collectively, the Health Care Reform Law), and its implementing regulations, requires certain manufacturers of drugs, devices, biologicals and medical supplies to report to the U.S. Department of Health and Human Services information related to payments and other transfers of value provided to physicians and teaching hospitals, as well as ownership and investment interests held by physicians and their immediate family members;

- analogous state laws that may apply to our business practices, including but not limited to, state laws that require pharmaceutical companies to implement compliance programs and/or comply with the pharmaceutical industry's voluntary compliance guidelines; state laws that impose restrictions on pharmaceutical companies' marketing practices and require manufacturers to track and file reports relating to pricing and marketing information, which requires tracking and reporting gifts, compensation and other remuneration and items of value provided to healthcare professionals and entities; and

- the federal Foreign Corrupt Practices Act of 1977 and other similar anti-bribery laws in other jurisdictions generally prohibit companies and their intermediaries from providing money or anything of value to officials of foreign governments, foreign political parties, or international organizations with the intent to obtain or retain business or seek a business advantage. Recently, there has been a substantial increase in anti-bribery law enforcement activity by U.S. regulators, with more frequent and aggressive investigations and enforcement proceedings by both the Department of Justice and the U.S. Securities and Exchange Commission. A determination that our operations or activities are not, or were not, in compliance with United States or foreign laws or regulations could result in the imposition of substantial fines, interruptions of business, loss of supplier, vendor or other third-party relationships, termination of necessary licenses and permits, and other legal or equitable sanctions. Other internal or government investigations or legal or regulatory proceedings, including lawsuits brought by private litigants, may also follow as a consequence.

Efforts to ensure that our business arrangements with third parties will comply with applicable healthcare laws will involve substantial costs. It is possible that governmental authorities will conclude that our business practices may not comply with current or future statutes, regulations, agency guidance or case law involving applicable fraud and abuse or other healthcare laws. If our operations are found to be in violation of any of these or any other healthcare regulatory laws or any other governmental regulations that may apply to us, we may be subject to significant civil, criminal and administrative penalties, damages, fines, disgorgement, individual imprisonment, exclusion from government funded healthcare programs, such as Medicare and Medicaid, contractual damages, reputational harm, increased losses and diminished profits and the curtailment or restructuring of our operations any of which could adversely affect our ability to operate our business and our financial results. Any action against us for violation of these laws, even if we successfully defend against it, could cause us to incur significant legal expenses or divert our management's attention from the operation of our business.

Business interruptions could delay us in the process of developing our products and could disrupt our sales.

Our headquarters is located in the San Francisco Bay Area, near known earthquake fault zones and is vulnerable to significant damage from earthquakes. We are also vulnerable to other types of natural disasters and other events that could disrupt our operations. We do not carry insurance for earthquakes or other natural disasters and we may not carry sufficient business interruption insurance to compensate us for losses that may occur. Any losses or damages we incur could have a material adverse effect on our business operations.

Our future success depends on our ability to retain key executives and to attract, retain and motivate qualified personnel.

We are highly dependent on principal members of our executive team, the loss of whose services may adversely impact the achievement of our objectives. While we have entered into offer letters with each of our executive officers, any of them could leave our employment at any time, as all of our employees are "at will" employees. Recruiting and retaining other qualified employees for our business, including scientific and technical personnel, will also be critical

to our success. There is currently a shortage of skilled executives in our industry, which is likely to continue. As a result, competition for skilled personnel is intense and the turnover rate can be high. We may not be able to attract and retain personnel on acceptable terms given the competition among numerous pharmaceutical companies for individuals with similar skill sets. In addition, failure to succeed in clinical trials, or delays in the regulatory approval process, may make it more challenging to recruit and retain qualified personnel. The inability to recruit or loss of the services of any executive or key employee might impede the progress of our research, development and commercialization objectives. On November 5, 2014, we announced that the Board of Directors has initiated a search to replace Richard King, our President and Chief Executive Officer. On March 31, 2015, Mr. King's employment with AcelRx terminated. On March 19, 2015, the Board of Directors of AcelRx appointed Howard B. Rosen, a member of AcelRx's Board of Directors, as interim Chief Executive Officer effective April 1, 2015. While Mr. Rosen has agreed to serve as our Chief Executive Officer and principal executive officer on an interim basis, there can be no assurance that a permanent replacement will be found on a timely basis, or at all. Our inability to find a suitable permanent replacement may have a detrimental impact on the organization and impede the progress of our research, development and commercialization objectives, as well as our ability to raise additional capital as needed.

In the future, we will need to expand our organization, and we may experience difficulties in managing this growth, which could disrupt our operations.

As of December 31, 2015, we had 36 full-time employees. On March 19, 2015, our Board of Directors, in connection with our efforts to reduce operating costs, conserve capital, focus the Company's financial and development resources on working with the FDA to seek marketing approval for Zalviso, and continuing development of ARX-04, implemented a cost reduction plan. The cost reduction plan reduced our workforce by 19 employees, approximately 36% of total headcount, in the first quarter of 2015. As our product candidates mature and approach potential commercialization in the United States, we plan to expand our employee base to increase our managerial, sales, marketing, operational, quality, engineering, financial and other resources and to hire more consultants and contractors. Future growth will impose significant additional responsibilities on our management, including the need to identify, recruit, maintain, motivate and integrate additional employees, consultants and contractors. 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. Our expected growth could require significant capital expenditures and may divert financial resources from other projects, such as the development of additional product candidates. If our management is unable to effectively manage our growth, our expenses may increase more than expected, our ability to generate and/or grow revenues could be reduced, and we may not be able to implement our business strategy. Our future financial performance and our ability to commercialize ARX-04, Zalviso and our other product candidates and compete effectively will depend, in part, on our ability to effectively manage any future growth.

We face potential product liability, and, if successful claims are brought against us, we may incur substantial liability.

The use of our product candidates in clinical trials and the sale of any products for which we obtain marketing approval exposes us to the risk of product liability claims. Product liability claims might be brought against us by consumers, health care providers, pharmaceutical companies or others selling or otherwise coming into contact with our products. If we cannot successfully defend against product liability claims, we could incur substantial liability and costs. In addition, regardless of merit or eventual outcome, product liability claims may result in:

- impairment of our business reputation;
- withdrawal of clinical trial participants;
- costs due to related litigation;
- distraction of management's attention from our primary business;
- substantial monetary awards to patients or other claimants;
- the inability to commercialize our product candidates; and
- decreased demand for our product candidates, if approved for commercial sale.

Our current product liability insurance coverage may not be sufficient to reimburse us for any expenses or losses we may suffer. Moreover, insurance coverage is becoming increasingly expensive and in the future we may not be able to maintain insurance coverage at a reasonable cost or in sufficient amounts to protect us against losses due to liability. If and when we obtain marketing approval for our product candidates, we intend to expand our insurance coverage to include the sale of commercial products; however, we may be unable to obtain product liability insurance on commercially reasonable terms or in adequate amounts. For example, with the recent approval of Zalviso in the EU, we have expanded our insurance coverage to include the sale of Zalviso to our commercial partner, Grünenthal. There can be no assurance that such coverage will be adequate to protect us against any future losses due to liability. On occasion, large judgments have been awarded in class action lawsuits based on drugs that had unanticipated adverse effects. A successful product liability claim or series of claims brought against us could cause our stock price to decline and, if judgments exceed our insurance coverage, could adversely affect our results of operations and business.

Our employees, independent contractors, principal investigators, consultants, commercial partners and vendors may engage in misconduct or other improper activities, including non-compliance with regulatory standards and requirements and insider trading.

We are exposed to the risk that our employees, independent contractors, investigators, consultants, commercial partners and vendors may engage in fraudulent conduct or other illegal activity. Misconduct by these parties could include intentional, reckless and/or negligent conduct that violates (1) the laws of the FDA and similar foreign regulatory bodies, including those laws requiring the reporting of true, complete and accurate information to such regulatory bodies; (2) healthcare fraud and abuse laws of the United States and similar foreign fraudulent misconduct laws; and (3) laws requiring the reporting of financial information or data accurately. Specifically, the promotion, sales and marketing of healthcare items and services, as well as certain business arrangements in the healthcare industry are subject to extensive laws designed to prevent misconduct, including fraud, kickbacks, self-dealing and other abusive practices. These laws may restrict or prohibit a wide range of pricing, discounting, marketing, structuring and commission(s), certain customer incentive programs and other business arrangements generally. Activities subject to these laws also involve the improper use of information obtained in the course of patient recruitment for clinical trials. It is not always possible to identify and deter employee and other third-party misconduct. The precautions we take to detect and prevent inappropriate conduct may not be effective in controlling unknown or unmanaged risks or losses or in protecting us from governmental investigations or other actions or lawsuits stemming from a failure to comply with these laws. If any such actions are instituted against us, and we are not successful in defending ourselves, those actions could have a significant impact on our business, including the imposition of civil, criminal and administrative penalties, damages, monetary fines, disgorgement, individual imprisonment, possible exclusion from participation in Medicare, Medicaid and other federal healthcare programs, contractual damages, reputational harm, diminished profits and future earnings, and curtailment of our operations, any of which could adversely affect our ability to operate our business and our results of operations.

Risks Related to Our Intellectual Property

If we cannot defend our issued patents from third party claims or if our pending patent applications fail to issue, our business could be adversely affected.

To protect our proprietary technology, we rely on patents as well as other intellectual property protections including trade secrets, nondisclosure agreements, and confidentiality provisions. As of December 31, 2015, we are the owner of record of 45 issued patents worldwide. These issued patents cover AcelRx's sufentanil sublingual tablet, medication delivery devices, packaging and other platform technology. These issued patents are expected to provide coverage through 2027 – 2031.

In addition, we are pursuing a number of U.S. non-provisional patent applications and foreign national applications directed to our product candidates. The patent applications that we have filed and have not yet been granted may fail to result in issued patents in the United States or in foreign countries. Even if the patents do successfully issue, third parties may challenge the patents.

Our commercial success will depend in part on successfully defending our current patents against third party challenges and expanding our existing patent portfolio to provide additional layers of patent protection, as well as extending patent protection. There can be no assurance that we will be successful in defending our existing and future patents against third party challenges, or that our pending patent applications will result in additional issued patents.

The patent positions of pharmaceutical companies, including us, can be highly uncertain and involve complex and evolving legal and factual questions. No consistent policy regarding the breadth of claims allowed in pharmaceutical patents has emerged to date in the United States. Legal developments may preclude or limit the scope of available patent protection.

There is also no assurance that any patents issued to us will not become the subject of adversarial proceedings such as opposition, inter partes review, post-grant review, reissue, supplemental examination, re-examination or other post-issuance proceedings. For example, an anonymous third party filed an Opposition on October 7, 2015 against European patent EP2182902B1, which claims a dosage form related to ARX-03. Although the Opposition is currently pending, the European Patent Office has neither reviewed nor made any initial comments regarding the validity of the EP2182902B1 patent. There is also no assurance that the respective court or agency in such adversarial proceedings would not make unfavorable decisions, such as reducing the scope of a patent of ours, or determining that a patent of ours is invalid or unenforceable. There is also no assurance that any patents issued to us will provide us with competitive advantages, will not be challenged by any third parties, or that the patents of others will not prevent the commercialization of products incorporating our technology. Furthermore, there can be no guarantee that others will

not independently develop similar products, duplicate any of our products, or design around our patents.

Litigation involving patents, patent applications and other proprietary rights is expensive and time consuming. If we are involved in such litigation, it could cause delays in bringing our product candidates or approved products to market and interfere with our business.

Our commercial success depends in part on not infringing patents and proprietary rights of third parties. Although we are not currently aware of litigation or other proceedings or third party claims of intellectual property infringement related to our product candidates, the pharmaceutical industry is characterized by extensive litigation regarding patents and other intellectual property rights.

As we enter our target markets, it is possible that competitors or other third parties will claim that our products and/or processes infringe their intellectual property rights. These third parties may have obtained and may in the future obtain patents covering products or processes that are similar to, or may include compositions or methods that encompass our technology, allowing them to claim that the use of our technologies infringes these patents.

In a patent infringement claim against us, we may assert, as a defense, that we do not infringe the relevant patent claims, that the patent is invalid or both. The strength of our defenses will depend on the patents asserted, the interpretation of these patents, and our ability to invalidate the asserted patents. However, we could be unsuccessful in advancing non-infringement and/or invalidity arguments in our defense. In the United States, issued patents enjoy a presumption of validity, and the party challenging the validity of a patent claim must present clear and convincing evidence of invalidity, which is a high burden of proof. Conversely, the patent owner need only prove infringement by a preponderance of the evidence, which is a lower burden of proof.

If we were found by a court to have infringed a valid patent claim, we could be prevented from using the patented technology and/or be required to pay the owner of the patent for damages for past sales and for the right to license the patented technology for future sales. If we decide to pursue a license to one or more of these patents, we may not be able to obtain a license on commercially reasonable terms, if at all, or the license we obtain may require us to pay substantial royalties or grant cross licenses to our patent rights. For example, if the relevant patent is owned by a competitor, that competitor may choose not to license patent rights to us. If we decide to develop alternative technology, we may not be able to do so in a timely or cost-effective manner, if at all.

In addition, because patent applications can take years to issue and are often afforded confidentiality for some period of time there may currently be pending applications, unknown to us, that later result in issued patents that could cover one or more of our products.

It is possible that we may in the future receive, particularly as a public company, communications from competitors and other companies alleging that we may be infringing their patents, trade secrets or other intellectual property rights, offering licenses to such intellectual property or threatening litigation. In addition to patent infringement claims, third parties may assert copyright, trademark or other proprietary rights against us. We may need to expend considerable resources to counter such claims and may not be able to successful in our defense. Our business may suffer if a finding of infringement is established.

It is difficult and costly to protect our proprietary rights, and we may not be able to ensure their protection.

The patent positions of pharmaceutical companies can be highly uncertain and involve complex legal and factual questions for which important legal principles remain unresolved. No consistent policy regarding the breadth of claims allowed in pharmaceutical patents has emerged to date in the United States. The pharmaceutical patent situation outside the United States is even more uncertain. Changes in either the patent laws or in interpretations of patent laws in the United States and other countries may diminish the value of our intellectual property. For example, on September 16, 2011, the Leahy-Smith America Invents Act, or the Leahy-Smith Act, was signed into law. The Leahy-Smith Act includes a number of significant changes to United States patent law. These include provisions that affect the way patent applications will be prosecuted and may also affect patent litigation. The United States Patent and Trademark Office has developed new regulations and procedures to govern the full implementation of the Leahy-Smith Act, and many of the substantive changes to patent law associated with the Leahy-Smith Act, and in particular, the first to file provisions, that became effective March 16, 2013. It is too early to tell what, if any, impact the Leahy-Smith Act will have on the operation of our business. However, the Leahy-Smith Act and its implementation could increase the uncertainties and costs surrounding the prosecution of our patent applications and the enforcement or defense of our issued patents, all of which could have a material adverse effect on our business and financial condition.

Accordingly, we cannot predict the breadth of claims that may be allowed or enforced in the patents that may be issued from the applications we currently or may in the future own or license from third parties. Claims could be brought regarding the validity of our patents by third parties and regulatory agencies. Further, if any patent license we obtain is deemed invalid and/or unenforceable, it could impact our ability to commercialize or partner our technology.

Competitors or third parties may infringe our patents. We may decide it is necessary to file patent infringement claims, which can be expensive and time-consuming. In addition, in an infringement proceeding, a court may decide that a patent of ours is not valid or is unenforceable, or that the third party’s technology does not in fact infringe upon our patents. An adverse determination of any litigation or defense proceedings could put one or more of our patents at

risk of being invalidated or interpreted narrowly and could put our related pending patent applications at risk of not issuing. Litigation may fail and, even if successful, may result in substantial costs and be a distraction to our management. We may not be able to prevent misappropriation of our proprietary rights, particularly in countries outside the United States where patent rights may be more difficult to enforce. Furthermore, because of the substantial amount of discovery required in connection with intellectual property litigation, there is a risk that some of our confidential or sensitive information could be compromised by disclosure in the event of litigation. In addition, during the course of litigation there could be public announcements of the results of hearings, motions or other interim proceedings or developments. If securities analysts or investors perceive these results to be negative, it could have a substantial adverse effect on the price of our common stock.

The degree of future protection for our proprietary rights is uncertain, and we cannot ensure that:

- we were the first to make the inventions covered by each of our pending patent applications or issued patents;
- our patent applications were filed before the inventions covered by each patent or patent application was published by a third party;
- we were the first to file patent applications for these inventions;
- others will not independently develop similar or alternative technologies or duplicate any of our technologies;
- any patents issued to us or our collaborators will provide a basis for commercially viable products, will provide us with any competitive advantages or will not be challenged by third parties; or
- the patents of others will not have an adverse effect on our business.

If we do not adequately protect our proprietary rights, competitors may be able to use our technologies and erode or negate any competitive advantage we may have, which could materially harm our business, negatively affect our position in the marketplace, limit our ability to commercialize our products and product candidates, and delay or render impossible our achievement of profitability.

We may be unable to adequately prevent disclosure of trade secrets and other proprietary information.

We rely on trade secrets to protect our proprietary know-how and technological advances, 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, outside scientific collaborators, sponsored researchers and other advisors to protect our trade secrets and other proprietary information. These agreements may not effectively prevent disclosure of confidential information and may not provide an adequate remedy in the event of unauthorized disclosure of confidential information. In addition, others may independently discover our trade secrets and proprietary information. Costly and time-consuming litigation could be necessary to enforce and determine the scope of our proprietary rights. Failure to obtain or maintain trade secret protection could enable competitors to use our proprietary information to develop products that compete with our products or cause additional, material adverse effects upon our competitive business position.

Periodic maintenance fees, renewal fees, annuity fees and various other governmental fees on patents and applications will be due to be paid to the United States Patent and Trademark Office and various foreign governmental patent agencies in several stages over the lifetime of the patents and/or applications.

We have systems in place, including use of third party vendors, to manage payment of periodic maintenance fees, renewal fees, annuity fees and various other patent and application fees. The United States Patent and Trademark Office, or the USPTO, and various foreign governmental patent agencies require compliance with a number of procedural, documentary, fee payment and other similar provisions during the patent application process. There are situations in which noncompliance can result in abandonment or lapse of the patent or patent application, resulting in partial or complete loss of patent rights in the relevant jurisdiction. If this occurs, our competitors might be able to enter the market, which would have a material adverse effect on our business.

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 United States. 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 the misappropriation of our other intellectual property rights. For example, many foreign countries have compulsory licensing laws under which a patent owner must 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. Accordingly, our efforts to protect our intellectual property rights in such countries may be inadequate. Additionally, claims may be brought regarding the validity of our patents by third parties and regulatory agencies in the United States and foreign countries. In addition, changes in the law and legal decisions by courts in the United States and foreign countries may affect our ability to obtain adequate protection for our technology and the enforcement of intellectual property.

We have not yet registered our trademarks in all of our potential markets, and failure to secure those registrations could adversely affect our business.

We have registered our ACELRX mark in the United States, Canada, the European Union and India. We have also registered the mark ACCELERATE. INNOVATE. ALLEVIATE. in the United States. We have additionally applied for registration of our ZALVISO mark in the United States on an intent-to-use basis and that application has been allowed. A statement of use was filed with the U.S. Patent and Trademark Office for the ZALVISO mark in January 2016 and we are currently awaiting a notice of registration. In early 2014, the FDA accepted the ZALVISO mark as part of the NDA review process. Although we are not currently aware of any oppositions to or cancellations of our registered trademarks or pending applications, it is possible that one or more of the applications could be subject to opposition or cancellation after the marks are registered. The registrations will be subject to use and maintenance requirements. It is also possible that we have not yet registered all of our trademarks in all of our potential markets, and that there are names or symbols other than “ACELRX” that may be protectable marks for which we have not sought registration, and failure to secure those registrations could adversely affect our business. Opposition or cancellation proceedings may be filed against our trademarks and our trademarks may not survive such proceedings.

Risks Related to Ownership of Our Common Stock

The market price of our common stock may be highly volatile.

Since our initial public offering, or IPO, in February 2011, the trading price of our common stock has experienced significant volatility and is likely to be volatile in the future. For example, our stock price declined by more than 40% on July 28, 2014, the first trading day following the announcement of the receipt of the CRL from the FDA. In addition, our stock price dropped by 37% on March 9, 2015, the day we announced the correspondence we received from the FDA requesting a clinical trial to assess the risk of inadvertent dispensing and overall risk of dispensing failures for Zalviso. Our stock price could be subject to wide fluctuations in response to a variety of factors, including the following:

- any delay in submitting the NDA for ARX-04 or resubmitting the NDA for Zalviso, and any adverse development or perceived adverse development with respect to the FDA's review of any NDA;
- adverse results or delays in current or future clinical trials, including the Phase 3 clinical development program for ARX-04 and Zalviso;
- inability to obtain additional funding, including funding necessary for the planned potential commercialization and manufacturing of ARX-04 and Zalviso in the United States;
- failure to successfully develop and commercialize our product candidates;
- changes in laws or regulations applicable to our products;
- inability to obtain adequate product supply for our product candidates, or the inability to do so at acceptable prices;
- adverse regulatory decisions;
- introduction of new products, services or technologies by our competitors;
- failure to meet or exceed financial projections we provide to the public;

- failure to meet or exceed the estimates and projections of the investment community;
- the perception of the pharmaceutical industry by the public, legislatures, regulators and the investment community;
- announcements of significant acquisitions, strategic partnerships, joint ventures, or other significant transactions, including disposition transactions, or capital commitments by us or our competitors;
- disputes or other developments relating to proprietary rights, including patents, litigation matters and our ability to obtain patent protection for our technologies;
- additions or departures of key scientific or management personnel;
- significant lawsuits, including patent or stockholder litigation;
- changes in the market valuations of similar companies;
- sales of our common stock by us or our stockholders in the future; and
- trading volume of our common stock.

In addition, the stock market in general, and The NASDAQ Global Market, or NASDAQ, in particular, have experienced extreme price and volume fluctuations that have often been unrelated or disproportionate to the operating performance of these companies. Broad market and industry factors may negatively affect the market price of our common stock, regardless of our actual operating performance.

Historically, our common stock has thinly traded, and in the future may continue to be thinly traded, and our stockholders may be unable to sell at or near asking prices, or at all if they need to sell their shares to raise money or otherwise desire to liquidate such shares.

Historically, we have not had a high volume of daily trades in our common stock on NASDAQ. For example, the average daily trading volume in our common stock on NASDAQ during the years ended December 31, 2015 and 2014 was approximately 600,000 and 700,000 shares per day, respectively. A more active market for our stock has only recently developed and may not be sustained. Our stockholders may be unable to sell their common stock at or near their asking prices, which may result in substantial losses to our investors.

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The market for our common stock may be characterized by significant price volatility when compared to seasoned issuers, and we expect that our share price will be more volatile than a seasoned issuer for the indefinite future. As noted above, our common stock may be sporadically and/or thinly traded. As a consequence of this lack of liquidity, the trading of relatively small quantities of shares by our stockholders may disproportionately influence the price of those shares in either direction. The price for our shares could, for example, decline significantly in the event that a large number of our common stock are sold on the market without commensurate demand, as compared to a seasoned issuer that could better absorb those sales without adverse impact on its share price.

Our principal stockholders and management own a significant percentage of our stock and are able to exert significant control over matters subject to stockholder approval.

Our executive officers and directors, together with the stockholders with whom our executive officers and directors are affiliated or associated, beneficially own a significant percentage of our voting stock. Therefore, these stockholders have the ability to influence us through this ownership position. These stockholders are able to determine all matters requiring stockholder approval. For example, these stockholders, acting together, are able to control elections of directors, amendments of our organizational documents, or approval of any merger, sale of assets, or other major corporate transaction. This may prevent or discourage unsolicited acquisition proposals or offers for our common stock that you may believe are in your best interest as one of our stockholders.

We incur significant increased costs as a result of operating as a public company, and our management is required to devote substantial time to new compliance initiatives.

As a public company, we incur significant legal, accounting and other expenses. In addition, the Sarbanes-Oxley Act of 2002, as amended, or the Sarbanes-Oxley Act, the Dodd-Frank Wall Street Reform and Consumer Protection Act, or Dodd-Frank Act, as well as the information and reporting requirements of the Exchange Act and other federal securities laws, and rules subsequently implemented by the SEC and NASDAQ, have imposed various requirements on public companies. The costs of compliance with the Sarbanes-Oxley Act and of preparing and filing annual and quarterly reports, proxy statements and other information with the SEC, the Dodd-Frank Act, and regulations promulgated under these statutes, are significant. Our management and other personnel need to devote a substantial amount of time to these compliance initiatives. Moreover, these rules and regulations increase our legal and financial compliance costs and make some activities more time-consuming and costly. For example, these rules and regulations make it more difficult and more expensive for us to obtain director and officer liability insurance and we may be required to incur substantial costs to maintain our current levels of such coverage.

As a public company, we are subject to the requirements of Section 404 of the Sarbanes-Oxley Act. If we are unable to comply with Section 404 in a timely manner, it may affect the reliability of our internal control over financial reporting. Assessing our staffing and training procedures to improve our internal control over financial reporting is an ongoing process.

We have been and will continue to be involved in a substantial effort to implement appropriate processes, document the system of internal control over key processes, assess their design, remediate any deficiencies identified and test their operation. If we fail to comply with the requirements of Section 404, it may affect the reliability of our internal control over financial reporting and negatively impact the quality of disclosure to our stockholders. If we, or our independent registered public accounting firm, identify and report a material weakness, it could adversely affect our stock price.

Sales of a substantial number of shares of our common stock in the public market by our existing stockholders could cause our stock price to fall.

Sales of a substantial number of shares of our common stock in the public market or the perception that these sales might occur, could depress the market price of our common stock and could impair our ability to raise capital through the sale of additional equity securities. A significant number of shares of our common stock are held by some of our original pre-IPO venture investors. These investors have previously distributed, and may in the future distribute their shares of AcelRx to their limited partners. Historically, these limited partners have subsequently sold those shares on the open market following the distribution. Sales of substantial number of shares of our common stock following such distributions may lead to a decline in the price of our common stock.

We are unable to predict the effect that sales may have on the prevailing market price of our common stock. All of our shares of common stock outstanding are eligible for sale in the public market, subject in some cases to the volume limitations and manner of sale requirements of Rule 144 under the Securities Act. Sales of stock by our stockholders could have a material adverse effect on the trading price of our common stock.

In addition, certain holders of our securities are entitled to certain rights with respect to the registration of their shares of common stock under the Securities Act. Registration of these shares under the Securities Act would result in the shares becoming freely tradable without restriction under the Securities Act. Any sales of securities by these stockholders could have a material adverse effect on the trading price of our common stock.

Future sales and issuances of our common stock or rights to purchase common stock, including pursuant to our equity incentive plans, could result in additional dilution of the percentage ownership of our stockholders and could cause our stock price to fall.

We expect that significant additional capital will be needed in the future to continue our planned operations. To the extent we raise additional capital by issuing equity securities, our stockholders may experience substantial dilution. We may sell common stock, convertible securities or other equity securities in one or more transactions at prices and in a manner we determine from time to time. If we sell common stock, convertible securities or other equity securities in more than one transaction, investors may be materially diluted by subsequent sales. These sales may also result in material dilution to our existing stockholders, and new investors could gain rights superior to our existing stockholders.

Pursuant to the 2011 Incentive Plan, our management is authorized to grant stock options and other equity-based awards to our employees, directors and consultants. The number of shares available for future grant under our 2011 Incentive Plan will automatically increase each year by 4% of all shares of our capital stock outstanding as of December 31 of the prior calendar year, subject to the ability of our board of directors to take action to reduce the size of the increase in any given year. Currently, we plan to register the increased number of shares available for issuance under our 2011 Incentive Plan each year. If our board of directors elects to increase the number of shares available for future grant by the maximum amount each year, our stockholders may experience additional dilution, which could cause our stock price to fall.

Our involvement in securities-related class action litigation could divert our resources and management's attention and harm our business.

The stock markets have from time to time experienced significant price and volume fluctuations that have affected the market prices for the common stock of pharmaceutical companies. These broad market fluctuations may cause the market price of our common stock to decline. In addition, the market price of our common stock may vary significantly based on AcelRx specific events, such as receipt of a CRL, negative clinical results, or other negative feedback from the FDA or other regulatory agencies. In the past, securities-related class action litigation has often been brought against a company following a decline in the market price of its securities. This risk is especially relevant for us because biotechnology and biopharmaceutical companies often experience significant stock price volatility in connection with their investigational drug candidate development programs and the FDA's review of their NDAs.

For example, on October 1, 2014, a securities class action complaint was filed in the U.S. District Court for the Northern District of California against AcelRx and certain of our current and former officers. On April 17, 2015, lead plaintiff filed an amended complaint. The amended complaint alleged that between September 30, 2013 and July 25, 2014, AcelRx and certain of our current and former officers violated Sections 10(b) and 20(a) of the Securities

Exchange Act of 1934 in connection with statements related to our lead drug candidate, Zalviso. On November 25, 2015, the Court granted our Motion to Dismiss. Plaintiffs had the opportunity to file an amended complaint within 30 days' which they declined to do. On January 18, 2016, the Court issued an order dismissing the case with prejudice.

If AcelRx experiences a decline in its stock price, we could face additional securities class action lawsuits. Securities class actions are often expensive and can divert management's attention and our financial resources, which could adversely affect our business.

Our ability to use our net operating loss carryforwards and certain other tax attributes may be limited.

Under Section 382 of the Internal Revenue Code of 1986, as amended, if a corporation undergoes an "ownership change," generally defined as a greater than 50% change (by value) in its equity ownership over a three year period, the corporation's ability to use its pre-change net operating loss carryforwards and other pre-change tax attributes (such as research tax credits) to offset its post-change income may be limited. The completion of the July 2013 public equity offering, together with our public equity offering in December 2012, our initial public offering, private placements and other transactions that have occurred, have triggered such an ownership change. In addition, since we will need to raise substantial additional funding to finance our operations, we may undergo further ownership changes in the future. In the year ended December 31, 2015, we used net operating losses to reduce our income tax liability. In the future, if we earn net taxable income, our ability to use our pre-change net operating loss carryforwards to offset United States federal taxable income may be subject to limitations, which could potentially result in increased future tax liability to us.

We do not intend to pay dividends on our common stock so any returns will be limited to the value of our stock.

We have never declared or paid any cash dividends on our capital stock, and we are prohibited from doing so under the terms of our Amended Loan Agreement with Hercules. Regardless of the restrictions in our Amended Loan Agreement with Hercules or the terms of any potential future indebtedness, we anticipate that we will retain all available funds and any future earnings to support our operations and finance the growth and development of our business and, therefore, we do not expect to pay cash dividends in the foreseeable future. Any future determination related to our dividend policy will be made at the discretion of our board of directors and will depend on then-existing conditions, including our financial condition, operating results, contractual restrictions, capital requirements, business prospects and other factors our board of directors may deem relevant.

Provisions in our amended and restated certificate of incorporation and bylaws, as well as provisions of Delaware law, could make it more difficult for a third party to acquire us or increase the cost of acquiring us, even if doing so would benefit our stockholders or remove our current management.

Some provisions of our charter documents and Delaware law may have anti-takeover effects that could discourage an acquisition of us by others, even if an acquisition would be beneficial to our stockholders and may prevent attempts by our stockholders to replace or remove our current management. These provisions include:

- authorizing the issuance of “blank check” preferred stock, the terms of which may be established and shares of which may be issued without stockholder approval;
- limiting the removal of directors by the stockholders;
- a staggered board of directors;
- prohibiting stockholder action by written consent, thereby requiring all stockholder actions to be taken at a meeting of our stockholders;
- eliminating the ability of stockholders to call a special meeting of stockholders; and
- establishing advance notice requirements for nominations for election to our board of directors or for proposing matters that can be acted upon at stockholder meetings.

These provisions may frustrate or prevent any attempts by our stockholders to replace or remove our current management by making it more difficult for stockholders to replace members of our board of directors, which is responsible for appointing the members of our management. In addition, we are subject to Section 203 of the Delaware General Corporation Law, which generally prohibits a Delaware corporation from engaging in any of a broad range of business combinations with an interested stockholder for a period of three years following the date on which the stockholder became an interested stockholder, unless such transactions are approved by our board of directors. This provision could have the effect of delaying or preventing a change of control, whether or not it is desired by or beneficial to our stockholders. Further, other provisions of Delaware law may also discourage, delay or prevent someone from acquiring us or merging with us.

Item 1B. Unresolved Staff Comments

None.

Item 2. Properties

We lease approximately 25,893 square feet of office and laboratory space in Redwood City, California under an agreement that expires in January 2018. On October 2, 2015, we executed an agreement to sublease 11,871 square feet of this space for a term of 26 months commencing on December 1, 2015. Upon the completion of the sublease, we have the option to take back the subleased space. We believe that our facilities are adequate to meet our current needs.

Item 3. Legal Proceedings

On October 1, 2014, a securities class action complaint was filed in the U.S. District Court for the Northern District of California against AcelRx and certain of our current and former officers. On April 17, 2015, lead plaintiff filed an amended complaint. The amended complaint alleged that between September 30, 2013 and July 25, 2014, AcelRx and certain of our current and former officers violated Sections 10(b) and 20(a) of the Securities Exchange Act of 1934 in connection with statements related to our lead drug candidate, Zalviso. On November 25, 2015, the Court granted our Motion to Dismiss. Plaintiffs had the opportunity to file an amended complaint within 30 days' which they declined to do. On January 18, 2016, the Court issued an order dismissing the case with prejudice.

From time to time we may be involved in additional legal proceedings arising in the ordinary course of business.

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

Market Information

Our common stock has been trading on the NASDAQ Global Market under the symbol "ACRX" since our IPO on February 11, 2011. Prior to this date, there was no public market for our common stock. The following table sets forth the high and low intraday sales prices of our common stock for the periods indicated as reported by the NASDAQ Global Market:

	Price	
	High	**Low**
Year ended 2015		
Fourth Quarter	$5.88	$2.97
Third Quarter	$5.10	$2.92
Second Quarter	$4.99	$2.96
First Quarter	$9.32	$3.58
Year ended 2014		
Fourth Quarter	$7.46	$5.22
Third Quarter	$11.65	$5.27
Second Quarter	$12.35	$8.13
First Quarter	$13.64	$9.91

Stock Price Performance Graph

The following graph illustrates a comparison of the total cumulative stockholder return on our common stock since February 11, 2011, which is the date our common stock first began trading on the NASDAQ Global Market, to two indices: the NASDAQ Composite Index and the NASDAQ Biotechnology Index. The stockholder return shown in the graph below is not necessarily indicative of future performance, and we do not make or endorse any predictions as to future stockholder returns.

The above Stock Price Performance Graph and related information shall not be deemed "soliciting material" or to be "filed" with the Securities and Exchange Commission, nor shall such information be incorporated by reference into any future filing under the Securities Act of 1933 or Securities Exchange Act of 1934, each as amended, except to the extent that we specifically incorporate it by reference into such filing.

Holders of Record

As of February 3, 2016, there were 16 holders of record of our common stock. This number does not include “street name” or beneficial holders, whose shares are held of record by banks, brokers, financial institutions and other nominees.

Dividend Policy

We have never declared or paid any cash dividends on our capital stock, and we are prohibited from doing so under the terms of our loan and security agreement with Hercules. Regardless of the restrictions in our loan and security agreement with Hercules or the terms of any potential future indebtedness, we anticipate that we will retain all available funds and any future earnings to support our operations and finance the growth and development of our business and, therefore, we do not expect to pay cash dividends in the foreseeable future. Any future determination related to our dividend policy will be made at the discretion of our board of directors and will depend on then-existing conditions, including our financial condition, operating results, contractual restrictions, capital requirements, business prospects and other factors our board of directors may deem relevant.

Recent Sales of Unregistered Securities

None.

Item 6. Selected Financial Data

The selected financial data set forth below should be read together with the Consolidated Financial Statements and related notes, "Item 7. Management's Discussion and Analysis of Financial Condition and Results of Operations," and the other information contained in this Form 10-K. The selected financial data is not intended to replace our audited financial statements and the accompanying notes. Our historical results are not necessarily indicative of our future results.

	Year Ended December 31,				
	2015	2014	2013	2012	2011
	(in thousands, except share and per share data)				
Consolidated Statements of Operations Data:					
Revenue:					
Collaboration agreement	$14,857	$5,217	$27,370	$—	$—
Contract and other	4,406	—	2,132	2,394	1,072
Total revenue	19,263	5,217	29,502	2,394	1,072
Operating Expenses:					
Cost of goods sold	$1,770	$—	$—	$—	$—
Research and development	22,488	24,520	26,292	24,908	13,624
General and administrative	14,203	18,346	9,877	7,199	6,800
Restructuring costs	756	—	—	—	—
Total operating expenses	39,217	42,866	36,169	32,107	20,424
Loss from operations	(19,954)	(37,649)	(6,667)	(29,713)	(19,352)
Interest expense	(2,977)	(2,639)	(1,518)	(2,283)	(2,309)
Interest income and other income (expense), net	1,720	6,935	(15,241)	(1,367)	1,560
Non-cash interest expense on liability related to sale of future royalties	(2,428)	—	—	—	—
Net loss before income taxes	$(23,639)	$(33,353)	$(23,426)	$(33,363)	$(20,101)
Provision for income taxes	(760)	—	—	—	—
Net loss	$(24,399)	$(33,353)	$(23,426)	$(33,363)	$(20,101)
Net loss per share of common stock, basic	$(0.55)	$(0.77)	$(0.59)	$(1.51)	$(1.16)
Shares used in computing net loss per share of common stock, basic	44,300,099	43,427,111	39,746,678	22,124,637	17,344,727
Net loss per share of common stock, diluted – see Note 14	$(0.60)	$(0.91)	$(0.59)	$(1.51)	$(1.16)
Shares used in computing net loss per share of common stock, diluted	44,468,440	44,322,297	39,746,678	22,124,637	17,344,727

	As of December 31,				
	2015	2014	2013	2012	2011
	(in thousands)				

Balance Sheet Data:					
Cash, cash equivalents and short-term investments	$113,464	$75,350	$103,663	$59,763	$35,785
Working capital	106,167	62,567	97,692	47,435	30,301
Total assets	127,785	86,416	110,031	64,520	40,835
Long-term debt	20,922	24,874	14,364	15,973	19,079
Liability related to sale of future royalties	63,612	—	—	—	—
PIPE warrant liability	913	5,577	13,111	7,418	—
Accumulated deficit	(203,205)	(178,806)	(145,453)	(122,027)	(88,664)
Total stockholders' equity	33,113	46,656	73,159	33,847	17,468

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

The following discussion and analysis should be read in conjunction with our audited financial statements and the related notes that appear elsewhere in this Annual Report on Form 10-K. This discussion contains forward-looking statements within the meaning of Section 21E of the Securities Exchange Act of 1934, as amended. Such forward-looking statements involve risks, uncertainties and other factors that may cause our actual results, levels of activity, performance or achievements to be materially different from the information expressed or implied by these forward-looking statements. Our actual results and the timing of selected events could differ materially from those anticipated in these forward-looking statements as a result of several factors, including those set forth under "Item 1A. Risk Factors" and elsewhere in this Annual Report on Form 10-K. Please refer to the section entitled "Forward-Looking Statements" in this Annual Report on Form 10-K.

Overview

We are a specialty pharmaceutical company focused on the development and commercialization of innovative therapies for the treatment of acute pain. Our lead product candidates, ARX-04 and Zalviso, utilize sublingual sufentanil, delivered via a non-invasive route of administration. We intend to commercialize our product candidates in the United States and license the development and commercialization rights to our product candidates for sale outside of the United States through strategic partnerships and collaborations. We may also consider the option to enter into strategic partnerships for our product candidates in the United States.

ARX-04 (sufentanil sublingual tablet, 30 mcg)

ARX-04 is an investigational product candidate consisting of a single tablet delivered via a disposable, pre-filled, single-dose applicator, or SDA. We are developing ARX-04 for the treatment of moderate-to-severe acute pain to be administered by a healthcare professional to a patient in medically supervised settings of acute pain. If approved, examples of potential patient populations and settings in which ARX-04 could be used include: emergency room patients; patients who are recovering from short-stay or ambulatory surgery and do not require more long-term patient-controlled analgesia; post-operative patients who are transitioning from the operating room to the recovery floor; patients being treated and transported by paramedics; and for battlefield casualties.

In September 2015, we reported that SAP301, a pivotal Phase 3 multi-center, double-blind, placebo-controlled study of ARX-04, met primary and secondary endpoints in the short-term treatment of patients with moderate-to-severe acute pain following ambulatory abdominal surgery. SAP301 is considered the second of two pivotal placebo-controlled studies required to be included in the NDA submission.

In October 2015, we announced the initiation of an open-label Phase 3 study, SAP302, of ARX-04 for the treatment of adult patients who present in the emergency room with moderate-to-severe acute pain associated with trauma or injury. The primary efficacy endpoint is the summed pain intensity difference, or SPID, over 1-hour, or SPID-1. Safety endpoints, such as adverse events and vital signs will also be assessed, as will the patients' and healthcare providers' satisfaction with the method of pain control. Based on discussions with the FDA, we have amended the protocol for SAP302 to allow for multiple dosing of ARX-04. We are planning to enroll an additional 60 patients in the extension phase of the SAP302 study. The SAP302 study is expected to be completed by the third quarter of 2016.

We held a pre-NDA meeting with the FDA in December 2015 to review plans for an NDA for ARX-04. Based on discussions with the FDA, we intend to increase the safety database by expanding the clinical program for ARX-04 by approximately 160 additional patients to include individuals from specific populations and settings. Enrollment in the ongoing SAP302 open-label study in the emergency room will be increased as described above, and a new study, known as SAP303, was initiated in March 2016 in post-operative patients with moderate-to-severe acute pain. SAP303 will focus on enrolling patients greater than 40 years of age and will allow for administration of ARX-04 for up to 12 hours. With these modifications, assuming successful completion of SAP302 and SAP303 by the third quarter of 2016, AcelRx anticipates submitting the NDA for ARX-04 in the fourth quarter of 2016.

The FDA has also agreed to allow us to include as supporting safety information in the NDA for ARX-04, data from approximately 323 patients treated in the Zalviso clinical studies who had administered two 15 mcg tablets 20-to-25 minutes apart. AcelRx had previously completed and analyzed pharmacokinetic and modeling data, which demonstrated the equivalency of one sufentanil sublingual tablet, 30 mcg, to two sufentanil sublingual tablets, 15 mcg, taken 20-to-25 minutes apart.

On May 11, 2015, we entered into an award contract supported by the United States Army Medical Research and Materiel Command, or USAMRMC, within the U.S. Department of Defense, or the DoD, in which the DoD agreed to provide up to $17.0 million to support the development of ARX-04, referred to as the DoD Contract. Under the terms of the contract, the DoD will reimburse us for costs incurred for development, manufacturing, regulatory and clinical costs outlined in the contract in order to submit an NDA to the FDA, including reimbursement for certain personnel and overhead expenses. The period of performance under the DoD Contract began on May 11, 2015. The contract gives the DoD the option to extend the term of the contract and provide additional funding. On March 2, 2016, the DoD Contract was amended to approve enrollment of additional patients in the SAP302 study, approve the addition of the SAP303 study, and extend the contract period of performance by four months from November 10, 2016 to March 9, 2017, to accommodate the increased SAP302 patient enrollment and the SAP303 study. The costs for these changes will be absorbed within the current contract value. If ARX-04 is approved by the FDA, the DoD has the option to purchase a certain number of units of commercial product pursuant to the terms of the contract.

Zalviso™ (sufentanil sublingual tablet system)

Our product candidate, Zalviso, is intended for the management of moderate-to-severe acute pain in hospitalized adult patients. Zalviso consists of sufentanil sublingual tablets, 15 mcg, delivered by the Zalviso System, a needle-free, handheld, patient-administered, pain management system, or together, Zalviso.

Zalviso is a pre-programmed, non-invasive, system to allow hospital patients with moderate-to-severe acute pain to self-dose with sufentanil sublingual tablets, 15 mcg, to manage their pain. Zalviso is designed to help address certain problems associated with post-operative intravenous patient-controlled analgesia. Zalviso allows patients to self-administer sufentanil sublingual tablets via a pre-programmed, secure system designed to eliminate the risk of programming errors.

On December 16, 2013, AcelRx and Grünenthal entered into a Collaboration and License Agreement, which was amended effective July 17, 2015, or the Amended License Agreement, which grants Grünenthal rights to commercialize Zalviso in the countries of the European Union, or EU, Switzerland, Liechtenstein, Iceland, Norway and Australia, or the Territory, for human use in pain treatment within or dispensed by hospitals, hospices, nursing homes and other medically-supervised settings, or the Field. We retain rights with respect to Zalviso in countries outside the Territory, including the United States, Asia and Latin America. In September 2015, the European Commission approved the Marketing Authorization Application, or MAA, previously submitted to the European Medicines Agency, or EMA, for Zalviso for the management of acute moderate-to-severe post-operative pain in adult patients. The approval allows Grünenthal to market Zalviso in the 28 EU member states as well as in the European Economic Area countries of Norway, Iceland and Liechtenstein, or EEA.

Under the terms of the Amended License Agreement, we received an upfront cash payment of $30.0 million in December 2013, a milestone payment of $5.0 million related to the Marketing Authorization Application, or MAA,

submission to the European Medicines Agency, or EMA, in the third quarter of 2014, and an additional milestone payment of $15.0 million upon EC approval of the MAA for Zalviso in the third quarter of 2015. In addition, we are eligible to receive approximately $194.5 million in additional milestone payments, based upon successful regulatory and product development efforts ($28.5 million) and net sales target achievements ($166.0 million). PDL BioPharma, Inc., or PDL, will receive 75% of the European royalties under the Amended License Agreement with Grünenthal, as well as 80% of the first four commercial milestones worth $35.6 million (or 80% of $44.5 million), subject to a capped amount, as further described below. Grünenthal will also make tiered royalty, supply and trademark fee payments in the mid-teens up to the mid-twenties percent range, depending on the sales level achieved, on net sales of Zalviso in the Territory. A portion of the tiered royalty payment, exclusive of the supply and trademark fee payments, will be paid to PDL in connection with the Royalty Monetization, as discussed below.

Also on December 16, 2013, we entered into the related Manufacture and Supply Agreement with Grünenthal, which was amended effective July 17, 2015, or the Amended MSA, and together with the Amended License Agreement, the Amended Agreements. Under the Amended MSA, we will exclusively manufacture and supply Zalviso to Grünenthal for the Field in the Territory. For additional information on the Amended Agreements, see Note 6 “Collaboration Agreement” in the accompanying notes to the Consolidated Financial Statements.

In the Amended Agreements, the parties amended the Zalviso supply configurations and packaging of Zalviso components and accessories, and associated pricing therefor, which we will manufacture and supply to Grünenthal for the Territory. The parties agreed to increase the pricing of the Zalviso components and accessories, while reducing the total milestone payments due from Grünenthal, contingent upon achieving specified net sales targets, from a total of $171.5 million to $166.0 million. The parties also updated the development plan for Zalviso in the Territory, providing for additional near-term development services to be rendered by AcelRx in exchange for payments of approximately $0.7 million, primarily in 2015. Simultaneously, AcelRx also received a binding Zalviso product forecast from Grünenthal for approximately $3.7 million.

On September 18, 2015, we sold a portion of the expected royalty stream and commercial milestones from the sales of Zalviso in the EU by Grünenthal to PDL, or the Royalty Monetization. AcelRx received gross proceeds of $65.0 million in the Royalty Monetization. PDL will receive 75% of the European royalties under the Amended License Agreement with Grünenthal, as well as 80% of the first four commercial milestones worth $35.6 million (or 80% of $44.5 million), subject to the capped amount of $195.0 million. For additional information on the Royalty Monetization with PDL, see Note 8 “Liability Related to Sale of Future Royalties” in the accompanying notes to the Consolidated Financial Statements.

Grünenthal will be responsible for all commercial activities for Zalviso, including obtaining and maintaining pharmaceutical product regulatory approval in the Territory. We will be responsible for obtaining and maintaining device regulatory approval in the Territory and the manufacturing and supply of Zalviso to Grünenthal for commercial sales.

In association with the impending commercialization of Zalviso in the European Union, we completed the Conformite Europeenne approval process for the Zalviso device, more commonly known as a CE Mark approval process. We received CE Mark approval in December 2014, which permits the commercial sale of the Zalviso device in the European Union. In connection with the CE Mark approval, we were also granted International Standards Organization, or ISO, 13485:2003 certification of our quality management system in November 2014. This is an internationally recognized quality standard for medical devices. Certification of our quality management system was issued by the British Standards Institution, or BSI, a Notified Body. The certification applies to the Redwood City, California location which designs, manufactures and distributes finished medical devices, and includes critical suppliers.

We submitted an NDA for Zalviso in September 2013, which the FDA accepted for filing in December 2013. On July 25, 2014, the FDA issued a Complete Response Letter, or CRL, for the Zalviso NDA. The CRL contains requests for additional information on the Zalviso System to ensure proper use of the device. The requests include submission of data demonstrating a reduction in the incidence of optical system errors, changes to address inadvertent dosing, among other items, and submission of additional data to support the shelf life of the product. Although there were no requests for additional clinical studies in the CRL, in March 2015, we received correspondence from the FDA stating that, in addition to the work we had performed to address the items in the CRL, a clinical study would be required to test modifications to the Zalviso device.

Our IAP312 study is designed to evaluate the effectiveness of changes made to enhance performance of the Zalviso device and takes into account comments from the FDA on the protocol. The IAP312 study will include approximately 315 post-operative patients and collect information requested by the Division to supplement the three positive Phase 3 trials already completed. AcelRx plans to initiate the study in the first quarter of 2016.

Financial Overview

We have incurred net losses and generated negative cash flows from operations since inception and expect to incur losses in the future as we continue our research and development activities and pre-commercialization activities. As we pursue development of our product candidates, including regulatory review and potential commercial development, subject to FDA approval, of our product candidates, we expect the business aspects of our company to become more complex. In the future, we plan to add personnel and incur additional costs related to the maturation of our business and the potential commercialization of ARX-04 and Zalviso in the United States. In addition, we believe that continued investment in research and development is critical to attaining our strategic objectives. In order to develop our product candidates as commercially viable therapeutics, we expect to expend significant resources for expertise in manufacturing, regulatory affairs, clinical research and other aspects of pharmaceutical development.

To date, we have funded our operations primarily through the issuance of equity securities, borrowings, payments from our commercial partner, Grünenthal, monetization of certain future royalties and commercial sales milestones from the sales of Zalviso by Grünenthal, and funding from the DoD.

Our revenues since inception have consisted primarily of revenues from our Amended License Agreement with Grünenthal and our research contracts with the USAMRMC within the DoD. As mentioned above, in May 2015, the DoD agreed to provide us up to $17.0 million to support the development of ARX-04. Under the terms of the contract, the DoD will reimburse us for costs incurred for development, manufacturing, regulatory and clinical costs outlined in the contract in order to submit an NDA to the FDA, including reimbursement for certain personnel and overhead expenses.

There can be no assurance that we will enter into other collaborative agreements or receive research-related contract awards in the future. We expect revenues to continue to fluctuate from period-to-period. There can be no assurance that our relationship with our existing commercial partner, Grünenthal, will continue beyond the initial term, or that we will be able to meet the milestones specified in the Amended License Agreement, or that the funding provided by the DoD Contract will be sufficient for an NDA submission for ARX-04, or that we will obtain marketing approval for any of our product candidates outside of Zalviso in the EU and EEA and subsequently generate revenue from those product candidates in excess of our operating expenses.

Our net losses were $24.4 million and $33.4 million during the years ended December 31, 2015 and 2014, respectively. As of December 31, 2015, we had an accumulated deficit of $203.2 million. As of December 31, 2015, we had cash, cash equivalents and investments totaling $113.5 million compared to $75.4 million as of December 31, 2014.

As mentioned above, on September 18, 2015, we sold a portion of the expected royalty stream and commercial milestones from the sales of Zalviso in the EU by Grünenthal to PDL under the Royalty Monetization. We received gross proceeds of $65.0 million from the Royalty Monetization.

In the first step of the Royalty Monetization, we sold certain royalty and milestone payment rights to our newly formed wholly owned subsidiary, ARPI LLC, pursuant to a Purchase and Sale Agreement, or PSA. In the second step of the Royalty Monetization, ARPI LLC sold the royalty and milestone payment rights to PDL for an upfront cash purchase price of $65.0 million, subject to a capped amount of $195.0 million pursuant to the Subsequent Purchase and Sale Agreement, or SPSA. Under the SPSA, PDL will receive 75% of the European royalties under the Amended License Agreement with Grünenthal, as well as 80% of the first four commercial milestones worth $35.6 million (or 80% of $44.5 million), subject to the capped amount of $195.0 million. We are entitled to receive all remaining amounts under the Amended License Agreement which include 25% of the European royalties, 20% of the first four commercial milestones, 100% of the remaining commercial milestones and all development milestones of $43.5 million, including the $15.0 million payment for the approval of the MAA for Zalviso, which the European Commission approved in September 2015.

The total liability related to sale of future royalties to PDL as of December 31, 2015 was $63.6 million.

On December 16, 2013, we entered into an Amended and Restated Loan and Security Agreement with Hercules Technology II, L.P. and Hercules Technology Growth Capital, Inc., together, the Lenders, or the Amended Loan Agreement, under which we may borrow up to $40.0 million in three tranches. The loans are represented by secured convertible term promissory notes, collectively, the Notes. The Amended Loan Agreement amends and restates the Loan and Security Agreement between AcelRx and the Lenders dated as of June 29, 2011. We borrowed the first tranche of $15.0 million upon closing of the transaction on December 16, 2013, and the second tranche of $10.0 million on June 16, 2014. We used approximately $8.6 million of the proceeds from the first tranche to repay our obligations under the Loan and Security Agreement with the Lenders. We recorded the new debt at an estimated fair value of $24.9 million as of December 31, 2014.

On September 24, 2014, we entered into Amendment No. 1 to the Amended Loan Agreement with Hercules. Amendment No. 1 extended the time period under which we could draw down the third tranche, of up to $15.0 million, from March 15, 2015 to August 1, 2015, subject to AcelRx obtaining approval for Zalviso from the FDA. We did not receive FDA approval of Zalviso by August 1, 2015 and as such, did not have access to the third tranche.

On September 18, 2015, concurrently with the closing of the Royalty Monetization, we entered into a Consent and Amendment No. 2, or Amendment No. 2, to the Amended Loan Agreement with the Lenders. Amendment No. 2 includes an interest only period from October 1, 2015 through March 31, 2016, with the potential for further extension to September 30, 2016 upon satisfaction of certain conditions, which have since been satisfied. After the expiration of the interest only period, we will make 13 monthly payments of $1.7 million beginning in October 2016 through October 2017. In addition, a final payment equal to $1.7 million will be due in October 2017. Loans under the Amended Loan Agreement mature on October 31, 2017. In consideration for the modifications made in Amendment No. 2, we reduced the exercise price of the warrants already held by the Lenders, which are exercisable for an aggregate of 176,730 shares of Common Stock, from the previous exercise price of $6.79 per share to $3.88 per share, or the Warrant Amendments. These warrants expire on the earlier to occur of five years from the date of issuance, or December 16, 2018, or the consummation of certain acquisitions of AcelRx, as set forth in the warrants.

The interest rate for each tranche will be calculated at a rate equal to the greater of either (i) 9.10% plus the prime rate as reported from time to time in The Wall Street Journal minus 5.25%, and (ii) 9.10%. Payments under the Amended Loan Agreement were interest only until April 1, 2015, followed by equal monthly payments of principal and interest through September 30, 2015, to be followed by an interest only period from October 1, 2015 through September 30, 2016, and by equal monthly payments of principal and interest from October 1, 2016 through the scheduled maturity date on October 1, 2017, or the Loan Maturity Date. In addition, a final payment equal to $1.7 million will be due on the Loan Maturity Date, or such earlier date specified in the Amended Loan Agreement. Our obligations under the Amended Loan Agreement are secured by a security interest in substantially all of our assets, other than our intellectual property and those assets sold under the Royalty Monetization.

As of December 31, 2015, the outstanding principal owed to Hercules was $20.9 million.

On December 16, 2013, we and Grünenthal entered into a Collaboration and License Agreement, or the License Agreement, and related Manufacture and Supply Agreement, or the MSA, and together with the License Agreement, the Agreements. The License Agreement grants Grünenthal rights to commercialize Zalviso, or the Product, in the Territory for human use in pain treatment in the Field. We retain rights with respect to the Product in countries outside the Territory, including the United States, Asia and Latin America. Under the MSA, we will exclusively manufacture and supply the Product to Grünenthal for the Field in the Territory. On July 22, 2015, we entered into amendments to the License Agreement, or the License Amendment, and together with the License Agreement, the Amended License Agreement, and the MSA, or the MSA Amendment, and together with the MSA, the Amended MSA, between AcelRx and Grünenthal, each effective as of July 17, 2015, and together, the Amended Agreements.

In the Amended Agreements, the parties amended the Product supply configurations and packaging of Product components and accessories, and associated pricing therefor, which we will manufacture and supply to Grünenthal for the Territory. The parties agreed to increase the pricing of the Product components and accessories, while reducing the total milestone payments due from Grünenthal contingent upon achieving specified net sales targets from a total of $171.5 million to $166.0 million. As mentioned above, PDL will receive 75% of the European royalties under the Amended License Agreement with Grünenthal, as well as 80% of the first four commercial milestones worth $35.6 million (or 80% of $44.5 million), subject to the capped amount of $195.0 million. The parties also updated the development plan for the Product in the Territory, providing for additional near-term development services to be rendered by AcelRx in exchange for payments of approximately $0.7 million, primarily in 2015. Simultaneously, AcelRx also received a binding Product forecast from Grünenthal for approximately $3.7 million.

Under the terms of the Amended Agreements with Grünenthal, we received an upfront cash payment of $30.0 million in December 2013, and in the third quarter of 2014, we received a milestone payment of $5.0 million related to the MAA submission to EMA and an additional milestone payment of $15.0 million related to the EC approval of the MAA for Zalviso in the third quarter of 2015. Under the Amended License Agreement, we are eligible to receive approximately $194.5 million in additional milestone payments, based upon successful regulatory and product development efforts ($28.5 million) and net sales target achievements ($166.0 million). Grünenthal will also make tiered royalty, supply and trademark fee payments in the mid-teens up to the mid-twenties percent range, depending on the level of sales achieved, on net sales of Zalviso in the Territory. A portion of the tiered royalty payment, exclusive of the supply and trademark fee payments, will be paid to PDL in connection with the Royalty Monetization. For additional information on the Royalty Monetization with PDL, see Note 8 “Liability Related to Sale of Future Royalties” in the accompanying notes to the Consolidated Financial Statements.

Grünenthal will be responsible for all commercial activities for Zalviso, including obtaining and maintaining pharmaceutical product regulatory approval in the Territory. We will be responsible for obtaining and maintaining device regulatory approval in the Territory and manufacturing and supply of Zalviso to Grünenthal for commercial sales.

Critical Accounting Estimates

Based on a critical assessment of our accounting policies and the underlying judgments and uncertainties affecting the application of those policies, management believes that our Consolidated Financial Statements are fairly stated in accordance with accounting principles generally accepted in the United States, and meaningfully present our financial condition and results of operations.

The accompanying discussion and analysis of our financial condition and results of operations are based upon our Consolidated Financial Statements and the related disclosures, which have been prepared in accordance with accounting principles generally accepted in the United States. The preparation of these financial statements requires us to make estimates, assumptions and judgments that affect the reported amounts in our Consolidated Financial Statements and accompanying notes. We base our estimates on historical experience and on various other assumptions that we believe to be reasonable under the circumstances, the results of which form the basis for making judgments about the carrying values of assets and liabilities that are not readily apparent from other sources. Actual results may differ from these estimates under different assumptions or conditions. To the extent that there are material differences between these estimates and actual results, our future financial statement presentation, financial condition, results of operations and cash flows will be affected. Note 1 “Organization and Summary of Significant Accounting Policies” in the accompanying Notes to Consolidated Financial Statements describes the significant accounting policies used in the preparation of the financial statements. Certain of these significant accounting policies are considered to be critical accounting policies, as defined below.

A critical accounting policy is defined as one that is both material to the presentation of our financial statements and requires management to make difficult, subjective or complex judgments that could have a material effect on our financial condition and results of operations. Specifically, critical accounting estimates have the following attributes: (i) we are required to make assumptions about matters that are highly uncertain at the time of the estimate; and (ii) different estimates we could reasonably have used, or changes in the estimate that are reasonably likely to occur, would have a material effect on our financial condition or results of operations.

We believe the following policies to be the most critical to an understanding of our financial condition and results of operations because they require us to make estimates, assumptions and judgments about matters that are inherently uncertain. Management has discussed the development, selection and disclosure of the following estimates with the Audit Committee.

Revenue Recognition

We recognize revenue when all of the following four basic revenue recognition criteria are met: (i) persuasive evidence of an arrangement exists; (ii) delivery has occurred or services have been rendered; (iii) the fee is fixed or determinable; and (iv) collectability is reasonably assured.

Revenue generated from collaboration agreements typically includes upfront signing or license fees, cost reimbursements, development and manufacturing services, milestone payments and royalties on future licensee's product sales.

Revenue from non-refundable license, technology access or other payments under license and collaborative agreements where we have a continuing obligation to perform is recognized as revenue over the expected period of the continuing performance obligation. We estimate the performance period at the inception of the arrangement and re-evaluate it each reporting period. This re-evaluation may shorten or lengthen the period over which the remaining revenue is recognized. Changes to these estimates are recorded on a prospective basis.

We account for multiple-element arrangements, such as license and commercialization agreements in which a customer may purchase several deliverables, in accordance with ASC Topic 605-25, *Revenue Recognition—Multiple-Element Arrangements*, or ASC 605-25. We evaluate if the deliverables in the arrangement represent separate units of accounting. In determining the units of accounting, we evaluate certain criteria, including whether the deliverables have value to our customers on a stand-alone basis. Factors considered in this determination include whether the deliverable is proprietary to us, whether the customer can use the license or other deliverables for their intended purpose without the receipt of the remaining elements, whether the value of the deliverable is dependent on the undelivered items, and whether there are other vendors that can provide the undelivered items. Deliverables

that meet these criteria are considered a separate unit of accounting. Deliverables that do not meet these criteria are combined and accounted for as a single unit of accounting.

For revenue agreements with multiple-element arrangements, such as the collaboration and license agreement with Grünenthal, we allocate revenue to each non-contingent element based on the relative selling price of each element. When applying the relative selling price method, we determine the selling price for each deliverable using vendor-specific objective evidence, or VSOE, of selling price or third-party evidence, or TPE, of selling price. If neither exists we use best estimated selling price, or BESP, for that deliverable. Revenue allocated is then recognized when the four basic revenue recognition criteria, mentioned above, are met for each element.

Additionally, we recognize milestone payments, which are subject to substantive contingencies, upon completion of specified milestones, which represents the culmination of an earnings process, according to contract terms. Royalty revenues are generally recognized when earned and collectability of the related royalty payment is reasonably assured.

In May 2015, we entered into an award contract with the USAMRMC to support the development of ARX-04. The contract provides for the reimbursement of qualified expenses for research and development activities as defined under the terms of the contract. Revenue under the contract is recognized when the related qualified research expenses are incurred. We are entitled to reimbursement of overhead costs associated with the study costs incurred under the DoD Contract. We estimate this overhead rate by utilizing forecasted expenditures. Final reimbursable overhead expenses are dependent on direct labor and direct reimbursable expenses throughout the life of the contract, which may increase or decrease based on actual expenses incurred.

Deferred revenue represents the portion of research or license payments received which have not been earned.

Inventories

Inventories are valued at the lower of cost or market. Cost is determined using the first-in, first-out method for all inventories. Inventory includes the cost of active pharmaceutical ingredients, or API, raw materials and third-party contract manufacturing and packaging services. Indirect overhead costs associated with production and distribution are allocated to the appropriate cost pool and then absorbed into inventory based on the units produced or distributed, assuming normal capacity, in the applicable period. Indirect overhead costs in excess of normal capacity are recorded as period costs in the period incurred.

Our policy is to write down inventory that has become obsolete, inventory that has a cost basis in excess of its expected net realizable value and inventory in excess of expected requirements. We periodically evaluate the carrying value of inventory on hand for potential excess amount over demand using the same lower of cost or market approach as that used to value the inventory. Because selling prices to Grünenthal are set to recover only direct costs with minimal markup, all inventories are carried at net realizable value.

Cost of Goods Sold

Cost of goods sold for Zalviso shipped to Grünenthal includes the inventory costs of API, third-party contract manufacturing costs, packaging and distribution costs, shipping, handling and storage costs, depreciation and costs of the employees involved with production.

Research and Development Expenses

We expense research and development expenses as incurred. Research and development expenses consist primarily of direct and research-related allocated overhead costs such as facilities costs, salaries and related personnel costs, and material and supply costs. In addition, research and development expenses include costs related to clinical trials to validate our testing processes and procedures and related overhead expenses. Expenses resulting from clinical trials are recorded when incurred based in part on factors such as estimates of work performed, patient enrollment, progress of patient studies and other events. We make good faith estimates that we believe to be accurate, but the actual costs and timing of clinical trials are highly uncertain, subject to risks and may change depending upon a number of factors, including our clinical development plan.

Share-Based Compensation

We measure and recognize compensation expense for all share-based payment awards made to our employees and directors, including employee stock options and employee stock purchases related to the Employee Share Purchase Plan, or ESPP, on estimated fair values. The fair value of equity-based awards is amortized over the vesting period of the award using a straight-line method.

To estimate the value of an award, we use the Black-Scholes option pricing model. This model requires inputs such as expected life, expected volatility and risk-free interest rate. These inputs are subjective and generally require significant analysis and judgment to develop. Estimates of expected life are primarily determined using the simplified method in accordance with guidance provided by the Securities and Exchange Commission, or SEC. Volatility is

derived from historical volatilities of several public companies within our industry that are deemed to be comparable to our business because we do not have sufficient history on the volatility of our common stock relative to our expected life assumptions. The risk-free rate is based on the U.S. Treasury yield curve in effect at the time of grant commensurate with the expected life assumption. We review our valuation assumptions quarterly and, as a result, it is likely we will change our valuation assumptions used to value share based awards granted in future periods. Further, we are required to estimate forfeitures at the time of grant and revise those estimates in subsequent periods if actual forfeitures differ from those estimates. We use historical data to estimate pre-vesting option forfeitures and record stock-based compensation expense only for those awards that are expected to vest. If factors change and different assumptions are employed in determining the fair value of stock based awards, the stock based compensation expense recorded in future periods may differ significantly from what was recorded in the current period.

Liabilities Associated with Warrants

Warrants to Purchase Common Stock

In connection with the private placement equity financing in June 2012, or PIPE, we issued PIPE warrants to purchase up to 2,630,103 shares of common stock. Under the terms of the PIPE warrants, upon certain transactions, including a merger, tender offer, sale of all or substantially all of the assets of AcelRx or if a person or group shall become the owner of 50% of our issued and outstanding common stock, which is outside of our control, each PIPE warrant holder may elect to receive a cash payment in exchange for the warrant, in an amount determined by application of the Black-Scholes option-pricing model. Accordingly, the PIPE warrants are recorded as a liability at fair value at the end of each reporting period, as determined by the Black-Scholes option-pricing model and changes to the fair value are recorded in interest income and other income (expense), net. The inputs for the Black-Scholes option-pricing model include exercise price of the PIPE warrants, market price of the underlying common shares, expected term, volatility based on a group of our peers and the risk-free rate corresponding to the expected term of the PIPE warrants. These inputs are subjective and generally require significant analysis and judgment to develop. Changes to the inputs could significantly impact the estimated fair value of the PIPE warrants, and since issuance of the PIPE warrants through December 31, 2015, changes in our stock price have had a significant impact to the estimated fair value of the PIPE warrants.

Non-Cash Interest Expense on Liability Related to Sale of Future Royalties

In September 2015, we sold certain royalty and milestone payment rights from the sales of Zalviso in the European Union by our commercial partner, Grünenthal, pursuant to the Collaboration and License Agreement, dated as of December 16, 2013, as amended, to PDL for an upfront cash purchase price of $65.0 million. We continue to have significant continuing involvement in the Royalty Monetization primarily due to our obligation to act as the intermediary for the supply of Zalviso to Grünenthal. Under the relevant accounting guidance, because of our significant continuing involvement, the Royalty Monetization has been accounted for as a liability that will be amortized using the interest method over the life of the arrangement. In order to determine the amortization of the liability, we are required to estimate the total amount of future royalty and milestone payments to be received by PDL and payments we are required to make to PDL, up to a capped amount of $195.0 million, over the life of the arrangement. The sum of the capped amount of $195.0 million, less the $61.2 million of net proceeds we received will be recorded as interest expense over the life of the liability. Consequently, we impute interest on the unamortized portion of the liability and record interest expense using an estimated interest rate for an arms-length debt transaction. Our estimate of the interest rate under the arrangement is based on the amount of royalty and milestone payments expected to be received by PDL over the life of the arrangement. Our estimate of this total interest expense resulted in an effective annual interest rate of approximately 14%. We will periodically assess the expected royalty and milestone payments using a combination of historical results, internal projections and forecasts from external sources. To the extent such payments are greater or less than our initial estimates or the timing of such payments is materially different than our original estimates, we will prospectively adjust the amortization of the liability and the interest rate.

We will record non-cash royalty revenues and non-cash interest expense within our Consolidated Statements of Comprehensive Loss over the term of the PDL agreement.

Results of Operations

Our results of operations have fluctuated from period to period and may continue to fluctuate in the future, based upon the progress of our research and development efforts and variations in the level of expenses related to developmental efforts during any given period. Results of operations for any period may be unrelated to results of operations for any other period. In addition, historical results should not be viewed as indicative of future operating results. We are subject to risks common to companies in our industry and at our stage of development, including risks inherent in our research and development efforts, reliance upon our collaborator, enforcement of our patent and proprietary rights, need for future capital, potential competition and uncertainty of clinical trial results or regulatory approvals or clearances. In order for a product candidate to be commercialized based on our research, we and our collaborators must conduct preclinical tests and clinical trials, demonstrate the efficacy and safety of our product candidates, obtain regulatory approvals or clearances and enter into manufacturing, distribution and marketing arrangements, as well as obtain market acceptance.

Years Ended December 31, 2015, 2014 and 2013

Revenue

To date, we have not generated any commercial product revenue. In September 2015, the European Commission, or EC, granted marketing approval for Zalviso in the European Union to our commercial partner, Grünenthal. We do not expect to receive any commercial sales revenue until after we ship commercial product to Grünenthal, who anticipates launching Zalviso in the European Union in the first half of 2016.

Revenue during the year ended December 31, 2015, was $19.3 million, including $14.9 million recognized under our Amended License Agreement with Grünenthal. In addition, we recognized $4.4 million in revenue under the DoD Contract.

Revenue for the year ended December 31, 2014 was $5.2 million, related to our collaboration agreement with Grünenthal.

Revenue for the year ended December 31, 2013 was $29.5 million, $27.4 million of which related to our collaboration with Grünenthal and $2.1 million related to our grant with the USAMRMC.

Collaboration Agreement Revenue

Below is a summary of revenue recognized under the Amended Agreements during the years ended December 31, 2015, 2014 and 2013 (in thousands):

	Years Ended December 31,		
	2015	2014	2013
License	$13,167	$4,560	$27,370
Joint steering committee, research and development services and demonstration devices	1,690	657	—
Total	$14,857	$5,217	$27,370

Under the terms of the Amended Agreements with Grünenthal, we received an upfront cash payment of $30.0 million, and a milestone payment of $5.0 million related to the MAA submission, which occurred in July 2014, and a $15.0 million milestone payment due to the EC approval of the MAA for Zalviso in September 2015. We are eligible to receive approximately $194.5 million in additional milestone payments, based upon successful regulatory and product development efforts ($28.5 million) and net sales target achievements ($166.0 million). As a result of the Royalty Monetization (described below), PDL will receive 75% of the European royalties under the Amended License Agreement with Grünenthal, as well as 80% of the first four commercial milestones worth $35.6 million (or 80% of $44.5 million), subject to the capped amount of $195.0 million. Grünenthal will also make tiered royalty and supply and trademark fee payments in the mid-teens up to the mid-twenties percent range, depending on the sales level achieved, on net sales of Zalviso. Refer to Note 6 “Collaboration Agreement” for additional information. A portion of the tiered royalty payment, exclusive of the supply and trademark fee payments, will be paid to PDL in connection with the Royalty Monetization, as discussed below. In September 2015, we sold certain royalty and milestone payment rights from the sales of Zalviso in the European Union by Grünenthal, pursuant to the Amended Agreements, to PDL for an upfront cash purchase price of $65.0 million. Due to our significant continuing involvement in the Royalty Monetization, primarily due to an obligation to act as the intermediary for the supply of Zalviso to Grünenthal, the Royalty Monetization has been accounted for as a liability that will be amortized using the interest method over the life of the arrangement. As the portion of the royalties and milestone payments sold to PDL are remitted by Grünenthal, the balance of the liability related to the Royalty Monetization will be effectively reduced over the life of the agreement. As such, we will record non-cash royalty revenues and non-cash interest expense within our Consolidated Statements of Comprehensive Loss over the term of the PDL agreement. There was no such non-cash royalty revenue in the year ended December 31, 2015. We do not expect to receive any non-cash royalty revenue, or other commercial sales revenue, until after Grünenthal launches Zalviso in the European Union. Refer to Note 8 “Liability Related to Sale of Future Royalties” for additional information.

Contract and Other Revenue

In May 2011, we received a grant award of $5.6 million from the USAMRMC for the development of ARX-04. Revenue related to this grant award was recognized as the related research and development expenses were incurred. As of December 31, 2013, we had completed all grant-supported research and development activities and the $5.6 million grant had been recognized in full. Refer to Note 5 “U.S. Department of Defense Funding” for additional information.

On May 11, 2015, we entered into a new award contract supported by the USAMRMC within the DoD, in which the DoD agreed to provide up to $17.0 million to support the development of our product candidate ARX-04, a proprietary, non-invasive, single-use tablet in a disposable, pre-filled, single-dose applicator for the treatment of moderate-to-severe acute pain. The DoD Contract will support development of ARX-04. Under the terms of the contract, the DoD will reimburse us for costs incurred for development, manufacturing, regulatory and clinical costs outlined in the contract in order to submit an NDA to the FDA, including reimbursement for certain personnel and overhead expenses. The period of performance under the contract began on May 11, 2015. The contract gives the DoD the option to extend the term of the contract and provide additional funding for the research. On March 2, 2016, the DoD Contract was amended to approve enrollment of additional patients in the SAP302 study, approve the addition of the SAP303 study, and extend the contract period of performance by four months from November 10, 2016 to March 9, 2017, to accommodate the increased SAP302 patient enrollment and the SAP303 study. The costs for these changes will be absorbed within the current contract value. If ARX-04 is approved by the FDA, the DoD has the option to purchase a certain number of units of commercial product pursuant to the terms of the contract. Refer to Note 5 “U.S. Department of Defense Funding” for additional information.

Cost of goods sold

Total cost of goods sold was $1.8 million for the year ended December 31, 2015. As mentioned above, the EC approved Zalviso in late September 2015. We have commenced commercial production in preparation for Grünenthal’s European launch. Under the Amended Agreements with Grünenthal, we will sell Zalviso to Grünenthal at our cost with minimal markup and will not recover indirect costs through product sales. Cost of goods sold for Zalviso shipped to Grünenthal includes the inventory costs of API, third-party contract manufacturing costs, packaging and distribution costs, shipping, handling and storage costs, depreciation and costs of the employees involved with production.

Research and Development Expenses

Conducting research and development is central to our business model. The majority of our operating expenses to date have been for research and development activities related to Zalviso. Research and development expenses included the following:

- expenses incurred under agreements with contract research organizations and clinical trial sites;
- employee-related expenses, which include salaries, benefits and stock-based compensation;
- payments to third party pharmaceutical and engineering development contractors;
- payments to third party manufacturers;
- depreciation and other allocated expenses, which include direct and allocated expenses for rent and maintenance of facilities and equipment, and equipment and laboratory and other supply costs; and
- costs for equipment and laboratory and other supplies.

Product candidates in late stages of clinical development generally have higher development costs than those in earlier stages of clinical development, primarily due to the increased size and duration of late stage clinical trials. We will incur substantial future expenditures as we seek to continue development of Zalviso, including activities to address issues raised by the FDA during their regulatory review process, as well as activities associated with potential preparation for commercialization of Zalviso, should we receive approval from the FDA. In addition, we plan to continue to incur significant research and development expenses, including the expenses associated with the continued development of ARX-04 and the additional clinical trial for Zalviso, IAP312. We do not plan to continue development of ARX-03 unless additional funding or corporate partnership resources are available to support this program.

We track external development expenses on a program-by-program basis. Our development resources are shared among all of our programs. Compensation and benefits, facilities, depreciation, stock-based compensation, and development support services are not allocated specifically to projects and are considered research and development overhead. Below is a summary of our research and development expenses during the years ended December 31, 2015, 2014 and 2013 (in thousands):

	Years Ended December 31,		
	2015	**2014**	**2013**
Zalviso	$4,950	$10,638	$16,009
ARX-04	5,848	3,068	1,957
Overhead	11,690	10,814	8,326
Total research and development expenses	$22,488	$24,520	$26,292

Due to the inherently unpredictable nature of product development, development timelines and the probability of success, development costs can differ materially from expectations. While we are currently focused on advancing Zalviso and the continued development of ARX-04, our future research and development expenses will depend on the clinical success of each product candidate as well as ongoing assessments of the commercial potential of our product candidates. In addition, we cannot predict which product candidates may be subject to future collaborations, when these arrangements will be secured, if at all, and to what degree these arrangements would affect our development plans and capital requirements.

Total research and development expenses for years ended December 31, 2015, 2014 and 2013 were as follows (in thousands, except percentages):

	Years Ended December 31,			Increase/ (Decrease)	Increase/ (Decrease)	Percentage Increase/ (Decrease)	Percentage Increase/ (Decrease)
	2015	**2014**	**2013**	**2015 vs. 2014**	**2014 vs. 2013**	**2015 vs. 2014**	**2014 vs. 2013**
Research and development expenses	$22,488	$24,520	$26,292	$ (2,032)	$ (1,772)	(8)%	(7)%

The $2.0 million decrease in research and development expenses during the year ended December 31, 2015, as compared to the year ended December 31, 2014, was primarily attributable to a $5.7 million decrease related to the Zalviso development program in response to the CRL received from the FDA in March 2015, partially offset by a $2.8 million increase related to ARX-04 as we advanced development into Phase 3 clinical trials, and a $0.9 million increase in overhead-related costs, primarily facilities expense, and personnel-related expenses, including stock-based compensation.

The $1.8 million decrease in research and development expenses during the year ended December 31, 2014, as compared to the year ended December 31, 2013, was primarily attributable to a $5.4 million decrease related to our Zalviso Phase 3 clinical program conducted primarily in 2013, partially offset by an increase of $1.1 million related to our ARX-04 development program as we prepared for the Phase 3 clinical program and an increase of $2.5 million in overhead expenses, primarily due to increased personnel-related expenses, including stock-based compensation, primarily related to an increase in headcount to support continued development of Zalviso and ARX-04.

General and Administrative Expenses

General and administrative expenses consisted primarily of salaries, benefits and stock-based compensation for personnel in administration, finance, marketing and business development activities. Other significant expenses included legal expenses related to litigation and patent protection of our intellectual property, allocated facility costs and professional fees for general legal, audit and consulting services. We expect general and administrative expenses to continue to decrease in the first quarter of 2016 as compared to the first quarter of 2015, as a result of the cost reduction plan, and then for the remainder of 2016 to remain comparable to 2015 expenses, as we focus our efforts on further development and seeking marketing approval for Zalviso, and the continued development of ARX-04.

Total general and administrative expenses for the years ended December 31, 2015, 2014 and 2013 were as follows (in thousands, except percentages):

	Years Ended December 31,			Increase/ (Decrease)	Increase/ (Decrease)	Percentage Increase/ (Decrease)	Percentage Increase/ (Decrease)
	2015	2014	2013	2015 vs. 2014	2014 vs. 2013	2015 vs. 2014	2014 vs. 2013
General and administrative expenses	$14,203	$18,346	$9,877	$ (4,143)	$ 8,469	(23)%	86 %

The $4.1 million decrease in general and administrative expenses during the year ended December 31, 2015, as compared to the year ended December 31, 2014, was primarily due to a $3.9 million decrease in market research and outside services, primarily related to market research activities for Zalviso, and a $0.2 million decrease in headcount-related expenses, primarily due to the March 2015 restructuring.

The $8.5 million increase in general and administrative expenses during the year ended December 31, 2014, as compared to the year ended December 31, 2013, was primarily due to a $3.7 million increase in market research and use of outside services, primarily related to market research activities for Zalviso, and an increase of $4.8 million, primarily in headcount-related expenses, including recruiting efforts, to support organizational growth for the potential commercialization of Zalviso, and consulting and other professional services fees.

Restructuring Costs

In March 2015, we received correspondence from the FDA stating that in addition to the bench testing and two Human Factors studies we had performed in response to the issues identified in the CRL, a clinical trial is needed to assess the risk of inadvertent dispensing and overall risk of dispensing failures. On March 19, 2015, our Board of Directors, in connection with our efforts to reduce operating costs, conserve capital, focus the Company's financial and development resources on working with the FDA to seek marketing approval for Zalviso, and continuing development of ARX-04, implemented a cost reduction plan. The cost reduction plan reduced our workforce by 19 employees, approximately 36% of total headcount, in the first quarter of 2015.

	Years Ended December 31,			Increase/ (Decrease)
	2015	2014	2013	2015 vs. 2014
Restructuring costs	$756	$ —	$ —	$ 756

Restructuring cost in the year ended December 31, 2015 consists of employee termination benefit costs of $0.8 million. The restructuring liability has been fully disbursed as of December 31, 2015.

Other (Expense) Income

Total other (expense) income for the years ended December 31, 2015, 2014 and 2013 was as follows (in thousands, except percentages):

	Years Ended December 31,			Increase/ (Decrease)	Increase/ (Decrease)	Percentage Increase/ (Decrease)	Percentage Increase/ (Decrease)
	2015	2014	2013	2015 vs. 2014	2014 vs. 2013	2015 vs. 2014	2014 vs. 2013
Interest expense	$(2,977)	$(2,639)	$(1,518)	$ (338)	$ (1,121)	13 %	74 %
Interest income and other income (expense), net	1,720	6,935	(15,241)	(5,215)	22,176	(75)%	(146)%
Non-cash interest expense on liability related to sale of future royalties	(2,428)	—	—	(2,428)	—	— %	— %
Total other (expense) income	$(3,685)	$4,296	$(16,759)	$ (7,981)	$ 21,055	(186)%	(126)%

Interest expense consisted primarily of interest accrued or paid on our debt obligation agreements and amortization of debt discounts. Interest expense for all periods pertains to interest on our Loan and Security Agreement with Hercules. In December 2013, we entered into the Amended Loan Agreement with Hercules, which amends and restates the Loan and Security Agreement. The overall debt facility was increased to $40.0 million, and the maturity was extended to October 1, 2017. As of December 31, 2015, the outstanding principal owed to Hercules was $20.9 million. On June 16, 2014, we borrowed the second tranche of $10.0 million. We did not have access to the third tranche, of up to $15.0 million, as we did not receive FDA approval of Zalviso by August 1, 2015. As a result of the higher average principal balance in the year ended December 31, 2015 as compared to the year ended December 31, 2014, and in the year ended December 31, 2014 as compared to the year ended December 31, 2013, the amount of interest expense incurred increased in each consecutive year.

On September 18, 2015, concurrently with the closing of the Royalty Monetization, the Company entered into a Consent and Amendment No. 2, or Amendment No. 2, to the Amended Loan Agreement. Amendment No. 2 provided for an interest only period from October 1, 2015 through March 31, 2016, with the potential for further extension to September 30, 2016 upon satisfaction of certain conditions, which have since been satisfied.

Interest income and other income (expense), net, during the years ended December 31, 2015, 2014 and 2013 consisted primarily of the change in the fair value of our warrants, or PIPE warrants, issued in connection with our private placement of our common stock, which was completed in June 2012. During the year ended December 31, 2013, we also recorded a loss of $1.2 million associated with extinguishment of our original loan agreement with Hercules, which we entered into in 2011, and amended in December 2013.

The decrease in interest income and other income (expense), net, during the year ended December 31, 2015 as compared to the year ended December 31, 2014, was primarily attributable to fewer PIPE warrants outstanding at December 31, 2015, as compared to December 31, 2014, and a smaller decrease in our stock price during the year ended December 31, 2015, as compared to the year ended December 31, 2014, which is a primary driver in the Black-Scholes valuation model used to estimate the fair value of the PIPE warrants. Interest income and other income (expense), net, during the year ended December 31, 2015 also included $0.5 million in impairment charges related to leasehold improvements in our corporate offices.

The decrease in interest income and other income (expense), net, during the year ended December 31, 2014, as compared to the year ended December 31, 2013, of $22.2 million was primarily attributable to fewer PIPE warrants outstanding at December 31, 2014, compared to December 31, 2013, and a decrease in our stock price during the year ended December 31, 2014 as compared to a significant increase in our stock price during the year ended December 31, 2013, which is the primary driver in the Black-Scholes valuation model used to estimate the fair value of the PIPE warrants. This decrease was partially offset by the $1.2 million loss we recorded in 2013 related to the extinguishment of the original Hercules debt arrangement.

The increase in non-cash interest expense on liability related to the Royalty Monetization during the year ended December 31, 2015 as compared to the year ended December 31, 2014, is attributable to the royalty sale transaction that we completed in September 2015. As described above, the Royalty Monetization has been recorded as debt under the applicable accounting guidance. We impute interest on the liability and record interest expense based on the amount and timing of royalty and milestone payments expected to be received by PDL over the life of the arrangement. There are a number of factors that could materially affect the estimated interest rate and we will assess this estimate on a periodic basis. As a result, future interest rates could differ significantly and any such change in interest rate will be adjusted prospectively.

Provision for Income Taxes

The Royalty Monetization results in a taxable gain of more than $60.0 million, the majority of which is expected to be offset with net operating loss carryforwards; however, we are expected to be subject to U.S. federal alternative minimum taxes in 2015, as reflected in our provision for income taxes in the third quarter of 2015.

Total provision for income taxes for the years ended December 31, 2015, 2014 and 2013 was as follows (in thousands, except percentages):

	Years Ended December 31,			Increase/ (Decrease)
	2015	2014	2013	2015 vs. 2014
Provision for income taxes	$760	$ —	$ —	$760

Liquidity and Capital Resources

Liquidity

We have incurred losses and generated negative cash flows from operations since inception. We expect to continue to incur significant losses in 2016 and may incur significant losses and negative cash flows from operations for the foreseeable future. We have funded our operations primarily through issuance of equity securities, borrowings, payments from our commercial partner, Grünenthal, monetization of certain future royalties and commercial sales milestones from the sales of Zalviso by Grünenthal, and our contracts with the DoD.

As of December 31, 2015, we had cash, cash equivalents and investments totaling $113.5 million compared to $75.4 million as of December 31, 2014. The increase was primarily attributable to the $61.2 million in net proceeds in connection with the Royalty Monetization, partially offset by cash required to fund our continuing operations, as we continue our research and development activities. We anticipate that our existing capital resources will permit us to meet our capital and operational requirements through at least the first half of 2017. While we believe we have sufficient capital to meet our operational requirements through at least the first half of 2017, our expectations may change depending on a number of factors. For example, based on their review of the protocol we have submitted for the requested clinical trial for Zalviso, the FDA may require a scope or design change that is beyond what our current and estimated future capital resources can support. We believe that together with the support from the DoD Contract, we have sufficient resources to complete the Phase 3 development program for ARX-04 through submission of the NDA to the FDA. However, our existing capital resources will not be sufficient to fund our operations until such time as we may be able to generate sufficient revenues to sustain our operations.

On September 18, 2015, we sold a portion of the expected royalty stream and commercial milestone payments from the sales of Zalviso in the EU by Grünenthal to PDL. As mentioned above, we received net proceeds of $61.2 million in the Royalty Monetization. PDL will receive 75% of the European royalties under the Amended License Agreement with Grünenthal, as well as 80% of the first four commercial milestones worth $35.6 million (or 80% of $44.5 million), subject to the capped amount of $195.0 million. We are entitled to receive all remaining amounts under the Amended License Agreement which include 25% of the European royalties, 20% of the first four commercial milestones, 100% of the remaining commercial milestones and all development milestones of $43.5 million, including the $15.0 million payment for the EC approval of the MAA for Zalviso, which we received in the fourth quarter of 2015. The total liability related to sale of future royalties to PDL as of December 31, 2015 was $63.6 million.

On December 16, 2013, AcelRx and Grünenthal entered into the License Agreement, and related Manufacture and Supply Agreement, or the MSA, and together with the License Agreement, the Agreements. The License Agreement grants Grünenthal rights to commercialize Zalviso, or the Product, in the Territory for human use in pain treatment within or dispensed by hospitals, hospices, nursing homes and other medically-supervised settings. We retain rights with respect to the Product in countries outside the Territory, including the United States, Asia and Latin America. On July 22, 2015, the Company entered into amendments to the License Agreement, or the License Amendment, and together with the License Agreement, the Amended License Agreement, and the MSA, or the MSA Amendment, and together with the MSA, the Amended MSA, between the Company and Grünenthal, each effective as of July 17, 2015, and together, the Amended Agreements.

Under the terms of the Amended Agreements, we received an upfront cash payment of $30.0 million, a milestone payment of $5.0 million related to the MAA submission in the third quarter of 2014 and an additional $15.0 million milestone payment related to the EC approval of the MAA for Zalviso in September 2015. In addition, under the terms of the Amended Agreements, we are eligible to receive approximately $194.5 million in additional milestone payments, based upon successful regulatory and product development efforts ($28.5 million) and net sales target achievements ($166.0 million). Grünenthal will also make tiered royalty, supply and trademark fee payments in the mid-teens up to the mid-twenties percent range, depending on the level of sales achieved, on net sales of Zalviso in the Territory. A portion of the tiered royalty payment, exclusive of the supply and trademark fee payments, will be paid to PDL in connection with the Royalty Monetization, as discussed above.

On December 16, 2013, AcelRx entered into an Amended and Restated Loan and Security Agreement with Hercules Technology II, L.P. and Hercules Technology Growth Capital, Inc., together, the Lenders, or the Amended Loan Agreement, under which AcelRx may borrow up to $40.0 million in three tranches. The loans are represented by secured convertible term promissory notes, collectively, the Notes. The Amended Loan Agreement amends and restates the Loan and Security Agreement between AcelRx and the Lenders dated as of June 29, 2011. We borrowed the first tranche of $15.0 million upon closing of the transaction on December 16, 2013, and the second tranche of $10.0 million on June 16, 2014. We used approximately $8.6 million of the proceeds from the first tranche to repay our obligations under the Loan and Security Agreement with the Lenders. We recorded the new debt at an estimated fair value of $24.9 million as of December 31, 2014.

On September 24, 2014, we entered into Amendment No. 1 to the Amended Loan Agreement with Hercules. Amendment No. 1 extended the time period under which we could draw down the third tranche, of up to $15.0 million, from March 15, 2015 to August 1, 2015, subject to AcelRx obtaining approval for Zalviso from the FDA. We did not receive FDA approval of Zalviso by August 1, 2015 and as such, did not have access to the third tranche.

On September 18, 2015, concurrently with the closing of the Royalty Monetization, we entered into a Consent and Amendment No. 2, or Amendment No. 2, to the Amended Loan Agreement with the Lenders. Amendment No. 2 includes an interest only period from October 1, 2015 through March 31, 2016, with the potential for further extension to September 30, 2016 upon satisfaction of certain conditions, which have since been satisfied. Loans under the Amended Loan Agreement mature on October 31, 2017. As of December 31, 2015, the outstanding principal owed to Hercules was $20.9 million.

Our cash and investment balances are held in a variety of interest bearing instruments, including obligations of U.S. government agencies, money market funds and time deposits. Cash in excess of immediate requirements is invested with a view toward capital preservation and liquidity.

Cash Flows

	Years Ended December 31,		
	2015	**2014**	**2013**
	(in thousands)		
Net cash used in operating activities	$(19,953)	$(34,456)	$(487)
Net cash provided by (used in) investing activities	8,203	(5,776)	(6,920)
Net cash provided by financing activities	59,634	11,869	47,876

Cash Flows from Operating Activities

The primary use of cash for our operating activities during these periods was to fund the development of our product candidates, including commercial readiness activities for our product candidate, Zalviso. Our cash used for operating activities also reflected changes in our working capital, net of adjustments for non-cash charges, such as depreciation and amortization of our fixed assets, stock-based compensation, non-cash interest expense related to the sale of future royalties, interest expense related to our debt financings and the revaluation of our PIPE warrant liability and the contingent put option liability.

Cash used in operating activities of $20.0 million during the year ended December 31, 2015, reflected a net loss of $24.4 million, partially offset by aggregate non-cash charges of $8.8 million, and a net change of $4.4 million in our net operating assets and liabilities. Non-cash charges included $5.0 million for stock-based compensation, $2.0 million for depreciation and amortization of our fixed assets, and $2.4 million of non-cash interest expense related to the Royalty Monetization, partially offset by a $2.1 million for the change in fair value of our PIPE warrant liability and contingent put liability. The net change in our operating assets and liabilities included a $3.3 million increase in accounts receivable.

Cash used in operating activities of $34.5 million during the year ended December 31, 2014, reflected a net loss of $33.4 million, partially offset by aggregate non-cash charges of $1.1 million. Non-cash charges included $4.4 million for stock-based compensation, partially offset by $7.0 million for the change in fair value of our PIPE warrant liability and contingent put liability.

Net cash used in operating activities of $0.5 million during the year ended December 31, 2013 reflected a net loss of $23.4 million, partially offset by aggregate non-cash charges of $20.0 million and a net change of $2.9 million in our net operating assets and liabilities. Non-cash charges primarily included $14.1 million for the revaluation of the PIPE warrant liability and the contingent put option liability, $3.5 million in stock-based compensation and $1.2 million for the loss on extinguishment of debt associated with our original loan agreement with Hercules, which was amended in December 2013. The net change in our operating assets and liabilities was primarily a result of an increase in deferred revenue of $2.6 million associated with our collaboration agreement with Grünenthal and a decrease in prepaid expenses of $1.1 million due to completion of our Phase 3 clinical trials for Zalviso in 2013.

Cash Flows from Investing Activities

Our investing activities have consisted primarily of our capital expenditures and purchases and sales and maturities of our available-for-sale investments.

During the year ended December 31, 2015, cash provided by investing activities of $8.2 million was primarily as a result of $16.9 million in proceeds from maturity of investments, partially offset by $7.2 million for purchases of investments and $1.5 million for purchases of property and equipment.

During the year ended December 31, 2014, cash used in investing activities of $5.8 million was primarily as a result of $17.4 million for purchases of investments and $5.5 million for purchases of property and equipment, partially offset by $17.2 million in proceeds from maturity of investments.

During the year ended December 31, 2013, cash used in investing activities of $6.9 million was primarily a result of $28.0 million in purchases of investments and $3.3 million in purchases of property and equipment, partially offset by $24.4 million in maturities of investments.

Cash Flows from Financing Activities

Cash flows from financing activities primarily reflect proceeds from the sale of future royalties, proceeds from the sale of our securities, proceeds from our debt financings and payments made on such debt financings. As of December 31, 2015, the total liability related to the sale of future royalties was $63.6 million and the balance of the outstanding debt with Hercules was $20.9 million.

During the year ended December 31, 2015, cash provided by financing activities of $59.6 million was primarily due to net proceeds from the Royalty Monetization of $61.2 million, proceeds from the issuance of common stock upon the exercise of common stock options and ESPP issuances of $3.2 million, partially offset by payments of long-term debt of $4.5 million under the Amended Loan Agreement with Hercules.

During the year ended December 31, 2014, cash provided by financing activities of $11.9 million was primarily due to the drawdown of the second tranche of the Hercules debt of $10.0 million.

During the year ended December 31, 2013, cash provided by financing activities was primarily a result of the receipt of $47.9 million in proceeds from an underwritten public offering in July 2013, net of offering costs and underwriting discounts, and proceeds of $15.0 million from the Amended Loan Agreement with Hercules in December 2013, partially offset by payments of long-term debt of $16.3 million, including payment of the remaining principal of $8.5 million at the time of the amendment, and $7.8 million in principal payments made prior to the amendment.

Operating Capital and Capital Expenditure Requirements

We expect our rate of cash usage to increase in the future, in particular to support our product development activities, including continued development of Zalviso, ARX-04 and the potential commercialization of our product candidates, if approved outside of the Grünenthal Territory. Our future cash needs anticipate the receipt of reimbursement for qualified expenses under the DoD Contract. We anticipate that our existing capital resources will permit us to meet our capital and operational requirements through at least the first half of 2017. Our current operating plan includes the continued development of ARX-04, specifically the filing of the NDA in 2016. These assumptions may change as a result of many factors. For example, although the FDA has reviewed the protocol for the additional clinical trial for Zalviso and we've incorporated their comments into the trial design, pending the results of this additional clinical trial, the FDA may require us to complete additional work to resubmit the NDA for Zalviso. We will continue to evaluate the work necessary to gain approval of Zalviso in the U.S. The final pathway forward for Zalviso could have a material impact on our operating spend. Our forecast of the period of time through which our financial resources will be adequate to support our operations is a forward-looking statement that involves risks and uncertainties, and actual results could vary materially. Additional capital may not be available on terms acceptable to us, or at all. If adequate funds are not available, or if the terms underlying potential funding sources are unfavorable, our business and our ability to develop our product candidates would be harmed.

Our future capital requirements may vary materially from our expectations based on numerous forward looking factors, including but not limited to the following:

- the outcome, timing and cost of regulatory approvals;
- expenditures related to the activities required in support of our resubmission of the Zalviso NDA, including an additional clinical trial for Zalviso, as requested by the FDA;
- expenditures related to our commercialization preparation of Zalviso;
- future manufacturing, selling and marketing costs related to Zalviso, including our contractual obligations to Grünenthal;
- the initiation, progress, timing and completion of clinical trials for our product candidates, including ARX-04;
- changes in the focus and direction of our business strategy and/or research and development programs;
- milestone and royalty revenue we receive under our collaborative development and commercialization arrangements;

- delays that may be caused by changing regulatory requirements;
- the number of product candidates that we pursue;
- the initiation, progress, timing and completion of clinical trials for our product candidates and potential product candidates;
- the costs involved in filing and prosecuting patent applications and enforcing and defending patent claims;
- the timing and terms of future in-licensing and out-licensing transactions;
- the cost and timing of establishing sales, marketing, manufacturing and distribution capabilities;
- the cost of procuring clinical and commercial supplies of our product candidates;
- the extent to which we acquire or invest in businesses, products or technologies; and
- the expenses associated with the pending securities lawsuit, as well as any other litigation.

We will need substantial funds to:

- commercialize any products we market, including ARX-04 and Zalviso, if approved outside of the Grünenthal Territory;
- manufacture and market our product candidates;
- conduct preclinical and clinical testing of our product candidates; and
- conduct research and development programs.

Our existing capital resources may not be sufficient to fund our operations until such time as we may be able to generate sufficient revenues to sustain our operations. To the extent that our capital resources are insufficient to meet our future capital requirements, we will have to raise additional funds through the sale of our equity securities, monetization of current and future assets, issuance of debt or debt-like securities or from development and licensing arrangements to continue our development programs. We may be unable to raise such additional capital on favorable terms, or at all. If we raise additional capital by selling our equity or convertible debt securities, the issuance of such securities could result in dilution of our shareholders' equity positions. If adequate funds are not available we may have to:

- significantly curtail or put on hold commercialization or development efforts of our product candidates or other operations;

- obtain funds through entering into collaboration agreements on unattractive terms; and/or

- delay, postpone or terminate planned clinical trials.

Contractual Obligations

The following table summarizes our long-term contractual obligations at December 31, 2015:

	Payments Due by Period				
Contractual obligations	**Total**	**2016**	**2017-2019**	**2020-2021**	**Thereafter**
	(in thousands)				
Operating leases[1]	$1,516	$717	$ 799	$ —	$ —
Purchase obligations[2]	400	200	200	—	—
Principal payments on long-term debt[3]	22,166	4,541	17,625	—	—
Interest payments on long-term debt	2,539	1,859	680	—	—
Repayment of liability related to the sale of future royalties	195,000	118	11,709	29,798	153,375
Total contractual obligations	$221,621	$7,435	$ 31,013	$ 29,798	$ 153,375

(1) Operating lease includes base rent for facilities we occupy in Redwood City, California.

(2) We issue inventory and research and development program related purchase orders in the normal course of business. We do not consider purchase orders to be firm inventory or research and development program related commitments; therefore, they are excluded from the table above. If we choose to cancel a purchase order, we may be obligated to reimburse the vendor for unrecoverable outlays incurred prior to cancellation.

(3) The loan and security agreement with Hercules includes a $1.7 million balloon payment due on maturity of the loan, October 1, 2017, and is included in the table above.

Operating leases

In December 2011, we entered into a non-cancelable lease agreement, or the Existing Lease, for approximately 13,787 square feet of office and laboratory facilities in Redwood City, California, or the Current Premises, which serve as the Company headquarters, effective April 2012. The lease agreement expires in May 2016. Rent expense from the facility lease is recognized on a straight-line basis from the inception of the lease in December 2011, the early access date, through the end of the lease.

In May 2014, we entered into an amendment, or the Lease Amendment, to the Existing Lease. Pursuant to the Lease Amendment, the term of the Existing Lease has been extended for a period of twenty (20) months and twenty-two (22) days and expiring January 31, 2018, or the Expiration Date, unless sooner terminated pursuant to the terms of the Existing Lease. In addition, the Lease Amendment included a new lease on an additional 12,106 square feet of office space, or the Expansion Space, which is adjacent to the Current Premises. The new lease for the Expansion Space has a term of 42 months commencing on August 1, 2014, and expiring on the Expiration Date. We have an option to extend the term of the Lease Amendment for an additional five years, which would commence upon the Expiration Date, at a market rate determined according to the Existing Lease.

In October 2015, we executed an agreement to sublease 11,871 square feet of the Expansion Space for a term of 26 months commencing on December 1, 2015. The sublessee is entitled to abatement of the first two monthly installments of rent. Subsequent monthly installments of rent start at a rental rate of $2.05 per square foot (subject to agreed nominal increases). Upon the completion of the sublease, we have the option to take back the subleased space.

Purchase obligations

Patheon

In January 2013, we entered into a Manufacturing Services Agreement, or the Services Agreement, with Patheon Pharmaceuticals, Inc., or Patheon, relating to the manufacture of sufentanil sublingual tablets, for use with Zalviso.

Under the terms of the Services Agreement, we have agreed to purchase, subject to Patheon's continued material compliance with the terms of the Services Agreement, all of our sufentanil sublingual tablet requirements for the United States, Canada and Mexico from Patheon during the Initial Term of the Services Agreement (as defined below), and at least eighty percent (80%) of its sufentanil sublingual tablet requirements for such territories after the Initial Term. The term of the Services Agreement extends until December 31, 2017, or the Initial Term, and will automatically renew thereafter for periods of two years, unless terminated by either party upon eighteen months' prior written notice; provided, however, that the Services Agreement may not be terminated without cause prior to the end of the Initial Term.

We also entered into a Capital Expenditure and Equipment Agreement, or the Capital Agreement, with Patheon. Under the terms of the Capital Agreement, as amended in January 2014, or the Amended Capital Agreement, we have made and have the option to make certain future modifications to Patheon's Cincinnati facility and which would be our responsibility. If additional equipment and facility modifications are required to meet our Product needs, we may be required to contribute to the cost of such additional equipment and facility modifications. Under the Amended Capital Agreement, we made payments in 2012 and 2013 totaling $480,000 to Patheon to partially offset taxes incurred and paid by Patheon in connection with facility modifications already completed by Patheon. We can seek reimbursement from Patheon for these payments if we receive approval from the U.S. Food and Drug Administration for Zalviso. The Amended Capital Agreement further requires that we pay a maximum "overhead fee" of $200,000 annually during the term of the Services Agreement, which amount may be reduced to $0 based on the amount of annual revenues earned by Patheon under the Services Agreement and pre-existing development agreements with Patheon. No fee was due in 2014 or 2015 based on the amount of revenues earned by Patheon from AcelRx in 2014 and 2015.

Long-term debt

Hercules Loan

On December 16, 2013, we entered into an Amended and Restated Loan and Security Agreement with Hercules Technology II, L.P. and Hercules Technology Growth Capital, Inc., together, the Lenders, or the Amended Loan Agreement, under which we may borrow up to $40.0 million in three tranches. On September 24, 2014, we entered into Amendment No. 1 to the Amended Loan Agreement with Hercules. Amendment No. 1 extended the time period under which we could draw down the third tranche, of up to $15.0 million, from March 15, 2015 to August 1, 2015, subject to AcelRx obtaining approval for Zalviso from the FDA. We did not receive FDA approval of Zalviso by August 1, 2015 and as such, did not have access to the third tranche. On September 18, 2015, concurrently with the closing of the Royalty Monetization, we entered into a Consent and Amendment No. 2, or Amendment No. 2, to the Amended Loan Agreement with the Lenders. Amendment No. 2 includes an interest only period from October 1, 2015 through March 31, 2016, with the potential for further extension to September 30, 2016 upon satisfaction of certain conditions, which have since been satisfied. After the expiration of the interest only period, we will make 13 monthly payments of $1.7 million beginning in October 2016 through October 2017. In addition, a final payment equal to $1.7 million will be due in October 2017. Loans under the Amended Loan Agreement mature on October 31, 2017.

The interest rate for each tranche will be calculated at a rate equal to the greater of either (i) 9.10% plus the prime rate as reported from time to time in The Wall Street Journal minus 5.25%, and (ii) 9.10%. Our obligations under the Amended Loan Agreement are secured by a security interest in substantially all of our assets, other than our intellectual property and those assets sold under the Royalty Monetization.

Liability related to the sale of future royalties

Royalty Monetization with PDL

In September 2015, we sold certain royalty and milestone payment rights from the sales of Zalviso in the European Union by our commercial partner, Grünenthal, pursuant to the Collaboration and License Agreement, dated as of December 16, 2013, as amended, to PDL for an upfront cash purchase price of $65.0 million. PDL will receive 75% of the European royalties under the Amended License Agreement with Grünenthal, as well as 80% of the first four commercial milestones worth $35.6 million (or 80% of $44.5 million), subject to the capped amount of $195.0 million. The Royalty Monetization has been accounted for as a liability that will be amortized using the interest method over the life of the arrangement. The timing and the amount of the repayment of this liability is contingent upon the receipt of the related royalty and milestone payments from Grünenthal. Upon receipt of these royalty and milestone payments from Grünenthal, we will remit the applicable portion to PDL.

Off-Balance Sheet Arrangements

Through December 31, 2015, we have not entered into any off-balance sheet arrangements and do not have any holdings in variable interest entities.

Item 7A. Quantitative and Qualitative Disclosures About Market Risk

Our cash, cash equivalents and short-term investments as of December 31, 2015, consisted primarily of money market funds and U.S. government agency securities. We do not have any auction rate securities on our Consolidated Balance Sheet, as they are not permitted by our investment policy. Our cash is invested in accordance with an investment policy approved by our board of directors which specifies the categories, allocations, and ratings of securities we may consider for investment. We do not believe our cash, cash equivalents and short-term investments have significant risk of default or illiquidity.

Our primary exposure to market risk is interest income sensitivity, which is affected by changes in the general level of U.S. interest rates, particularly because the majority of our investments are in short-term marketable debt securities. The primary objective of our investment activities is to preserve principal while at the same time maximizing the income we receive from our investments without significantly increasing risk. In an attempt to limit interest rate risk, we follow guidelines to limit the average and longest single maturity dates, place our investments with high quality issuers and follow internally developed guidelines to limit the amount of credit exposure to any one issuer. Some of

the securities that we invest in may be subject to market risk. This means that a change in prevailing interest rates may cause the value of the investment to fluctuate. For example, if we purchase a security that was issued with a fixed interest rate and the prevailing interest rate later rises, the value of our investment may decline. If a 10 percent change in interest rates were to have occurred on December 31, 2015, this change would not have had a material effect on the fair value of our investment portfolio as of that date. In general, money market funds are not subject to market risk because the interest paid on such funds fluctuates with the prevailing interest rate.

In addition, domestic and international equity markets have experienced and may continue to experience heightened volatility and turmoil based on domestic and international economic conditions and concerns. In the event these economic conditions and concerns continue and the markets continue to remain volatile, our results of operations could be adversely affected by those factors in many ways, including making it more difficult for us to raise funds if necessary and our stock price may further decline. In addition, we maintain significant amounts of cash and cash equivalents that are not federally insured. If economic instability continues, we cannot provide assurance that we will not experience losses on these investments.

Item 8. Financial Statements and Supplementary Data

The financial statements required by this item are attached to this Form 10-K beginning with page F-1.

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

We have carried out an evaluation, under the supervision, and with the participation, of management including our principal executive officer and principal financial officer, of our disclosure controls and procedures (as defined in Rule 13a-15(e)) of the Securities Exchange Act of 1934, as amended, or the Exchange Act) as of the end of the period covered by this Annual Report on Form 10–K. Based on their evaluation, our principal executive officer and principal financial officer concluded that, subject to the limitations described below, our disclosure controls and procedures were effective as of December 31, 2015.

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Limitations on the Effectiveness of Controls. A control system, no matter how well conceived and operated, can provide only reasonable, not absolute, assurance that the objectives of the control system are met. Because of inherent limitations in all control systems, no evaluation of controls can provide absolute assurance that all control issues, if any, within an organization have been detected. Accordingly, our disclosure controls and procedures are designed to provide reasonable, not absolute, assurance that the objectives of our disclosure control system are met and, as set forth above, our principal executive officer and principal financial officer have concluded, based on their evaluation as of the end of the period covered by this report, that our disclosure controls and procedures were sufficiently effective to provide reasonable assurance that the objectives of our disclosure control system were met. We continue to implement, improve and refine our disclosure controls and procedures and our internal control over financial reporting.

Changes in Internal Control over Financial Reporting

There have been no significant changes in our internal control over financial reporting that have materially affected, or are reasonably likely to materially affect, internal control over financial reporting during the fiscal quarter ended December 31, 2015.

Management's Annual Report on Internal Control over Financial Reporting

The following report is provided by management in respect of AcelRx Pharmaceuticals' internal control over financial reporting (as defined in Rules 13a-15(f) and 15d-15(f) under the Exchange Act):

1. AcelRx Pharmaceuticals' management is responsible for establishing and maintaining adequate internal control over financial reporting.

2. AcelRx Pharmaceuticals management has used the Committee of Sponsoring Organizations of the Treadway Commission, or COSO, framework (2013 framework) to evaluate the effectiveness of internal control over financial reporting. Management believes that the COSO framework is a suitable framework for its evaluation of financial reporting because it is free from bias, permits reasonably consistent qualitative and quantitative measurements of AcelRx Pharmaceuticals' internal control over financial reporting, is sufficiently complete so that those relevant factors that would alter a conclusion about the effectiveness of AcelRx Pharmaceuticals' internal control over financial reporting are not omitted and is relevant to an evaluation of internal control over financial reporting.

3. Management has assessed the effectiveness of AcelRx Pharmaceuticals' internal control over financial reporting as of December 31, 2015 and has concluded that such internal control over financial reporting was effective.

OUM & Co. LLP, our independent registered public accounting firm, has attested to and issued a report on the effectiveness of our internal control over financial reporting, which is included herein.

The Board of Directors and Stockholders of

AcelRx Pharmaceuticals, Inc.

We have audited AcelRx Pharmaceuticals, Inc.'s internal control over financial reporting as of December 31, 2015, based on criteria established in *Internal Control – Integrated Framework (2013)* issued by the Committee of Sponsoring Organizations of the Treadway Commission (the COSO criteria). AcelRx Pharmaceuticals, Inc.'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 Annual Report on Internal Control over Financial Reporting* included in Item 9A. Our responsibility is to express an opinion on the Company's internal control over financial reporting based on our audit.

We conducted our audit in accordance with the standards of the Public Company Accounting Oversight Board (United States). 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, and testing and evaluating the design and operating effectiveness of internal control based on the assessed risk. Our audit also included performing such other procedures as we considered necessary in the circumstances. We believe that our audit provides a reasonable basis for our opinion.

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.

In our opinion, AcelRx Pharmaceuticals, Inc. maintained, in all material respects, effective internal control over financial reporting as of December 31, 2015, based on the COSO criteria.

We also have audited, in accordance with the standards of the Public Company Accounting Oversight Board (United States), the consolidated balance sheet of AcelRx Pharmaceuticals, Inc. as of December 31, 2015, and the related consolidated statements of comprehensive loss, stockholders' equity, and cash flows for the year then ended, and our report dated March 7, 2016 expressed an unqualified opinion thereon.

/s/ OUM & CO. LLP

Item 9B. Other Information

None.

PART III

Item 10. Directors, Executive Officers and Corporate Governance

The information required by this item is hereby incorporated by reference from the information under the captions "Election of Directors," "Board of Directors Meetings and Committees—Board Committees" and "Executive Officers" contained in the Company's definitive Proxy Statement, to be filed with the Securities and Exchange Commission no later than 120 days from the end of the Company's last fiscal year in connection with the solicitation of proxies for its 2016 Annual Meeting of Stockholders. The information required by Section 16(a) is incorporated by reference from the information under the caption "Security Ownership of Certain Beneficial Owners and Management—Section 16(a) Beneficial Ownership Reporting Compliance" in the Proxy Statement.

The Company has adopted a code of ethics that applies to its Chief Executive Officer, Chief Financial Officer, and to all of its other officers, directors, employees and agents. The code of ethics is available at the Corporate Governance section of the Investor Relations page on the Company's website at *www.acelrx.com*. The Company intends to disclose future amendments to, or waivers from, certain provisions of its code of ethics on the above website within five business days following the date of such amendment or waiver.

Item 11. Executive Compensation

The information required by this item is incorporated by reference from the information under the caption "Board of Directors Meetings and Committees—Compensation Committee Interlocks and Insider Participation," "Executive Compensation" and "Executive Compensation—Compensation Committee Report" in the Company's Proxy Statement referred to in Item 10 above.

Item 12. Security Ownership of Certain Beneficial Owners and Management and Related Stockholder Matters

Equity Compensation Plan Information

The following table provides certain information with respect to our equity compensation plans in effect as of December 31, 2015.

Plan Category	Column A Number of securities to be issued upon exercise of outstanding options, warrants and rights	Column B Weighted-average exercise price of outstanding options, warrants and rights	Column C Number of securities remaining available for future issuance under equity compensation plans (excluding securities reflected in column A) [3]
Equity compensation plans approved by security holders[1]	4,618,949	$ 5.77	2,945,509
Equity compensation plans not approved by security holders	—	$ —	—
Total	4,618,949		2,945,509

(1) Consists of the 2006 Plan, the 2011 Plan and the ESPP.

(2) Consists of shares available for future issuance under the 2011 Incentive Plan, including shares that were previously available for future issuance under the 2006 Plan at the time of the execution and delivery of the underwriting agreement for our IPO, and the ESPP. As of December 31, 2015, 2,654,302 shares of common stock were available for issuance under the 2011 Incentive Plan and 291,207 shares of common stock were available for issuance under the ESPP.

(3) The initial aggregate number of shares of our common stock that may be issued pursuant to stock awards under the 2011 Incentive Plan was 1,875,000 shares, which number was the sum of (i) 51,693 shares remaining available for future grant under the 2006 Plan at the time of the execution and delivery of the underwriting agreement for our IPO, and (ii) an additional 1,823,307 new shares. The number of shares of our common stock reserved for issuance under the 2011 Incentive Plan will automatically increase on January 1st each year, starting on January 1, 2012 and continuing through January 1, 2020, by 4% of the total number of shares of our common stock outstanding on December 31 of the preceding calendar year, or such lesser number of shares of common stock as determined by our board of directors. The initial aggregate number of shares of common stock that may be issued pursuant to purchase rights granted to our employees or to employees of any of our designated affiliates under the ESPP was 250,000 shares. The number of shares of our common stock reserved for issuance will automatically increase on January 1st each year, starting January 1, 2012 and continuing through January 1, 2020, in an amount equal to the lower of (i) 2% of the total number of shares of our common stock outstanding on December 31 of the preceding calendar year, and (ii) a number of shares of common stock as determined by our board of directors.

The information required by this item is incorporated by reference from the information under the caption "Security Ownership of Certain Beneficial Owners and Management" in the Company's Proxy Statement referred to in Item 10 above.

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Item 13. Certain Relationships and Related Transactions and Director Independence

The information required by this item is incorporated by reference from the information under the caption "Certain Relationships and Related Transactions" and "Board of Directors Meetings and Committees—Board Independence" in the Company's Proxy Statement referred to in Item 10 above.

Item 14. Principal Accounting Fees and Services

The information required by this item is incorporated by reference from the information under the caption "Ratification of Appointment of Independent Registered Public Accounting Firm" in the Company's Proxy Statement referred to in Item 10 above.

PART IV

Item 15. Exhibits, Financial Statement Schedules

(a) The following documents are filed as part of this Form 10-K:

1. Financial Statements:

See Index to Financial Statements in Item 8 of this Form 10-K.

2. Financial Statement Schedules:

No schedules are provided because they are not applicable, not required under the instructions, or the requested information is shown in the financial statements or related notes thereto.

(b) Exhibits – The exhibits listed in the accompanying index to exhibits are filed or incorporated by reference as part of this Annual Report on Form 10-K

SIGNATURES

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

Date: March 7, 2016 **AcelRx Pharmaceuticals, Inc.**
(Registrant)

/s/ Howard B. Rosen
Howard B. Rosen

Interim Chief Executive Officer and Director

(Principal Executive Officer)

/s/ Timothy E. Morris
Timothy E. Morris

Chief Financial Officer and Head of Business Development

(Principal Financial and Accounting Officer)

POWER OF ATTORNEY

KNOW ALL PERSONS BY THESE PRESENTS, that each person whose signature appears below constitutes and appoints Howard B. Rosen and Timothy E. Morris, and each of them, as his or her true and lawful attorneys-in-fact and agents, with full power of substitution for him or her, and in his or her name in any and all capacities, to sign any and all amendments to this Annual Report on Form 10-K, and to file the same, with exhibits thereto and other documents in connection therewith, with the Securities and Exchange Commission, granting unto said attorneys-in-fact and agents, and each of them, full power and authority to do and perform each and every act and thing requisite and necessary to be done therewith, as fully to all intents and purposes as he or she might or could do in person, hereby ratifying and confirming all that said attorneys-in-fact and agents, and any of them, his or her substitute or substitutes, may lawfully do or cause to be done by virtue hereof.

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 and on the dates indicated:

Signature	Title	Date
/s/ Howard B. Rosen **Howard B. Rosen**	Interim Chief Executive Officer and Director *(Principal Executive Officer)*	March 7, 2016
/s/ Timothy E. Morris **Timothy E. Morris**	Chief Financial Officer *(Principal Financial and Accounting Officer)*	March 7, 2016
/s/ Adrian Adams **Adrian Adams**	Chairman	March 7, 2016
/s/ Pamela P. Palmer, M.D., Ph.D. **Pamela P. Palmer, M.D., Ph.D.**	Chief Medical Officer and Director	March 7, 2016
/s/ Mark G. Edwards **Mark G. Edwards**	Director	March 7, 2016
/s/ Stephen J. Hoffman, Ph.D., M.D. **Stephen J. Hoffman, Ph.D., M.D.**	Director	March 7, 2016
/s/ Richard Afable, M.D. **Richard Afable, M.D.**	Director	March 7, 2016
/s/ Mark Wan **Mark Wan**	Director	March 7, 2016

ACELRX PHARMACEUTICALS, INC.

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Report of Independent Registered Public Accounting Firm

The Board of Directors and Stockholders

AcelRx Pharmaceuticals, Inc.

We have audited the accompanying consolidated balance sheet of AcelRx Pharmaceuticals, Inc. as of December 31, 2015, and the related consolidated statements of comprehensive loss, stockholders' equity, and cash flows for the year then ended. These financial statements are the responsibility of the Company's management. Our responsibility is to express an opinion on these financial statements based on our audit.

We conducted our audit in accordance with the standards of the Public Company Accounting Oversight Board (United States). Those standards require that we plan and perform the audit to obtain reasonable assurance about whether the financial statements are free of material misstatement. An audit includes examining, on a test basis, evidence supporting the amounts and disclosures in the financial statements, assessing the accounting principles used and significant estimates made by management, as well as evaluating the overall financial statement presentation. We believe that our audit provides a reasonable basis for our opinion.

In our opinion, the financial statements referred to above present fairly, in all material respects, the consolidated financial position of AcelRx Pharmaceuticals, Inc. at December 31, 2015, and the consolidated results of its operations and its cash flows for the year then ended in conformity with U.S. generally accepted accounting principles.

As discussed in Note 1 to the consolidated financial statements, in 2015 the Company changed the manner in which it accounts for the classification of debt issuance cost in the consolidated balance sheets due to the adoption of ASU 2015-03, Interest-Imputation of Interest.

We also have audited, in accordance with the standards of the Public Company Accounting Oversight Board (United States), AcelRx Pharmaceuticals, Inc.'s internal control over financial reporting as of December 31, 2015, based on criteria established in Internal Control – Integrated Framework (2013) issued by the Committee of Sponsoring Organizations of the Treadway Commission (COSO) and our report dated March 7, 2016 expressed an unqualified opinion thereon.

/s/ OUM & CO. LLP

San Francisco, California

March 7, 2016

Report of Independent Registered Public Accounting Firm

The Board of Directors and Stockholders of AcelRx Pharmaceuticals, Inc.

We have audited the accompanying consolidated balance sheet of AcelRx Pharmaceuticals, Inc. as of December 31, 2014, and the related consolidated statements of operations, comprehensive income, stockholders‘ equity, and cash flows for each of the two years in the period ended December 31, 2014. These financial statements are the responsibility of the Company's management. Our responsibility is to express an opinion on these financial statements and schedule based on our audits.

We conducted our audits in accordance with the standards of the Public Company Accounting Oversight Board (United States). Those standards require that we plan and perform the audit to obtain reasonable assurance about whether the financial statements are free of material misstatement. An audit includes examining, on a test basis, evidence supporting the amounts and disclosures in the financial statements. An audit also includes assessing the accounting principles used and significant estimates made by management, as well as evaluating the overall financial statement presentation. We believe that our audits provide a reasonable basis for our opinion.

In our opinion, the financial statements referred to above present fairly, in all material respects, the consolidated financial position of AcelRx Pharmaceuticals, Inc. at December 31, 2014, and the consolidated results of its operations and its cash flows for each of the two years in the period ended December 31, 2014, in conformity with U.S. generally accepted accounting principles.

/s/ Ernst & Young LLP

San Jose, California

March 12, 2015

except for Note 1 and 7, as to which the date is

March 7, 2016

AcelRx Pharmaceuticals, Inc.

Consolidated Balance Sheets

(in thousands, except share data)

	December 31, 2015	December 31, 2014
Assets		
Current Assets:		
Cash and cash equivalents	$107,922	$60,038
Short-term investments	5,542	15,312
Accounts receivable, net	3,286	—
Inventories	466	—
Prepaid expenses and other current assets	1,731	948
Total current assets	118,947	76,298
Property and equipment, net	8,610	9,818
Restricted cash	178	250
Other assets	50	50
Total Assets	$127,785	$86,416
Liabilities and Stockholders' Equity		
Current Liabilities:		
Accounts payable	$1,561	$2,431
Accrued liabilities	3,956	3,654
Long-term debt, current portion	4,541	6,859
Deferred revenue, current portion	2,604	787
Liability related to the sale of future royalties, current portion	118	—
Total current liabilities	12,780	13,731
Deferred rent, net of current portion	245	529
Long-term debt, net of current portion	16,381	18,015
Deferred revenue, net of current portion	593	1,626
Liability related to the sale of future royalties, net of current portion	63,494	—
Contingent put option liability	266	282
Warrant liability	913	5,577
Total liabilities	94,672	39,760
Commitments and Contingencies		
Stockholders' Equity:		
Common stock, $0.001 par value—100,000,000 shares authorized as of December 31, 2015 and December 31, 2014; 45,273,772 and 43,712,363 shares issued and outstanding as of December 31, 2015 and December 31, 2014	45	43
Additional paid-in capital	236,274	225,423
Accumulated deficit	(203,205)	(178,806)
Accumulated other comprehensive loss	(1)	(4)

Total stockholders' equity	33,113	46,656
Total Liabilities and Stockholders' Equity	$127,785	$86,416

See notes to consolidated financial statements.

AcelRx Pharmaceuticals, Inc.

Consolidated Statements of Comprehensive Loss

(in thousands, except share and per share data)

	Year Ended December 31,		
	2015	**2014**	**2013**
Revenue:			
Collaboration agreement	$14,857	$5,217	$27,370
Contract and other	4,406	—	2,132
Total revenue	19,263	5,217	29,502
Operating costs and expenses:			
Cost of goods sold	1,770	—	—
Research and development	22,488	24,520	26,292
General and administrative	14,203	18,346	9,877
Restructuring costs	756	—	—
Total operating costs and expenses	39,217	42,866	36,169
Loss from operations	(19,954)	(37,649)	(6,667)
Other (expense) income:			
Interest expense	(2,977)	(2,639)	(1,518)
Interest income and other income (expense), net	1,720	6,935	(15,241)
Non-cash interest expense on liability related to sale of future royalties	(2,428)	—	—
Total other (expense) income	(3,685)	4,296	(16,759)
Net loss before income taxes	(23,639)	(33,353)	(23,426)
Provision for income taxes	(760)	—	—
Net loss	(24,399)	(33,353)	(23,426)
Other comprehensive income (loss):			
Unrealized gains (losses) on available for sale securities	3	(5)	—
Comprehensive loss	$(24,396)	$(33,358)	$(23,426)
Net loss per share of common stock, basic	$(0.55)	$(0.77)	$(0.59)
Net loss per share of common stock, diluted	$(0.60)	$(0.91)	$(0.59)
Shares used in computing net loss per share of common stock, basic	44,300,099	43,427,111	39,746,678
Shares used in computing net loss per share of common stock, diluted –see Note 14	44,468,440	44,322,297	39,746,678

See notes to consolidated financial statements.

AcelRx Pharmaceuticals, Inc.

Consolidated Statements of Stockholders' Equity

(in thousands, except share data)

	Common Stock		Additional Paid-in Capital	Accumulated Deficit	Other Comprehensive Income (loss)	Total Stockholders' Equity
	Shares	Amount				
Balance as of December 31, 2012	37,055,027	$ 37	$ 155,836	$ (122,027)	$ 1	$ 33,847
Issuance of Warrants	—	—	1,130	—	—	1,130
Stock-based compensation	—	—	3,479	—	—	3,479
Issuance of common stock upon exercise of stock options and in connection with restricted stock units	520,365	1	1,276	—	—	1,277
Issuance of common stock upon exercise of stock warrants	1,050,062	1	8,689	—	—	8,690
Issuance of common stock upon ESPP purchase	55,126	—	219	—	—	219
Issuance of common stock upon underwritten public offering, net of offering-related costs	4,370,000	4	47,939	—	—	47,943
Change in unrealized gains and losses on investments	—	—	—	—	—	—
Net loss	—	—	—	(23,426)	—	(23,426)
Balance as of December 31, 2013	43,050,580	43	218,568	(145,453)	1	73,159
Stock-based compensation	—	—	4,440	—	—	4,440
Issuance of common stock upon exercise of stock options and in connection with restricted stock units	487,124	—	1,507	—	—	1,507
Issuance of common stock upon exercise of stock warrants	91,488	—	546	—	—	546
Issuance of common stock upon ESPP purchase	83,171	—	362	—	—	362
Change in unrealized gains and losses on investments	—	—	—	—	(5)	(5)
Net loss	—	—	—	(33,353)	—	(33,353)
Balance as of December 31, 2014	43,712,363	43	225,423	(178,806)	(4)	46,656
Stock-based compensation	—	—	5,010	—	—	5,010
	938,497	1	2,769	—	—	2,770

Issuance of common stock upon exercise of stock options						
Issuance of common stock upon exercise of stock warrants	527,101	1	2,543	—	—	2,544
Modification of warrants	—	—	100	—	—	100
Issuance of common stock upon ESPP purchase	95,811	—	429	—	—	429
Change in unrealized gains and losses on investments	—	—	—	—	3	3
Net loss	—	—	—	(24,399)	—	(24,399)
Balance as of December 31, 2015	45,273,772	$ 45	$ 236,274	$ (203,205)	$ (1)	$ 33,113

See notes to consolidated financial statements.

AcelRx Pharmaceuticals, Inc.

Consolidated Statements of Cash Flows

(in thousands)

	Year Ended December 31,		
	2015	**2014**	**2013**
CASH FLOWS FROM OPERATING ACTIVITIES:			
Net loss	$(24,399)	$(33,353)	$(23,426)
Adjustments to reconcile net loss to net cash used in operating activities:			
Non-cash interest expense on liability related to royalty monetization	2,428	—	—
Depreciation and amortization	1,984	866	593
Amortization of premium/discount on investments, net	114	216	202
Interest expense related to debt financing	897	553	442
Stock-based compensation	5,010	4,440	3,479
Revaluation of put option and PIPE warrant liabilities	(2,136)	(7,040)	14,071
Loss on extinguishment of debt	—	—	1,202
Loss on disposal and impairment of property and equipment	573	—	—
Changes in operating assets and liabilities:			
Accounts receivable	(3,286)	—	—
Inventories	(466)	—	—
Prepaid expenses and other assets	(783)	137	1,132
Restricted cash	72	—	(45)
Accounts payable	(786)	90	106
Accrued liabilities	325	(126)	(760)
Deferred revenue	784	(217)	2,630
Deferred rent	(284)	(22)	(113)
Net cash used in operating activities	(19,953)	(34,456)	(487)
CASH FLOWS FROM INVESTING ACTIVITIES:			
Purchase of property and equipment	(1,456)	(5,505)	(3,287)
Purchase of investments	(7,266)	(17,430)	(28,009)
Proceeds from maturities of investments	16,925	17,159	24,376
Net cash provided by (used in) investing activities	8,203	(5,776)	(6,920)
CASH FLOWS FROM FINANCING ACTIVITIES:			
Net proceeds from sale of future royalties	61,184	—	—
Proceeds from issuance of common stock in equity offerings, net of offering costs	—	—	47,943
Proceeds from the issuance of long-term debt	—	10,000	14,958
Payment of long-term debt	(4,534)	—	(16,345)
Payment of debt modification transaction costs	(215)	—	—
Extinguishment of debt	—	—	(437)
Net proceeds from issuance of common stock through equity plans and exercise of warrants	3,199	1,869	1,757
Net cash provided by financing activities	59,634	11,869	47,876

NET INCREASE (DECREASE) IN CASH AND CASH EQUIVALENTS	47,884	(28,363)	40,469
CASH AND CASH EQUIVALENTS—Beginning of period	60,038	88,401	47,932
CASH AND CASH EQUIVALENTS—End of period	$107,922	$60,038	$88,401
SUPPLEMENTAL DISCLOSURES OF CASH FLOW INFORMATION:			
Cash paid for interest	$2,115	$1,752	$1,105
Income taxes paid	$782	$—	$—
NONCASH INVESTING AND FINANCING ACTIVITIES:			
Issuance of common stock upon cashless exercise of warrants	$2,544	$546	$8,428
Issuance of warrants for common stock	$—	$—	$1,130
Modification of warrants for common stock	$100	$—	$—
Tenant improvement allowance receivable	$—	$239	$—
Contingent put option liability	$—	$—	$334
Purchases of property and equipment in Accounts payable	$98	$182	$—
Purchases of property and equipment in Accrued liabilities	$—	$23	$725

See notes to consolidated financial statements.

AcelRx Pharmaceuticals, Inc.

Notes to Consolidated Financial Statements

1. Organization and Summary of Significant Accounting Policies

The Company

AcelRx Pharmaceuticals, Inc., or the Company or AcelRx, was incorporated in Delaware on July 13, 2005 as SuRx, Inc., and in January 2006, the Company changed its name to AcelRx Pharmaceuticals, Inc. The Company's operations are based in Redwood City, California.

AcelRx is a specialty pharmaceutical company focused on the development and commercialization of innovative therapies for the treatment of acute pain. AcelRx intends to commercialize its product candidates in the United States and license the development and commercialization rights to its product candidates for sale outside of the United States through strategic partnerships and collaborations. AcelRx may also consider the option to enter into strategic partnerships for its product candidates in the United States.

In September 2015, the Company reported that SAP301, a pivotal Phase 3 study for ARX-04 (sufentanil sublingual tablet, 30 mcg), a proprietary, non-invasive, single-use tablet in a disposable, pre-filled single-dose applicator, or SDA, for the treatment of moderate-to-severe acute pain, met primary and secondary endpoints in a multi-center, double-blind, placebo-controlled trial designed to study the short-term treatment of patients with moderate-to-severe acute pain following ambulatory abdominal surgery. In October 2015, we announced the initiation of SAP302, an open-label Phase 3 study of ARX-04 for the treatment of adult patients who present in the emergency room with moderate-to-severe acute pain associated with trauma or injury. The SAP302 study is expected to be completed by the third quarter of 2016. The Company has initiated SAP303, an open-label, single-arm study of ARX-04 in post-operative patients over 40 years of age that will allow for administration of ARX-04 for up to 12 hours. This study is also expected to be completed by the third quarter of 2016. The Company believes ARX-04 may be a candidate for use in a variety of medically supervised settings to manage moderate-to-severe acute pain, including emergency room patients; patients who are recovering from short-stay or ambulatory surgery and do not require more long-term patient-controlled analgesia; post-operative patients who are transitioning from the operating room to the recovery floor; patients being transported by paramedics; and battlefield casualties.

The Company's other late-stage investigational product candidate, Zalviso™, delivers 15 mcg sufentanil sublingually through a non-invasive delivery route via a pre-programmed, patient-controlled analgesia device. In response to the

New Drug Application, or NDA, the Company submitted to the U.S. Food and Drug Administration, or FDA, seeking approval for Zalviso, the Company received a Complete Response Letter, or CRL, on July 25, 2014. The FDA has requested an additional clinical study and the Company is planning to begin this study, IAP312, in the first quarter of 2016.

On December 16, 2013, AcelRx and Grünenthal GmbH, or Grünenthal, entered into a Collaboration and License Agreement, or the License Agreement, which was amended effective July 17, 2015, or the Amended License Agreement, which grants Grünenthal rights to commercialize Zalviso in the countries of the European Union, Switzerland, Liechtenstein, Iceland, Norway and Australia. In September 2015, the European Commission approved the Marketing Authorization Application, or MAA, previously submitted to the European Medicines Agency, or EMA, for Zalviso for the management of acute moderate-to-severe post-operative pain in adult patients. The approval allows Grünenthal to market Zalviso in the 28 European Union member states as well as for the European Economic Area countries, Norway, Iceland and Liechtenstein, or EEA. Also on December 16, 2013, AcelRx and Grünenthal, entered into a related Manufacture and Supply Agreement, or the MSA, and together with the License Agreement, the Agreements. Under the MSA, the Company will exclusively manufacture and supply the Product to Grünenthal for the Field in the Territory. On July 22, 2015, the Company entered into an amendment to the MSA, or the MSA Amendment, and together with the MSA, the Amended MSA, between the Company and Grünenthal, each effective as of July 17, 2015, and together, with the Amended License Agreement, the Amended Agreements.

The Company has incurred recurring operating losses and negative cash flows from operating activities since inception and expects to continue to incur negative cash flows. Although Zalviso has been approved for sale in the European Union, the Company sold the majority of the royalty rights and certain commercial sales milestones it is entitled to receive under the Amended License Agreement with Grünenthal to PDL BioPharma, Inc., or PDL. As a result, the Company expects to continue to incur negative cash flows.

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When we refer to "we," "our," "us," the "Company" or "AcelRx" in this document, we mean the current Delaware corporation, or AcelRx Pharmaceuticals, Inc., and its predecessor, as well as its consolidated subsidiary.

Basis of Presentation

The preparation of financial statements in conformity with generally accepted accounting principles requires management to make estimates and assumptions that affect the amounts reported in the Consolidated Financial Statements and the accompanying notes. Actual results could differ from those estimates.

Reclassifications

Certain prior year amounts in the Consolidated Financial Statements have been reclassified to conform to the current year's presentation. Refer to “Recently Issued Accounting Standards” below for additional information.

Principles of Consolidation

The Consolidated Financial Statements include the accounts of the Company and its wholly-owned subsidiary, ARPI LLC, which was formed in September 2015 for the sole purpose of facilitating the monetization transaction with PDL of the expected royalty stream and milestone payments due from the sales of Zalviso in the European Union by its commercial partner, Grünenthal, pursuant to the Amended License Agreement, or the Royalty Monetization. All intercompany accounts and transactions have been eliminated in consolidation. Refer to Note 8 “Liability Related to Sale of Future Royalties” for additional information.

Use of Estimates

The preparation of financial statements in conformity with accounting principles generally accepted in the United States requires management to make estimates and assumptions that affect the amounts reported in the Consolidated Financial Statements and accompanying notes. Management evaluates its estimates on an ongoing basis including critical accounting policies. Estimates are based on historical experience and on various other market-specific and other relevant assumptions that the Company believes to be reasonable under the circumstances, the results of which form the basis for making judgments about the carrying values of assets and liabilities that are not readily apparent from other sources. Actual results could differ from those estimates.

Cash, Cash Equivalents and Marketable Securities

The Company considers all highly liquid investments with an original maturity (at date of purchase) of three months or less to be cash equivalents. Cash and cash equivalents consist of cash on deposit with banks and money market instruments.

All marketable securities are classified as available-for-sale and consist of U.S. Treasury and U.S. government sponsored enterprise debt securities. These securities are carried at estimated fair value, which is based on quoted market prices or observable market inputs of almost identical assets, with unrealized gains and losses included in accumulated other comprehensive income (loss). The amortized cost of securities is adjusted for amortization of premiums and accretion of discounts to maturity. Such amortization and accretion is included in interest income or expense. The cost of securities sold is based on specific identification. The Company’s investments are subject to a periodic impairment review for other-than-temporary declines in fair value. The Company’s review includes the consideration of the cause of the impairment including the creditworthiness of the security issuers, the number of securities in an unrealized loss position, the severity and duration of the unrealized losses and the Company’s intent and ability to hold the investment for a period of time sufficient to allow for any anticipated recovery in the market value. When the Company determines that the decline in fair value of an investment is below its accounting basis and this decline is other-than-temporary, it reduces the carrying value of the security it holds and records a loss in the amount of such decline.

Fair Value of Financial Instruments

The Company measures and reports its cash equivalents, investments and financial liabilities at fair value. Fair value is defined as the exchange price that would be received for an asset or an exit price paid to transfer a liability in the principal or most advantageous market for the asset or liability in an orderly transaction between market participants on the measurement date. Valuation techniques used to measure fair value must maximize the use of observable inputs and minimize the use of unobservable inputs. The fair value hierarchy defines a three-level valuation hierarchy for disclosure of fair value measurements as follows:

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Level I—Unadjusted quoted prices in active markets for identical assets or liabilities;

Level II—Inputs other than quoted prices included within Level I that are observable, unadjusted quoted prices in markets that are not active, or other inputs that are observable or can be corroborated by observable market data for substantially the full term of the related assets or liabilities; and

Level III—Unobservable inputs that are supported by little or no market activity for the related assets or liabilities.

The categorization of a financial instrument within the valuation hierarchy is based upon the lowest level of input that is significant to the fair value measurement.

Segment Information

The Company operates in a single segment, the development and commercialization of product candidates for the treatment of pain. The Company's contract revenue relates to sales in the United States. The Company's collaboration revenue relates to the Amended License Agreement with Grünenthal to commercialize Zalviso in the countries of the European Union, Switzerland, Liechtenstein, Iceland, Norway and Australia.

Concentration of Risk

The Company invests cash that is currently not being used for operational purposes in accordance with its investment policy in debt securities of the U.S. Treasury and U.S. government sponsored agencies and overnight deposits. The Company is exposed to credit risk in the event of default by the institutions holding the cash equivalents and available-for-sale securities to the extent recorded on the Consolidated Balance Sheet.

The Company relies on a single third-party supplier for the supply of sufentanil, the active pharmaceutical ingredient in Zalviso, and various sole-source third-party contract manufacturer organizations to manufacture the Zalviso drug cartridge and device components, including the controller, the dispenser kit and the accessories.

To date, the Company has had only two customers. These two customers account for 100% of the revenues for the years ended December 31, 2015, 2014 and 2013. One of these customers accounted for 84% of the accounts receivable balance as of December 31, 2015. The Company did not have an Accounts receivable balance as of December 31, 2014.

The Company has not experienced any losses with respect to the collection of its Accounts receivable and believes that the entire Accounts receivable balance as of December 31, 2015 is collectible.

Accounts Receivable, Net

The Company has receivables from its collaboration partner and the U.S. Department of Defense, or DoD. To date, the Company has not had a bad debt allowance because of the limited number of financially sound customers who have historically paid their balances timely. The need for a bad debt allowance is evaluated each reporting period based on the Company’s assessment of the credit worthiness of its customers or any other potential circumstances that could result in bad debt.

Inventories

Inventories are valued at the lower of cost or market. Cost is determined using the first-in, first-out method for all inventories. Inventory includes the cost of the active pharmaceutical ingredients, or API, raw materials and third-party contract manufacturing and packaging services. Indirect overhead costs associated with production and distribution are allocated to the appropriate cost pool and then absorbed into inventory based on the units produced or distributed, assuming normal capacity, in the applicable period. Indirect overhead costs in excess of normal capacity are recorded as period costs in the period incurred.

The Company's policy is to write down inventory that has become obsolete, inventory that has a cost basis in excess of its expected net realizable value and inventory in excess of expected requirements. The Company periodically evaluates the carrying value of inventory on hand for potential excess amount over demand using the same lower of cost or market approach as that used to value the inventory. Because selling prices to Grünenthal are set to recover only direct costs with minimal mark up, all inventories are carried at net realizable value.

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Property and Equipment

Property and equipment are stated at cost less accumulated depreciation and amortization. Depreciation is calculated using the straight-line method over the estimated useful lives of the assets, generally three to five years. Leasehold improvements are amortized over the shorter of the estimated useful life of the improvements or the remaining lease term. Expenditures for repairs and maintenance, which do not extend the useful life of the property and equipment, are expensed as incurred. Upon retirement, the asset cost and related accumulated depreciation are relieved from the accompanying Consolidated Balance Sheets. Gains and losses associated with dispositions are reflected as a component of Other (expense) income in the accompanying Consolidated Statements of Comprehensive Loss.

Impairment of Long-Lived Assets

The Company periodically assesses the impairment of long-lived assets and, if indicators of asset impairment exist, the Company assesses the recoverability of the affected long-lived assets by determining whether the carrying value of such assets can be recovered through an analysis of the undiscounted future expected operating cash flows. If impairment is indicated, the Company records the amount of such impairment for the excess of the carrying value of the asset over its estimated fair value. For example, purchased equipment and manufacturing-related facility improvements the Company has made at Patheon's facility in Ohio, are utilized for continued research and development, commercial manufacturing of Zalviso for Grünenthal and potential commercialization of its other product candidates. If the Company does not receive regulatory approval for its other product candidates, the Company may determine that it is no longer probable that the Company will realize the future economic benefit associated with the costs of these assets through future manufacturing activities, and if so, the Company would record an impairment charge associated with these assets. As of September 30, 2015, the Company remeasured on a non-recurring basis a portion of its leasehold improvements in its corporate offices using Level III valuation techniques. The write down to fair value of these long-lived assets resulted in an impairment charge of $0.5 million in the year ended December 31, 2015, which was recorded in interest income and other income (expense), net in the Consolidated Statements of Comprehensive Loss. As of December 31, 2015, the Company has not written down any additional long-lived assets as a result of impairment.

Restricted Cash

Under the Company's facility lease and corporate credit card agreements, the Company is required to maintain letters of credit as security for performance under these agreements. The letters of credit are secured by certificates of deposit in amounts equal to the letters of credit, which are classified as restricted cash on the Consolidated Balance Sheets.

Debt Issuance Costs

Debt issuance costs, which are included in long-term debt, net of current portion, are amortized as interest expense over the contractual terms of the related credit facilities.

Contingent put option

The contingent put option associated with the Company's loan and security agreement with Hercules Technology II, L.P. and Hercules Technology Growth Capital, Inc., collectively referred to as Hercules, is recorded as a liability. Changes in the fair value of the contingent put option are recognized as interest income and other income (expense), net in the Consolidated Statements of Comprehensive Loss. For additional information regarding the contingent put option, see Note 7 "Long-Term Debt."

Warrants

Warrants issued in connection with the Company's Private Placement, completed in June 2012, are recorded as liabilities as they have the potential for cash settlement upon the occurrence of certain transactions (as defined in the warrant; see Note 9 "Warrants"). Changes in the fair value of the warrants are recognized as interest income and other income (expense), net in the Consolidated Statements of Comprehensive Loss.

Revenue Recognition

The Company recognizes revenue when all of the following criteria are met: persuasive evidence of an arrangement exists; delivery has occurred or services have been rendered; the fee is fixed or determinable; and collectability is reasonably assured.

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Collaboration Revenue

Collaboration revenue, which is earned under license agreements with third parties, may include nonrefundable license fees, cost reimbursements, research and development services, commercial manufacturing services, contingent development and commercial milestones and royalties.

AcelRx accounts for multiple-element arrangements in accordance with ASC Topic 605-25, *Revenue Recognition—Multiple-Element Arrangements*, or ASC 605-25.The Company evaluates if the deliverables in the arrangement represent separate units of accounting. In determining the units of accounting, AcelRx evaluates certain criteria, including whether the deliverables have value to our customers on a stand-alone basis. Factors considered in this determination include whether the deliverable is proprietary to the Company, whether the customer can use the license or other deliverables for their intended purpose without the receipt of the remaining elements, whether the value of the deliverable is dependent on the undelivered items, and whether there are other vendors that can provide the undelivered items. Deliverables that meet these criteria are considered a separate unit of accounting. Deliverables that do not meet these criteria are combined and accounted for as a single unit of accounting.

For revenue agreements with multiple-element arrangements, such as the collaboration and license agreement with Grünenthal, the Company allocates revenue to each non-contingent element based on the relative selling price of each element. When applying the relative selling price method, the Company determines the selling price for each deliverable using vendor-specific objective evidence, or VSOE, of selling price or third-party evidence, or TPE, of selling price. If neither exists the Company uses best estimated selling price, or BESP, for that deliverable. Revenue allocated is then recognized when the four basic revenue recognition criteria are met for each element.

VSOE is based on the price charged when the element is sold separately and is the price actually charged for that deliverable. Establishing VSOE may not be possible for the elements of a license arrangement because each arrangement is unique, an arrangement typically consists of multiple elements and AcelRx has limited history of entering into license arrangements. When VSOE cannot be established, AcelRx attempts to establish the selling price of the elements of a license arrangement based on TPE. TPE is determined based on a competitor’s price for similar deliverables when sold separately. AcelRx may not be able to determine TPE for license arrangements, as they contain a significant level of differentiation such that the comparable pricing of a competitor’s license arrangement with

similar functionality cannot be obtained, and AcelRx is therefore unable to reliably determine what a similar competitor's license arrangement's selling price would be on a standalone basis.

When AcelRx is unable to establish the selling price of an element using VSOE or TPE, BESP is utilized in the allocation of the elements of the arrangement. The objective of the BESP is to determine the price at which AcelRx would transact a sale if the element of the license arrangement were sold on a standalone basis.

The process for determining BESPs involves management's judgment. AcelRx' process considers multiple factors such as discounted cash flows, estimated direct expenses and other costs and available data, which may vary over time, depending upon the circumstances, and relate to each deliverable. If the estimated obligation period of one or more deliverables should change, the future amortization of the revenue would also change.

AcelRx recognizes a contingent milestone payment as revenue in its entirety upon our achievement of the milestone. A milestone is substantive if the consideration earned from the achievement of the milestone (i) is consistent with performance required to achieve the milestone or the increase in value to the delivered item, (ii) relates solely to past performance and (iii) is reasonable relative to all of the other deliverables and payments within the arrangement.

Contract and Other Revenue

In May 2011, the Company received a grant from the USAMRMC to support the development of ARX-04. The grant provided for the reimbursement of qualified expenses for research and development activities as defined under the terms of the grant agreement. Revenue under the grant agreement was recognized when the related qualified research expenses were incurred.

In May 2015, the Company entered into the DoD Contract with the USAMRMC to support the development of ARX-04. The DoD Contract provides for the reimbursement of qualified expenses for development, manufacturing, regulatory and clinical costs outlined in the contract in order to submit an NDA to the FDA, including reimbursement for certain personnel and overhead expenses, as defined under the terms of the contract. Revenue under the contract is recognized when the related qualified expenses are incurred. The Company is entitled to reimbursement of overhead costs associated with the study costs incurred under the DoD Contract. The Company estimates this overhead rate by utilizing forecasted expenditures. Final reimbursable overhead expenses are dependent on direct labor and direct reimbursable expenses throughout the life of the DoD Contract, so it may increase or decrease based on actual expenses incurred.

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Cost of Goods Sold

Under the Amended Agreements with Grünenthal, the Company will sell Zalviso to Grünenthal at direct cost with minimal markup and will recognize indirect costs as period costs where they are in excess of normal capacity and not realizable on a lower of cost or market basis. Cost of goods sold for Zalviso shipped to Grünenthal includes the inventory costs of API, third-party contract manufacturing costs, packaging and distribution costs, shipping, handling and storage costs, depreciation and costs of the employees involved with production.

Research and Development Expenses

Research and development costs are charged to expense when incurred. Research and development expenses include salaries, employee benefits, including stock-based compensation, consultant fees, laboratory supplies, costs associated with clinical trials and manufacturing, including contract research organization fees, other professional services and allocations of corporate costs. The Company reviews and accrues clinical trial expenses based on work performed, which relies on estimates of total costs incurred based on patient enrollment, completion of patient studies and other events.

Stock-Based Compensation

Compensation expense for all share-based payment awards made to employees and directors, including employee stock options, restricted stock units and employee share purchases related to the 2011 Employee Stock Purchase Plan, or ESPP, is based on estimated fair values at grant date. The Company determines the grant date fair value of the awards using the Black-Scholes option-pricing model and generally recognizes the fair value as stock-based compensation expense on a straight-line basis over the vesting period of the respective awards.

The Black-Scholes option pricing model requires inputs such as expected term, expected volatility and risk-free interest rate. These inputs are subjective and generally require significant analysis and judgment to develop. Estimates of expected life are primarily determined using the simplified method in accordance with guidance provided by the

SEC. Such method was utilized as the Company did not believe its historical option exercise experience, which was limited, provided a reasonable basis upon which to estimate expected term. Volatility is derived from historical volatilities of several public companies within AcelRx's industry that are deemed to be comparable to AcelRx's business because AcelRx's has insufficient history on the volatility of its common stock relative to the expected life assumptions used by the Company. The risk-free rate is based on the U.S. Treasury yield curve in effect at the time of grant commensurate with the expected life assumption. Further, the Company estimates forfeitures at the time of grant and revises those estimates in subsequent periods if actual forfeitures differ from those estimates.

Restructuring Costs

The Company's restructuring costs consist of employee termination benefit costs. Liabilities for costs associated with the cost reduction plan are recognized when the liability is incurred and are measured at fair value. One-time termination benefits are expensed at the date the entity notifies the employee, unless the employee must provide future service, in which case the benefits are expensed ratably over the future service period.

Non-Cash Interest Expense on Liability Related to Sale of Future Royalties

In September 2015, the Company sold certain royalty and milestone payment rights from the sales of Zalviso in the European Union by its commercial partner, Grünenthal, pursuant to the Collaboration and License Agreement, dated as of December 16, 2013, as amended, to PDL for an upfront cash purchase price of $65.0 million, referred to as the Royalty Monetization. The Company continues to have significant continuing involvement in the Royalty Monetization primarily due to an obligation to act as the intermediary for the supply of Zalviso to Grünenthal. Under the relevant accounting guidance, because of the Company's significant continuing involvement, the Royalty Monetization has been accounted for as a liability that will be amortized using the interest method over the life of the arrangement. In order to determine the amortization of the liability, the Company is required to estimate the total amount of future royalty and milestone payments to be received by PDL and payments the Company is required to make to PDL, up to a capped amount of $195.0 million, over the life of the arrangement. The sum of the capped amount of $195.0 million, less the $61.2 million of net proceeds the Company received will be recorded as interest expense over the life of the liability. Consequently, the Company imputes interest on the unamortized portion of the liability and record interest expense using an estimated interest rate for an arms-length debt transaction. The Company's estimate of the interest rate under the arrangement is based on the amount of royalty and milestone payments expected to be received by PDL over the life of the arrangement. The Company's estimate of this total interest expense resulted in an effective annual interest rate of approximately 14%. The Company will periodically assess the expected royalty and milestone payments using a combination of historical results, internal projections and forecasts from external sources. To the extent such payments are greater or less than its initial estimates or the timing of such payments is materially different than its original estimates, the Company will prospectively adjust the amortization of the liability and the interest rate.

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Notes to Consolidated Financial Statements

The Company will record non-cash royalty revenues and non-cash interest expense within its Consolidated Statements of Comprehensive Loss over the term of the PDL agreement.

Comprehensive Loss

Comprehensive loss is comprised of net loss and other comprehensive income (loss) and is disclosed in the Consolidated Statements of Comprehensive Loss. For the Company, other comprehensive income (loss) consists of changes in unrealized gains and losses on the Company's investments.

Income Taxes

Deferred tax assets and liabilities are measured based on differences between the financial reporting and tax basis of assets and liabilities using enacted rates and laws that are expected to be in effect when the differences are expected to reverse. The Company records a valuation allowance for the full amount of deferred assets, which would otherwise be recorded for tax benefits relating to operating loss and tax credit carryforwards, as realization of such deferred tax assets cannot be determined to be more likely than not.

Net Loss per Share of Common Stock

The Company's basic net loss per share of common stock is calculated by dividing the net loss by the weighted average number of shares of common stock outstanding for the period. The diluted net loss per share of common stock is computed by giving effect to all potential common stock equivalents outstanding for the period determined using the treasury stock method. For purposes of this calculation, convertible preferred stock, options to purchase common stock, restricted stock subject to repurchase, warrants to purchase convertible preferred stock and warrants to purchase common stock were considered to be common stock equivalents. In periods with a reported net loss, such common stock equivalents are excluded from the calculation of diluted net loss per share of common stock if their effect is antidilutive. For additional information regarding the net loss per share, see Note 14 "Net Loss per Share of Common Stock."

Recently Issued Accounting Pronouncements

In May 2014, the Financial Accounting Standards Board, or FASB, issued Accounting Standards Update No. 2014-09, *Revenue from Contracts with Customers*, or ASU 2014-09, to provide guidance on revenue recognition. ASU 2014-09 requires a company to recognize revenue when it transfers promised goods or services to customers in an amount that reflects the consideration to which the company expects to be entitled in exchange for those goods or services. In doing so, companies will need to use more judgment and make more estimates than under today's guidance. These may include identifying performance obligations in the contract, estimating the amount of variable consideration to include in the transaction price and allocating the transaction price to each separate performance obligation. In August 2015, the FASB issued Update No. 2015-14, *Revenue from Contracts with Customers (Topic 606): Deferral of the Effective Date*, or ASU-2015-14, that provided for the adoption of the new standard for fiscal years beginning after December 15, 2017. Accordingly, ASU 2014-09 is effective for the Company in the first quarter of 2018. Early adoption up to the first quarter of 2017 is permitted. Upon adoption, ASU 2014-09 can be applied retrospectively to all periods presented or only to the most current period presented with the cumulative effect of changes reflected in the opening balance of retained earnings in the most current period presented. The Company is currently evaluating the method of adoption and the impact of adopting ASU 2014-09 on its results of operations, cash flows and financial position.

In July 2015, the FASB issued ASU 2015-11, *Inventory (Topic 330) Related to Simplifying the Measurement of Inventory* which applies to all inventory measured using first-in, first-out ("FIFO") or average cost. Inventory within the scope of the new guidance should be measured at the lower of cost and net realizable value. Net realizable value is the estimated selling prices in the ordinary course of business, less reasonably predictable costs of completion, disposal, and transportation. The amendments will be effective for AcelRx beginning in fiscal 2017, including interim periods within fiscal 2017. The new guidance should be applied prospectively, and earlier application is permitted as of the beginning of an interim or annual reporting period. The Company is currently evaluating the method of adoption and the impact of adopting ASU 2014-11 on its results of operations, cash flows and financial position.

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In April 2015, the FASB issued ASU 2015-03, *Interest—Imputation of Interest*. ASU 2015-03 will more closely align the presentation of debt issuance costs under U.S. GAAP with the presentation under comparable IFRS standards by requiring that debt issuance costs be presented on the balance sheet as a direct deduction from the carrying amount of the related debt liability, similar to the presentation of debt discounts or premiums. ASU 2015-03 is effective for fiscal years beginning after December 15, 2015 and is required to be applied retrospectively to all prior periods presented. As permitted by ASU 2015-03, the Company elected to early adopt this guidance beginning with the first quarter of fiscal 2015, in order to simplify the presentation of its debt issuance costs. The resulting reclassifications of unamortized debt issuance costs from other assets to long-term debt, net of current portion on the Consolidated Balance Sheets as of December 31, 2014 was $31,000. Refer to Note 7 “Long-Term Debt” for additional information.

2. Investments and Fair Value Measurement

Investments

The Company classifies its marketable securities as available-for-sale and records its investments at fair value. Available-for-sale securities are carried at estimated fair value based on quoted market prices or observable market inputs of almost identical assets, with the unrealized holding gains and losses included in accumulated other comprehensive income. Marketable securities which have maturities beyond one year as of the end of the reporting period are classified as non-current.

The table below summarizes the Company’s cash, cash equivalents and investments (in thousands):

	As of December 31, 2015			
	Amortized Cost	Gross Unrealized Gains	Gross Unrealized Losses	Fair Value
Cash and cash equivalents:				
Cash	$83,112	$ —	$ —	$83,112
U.S. government agency securities	24,809	1	—	24,810
Total cash and cash equivalents	107,921	1	—	107,922

Marketable securities:				
U.S. government agency securities	5,544	—	(2)	5,542
Total marketable securities	5,544	—	(2)	5,542
Total cash, cash equivalents and investments	$113,465	$ 1	$ (2)	$113,464

	As of December 31, 2014			
	Amortized Cost	**Gross Unrealized Gains**	**Gross Unrealized Losses**	**Fair Value**
Cash and cash equivalents:				
Cash	$60,005	$ —	$ —	$60,005
Money market funds	33	—	—	33
Total cash and cash equivalents	60,038	—	—	60,038
Marketable securities:				
U.S. government agency securities	15,316	—	(4)	15,312
Total marketable securities	15,316	—	(4)	15,312
Total cash, cash equivalents and investments	$75,354	$ —	$ (4)	$75,350

None of the available-for-sale securities held by the Company had material unrealized losses and there were no realized losses for the years ended December 31, 2015 and 2014. There were no other-than-temporary impairments for these securities as of December 31, 2015 or 2014. No gross realized gains or losses were recognized on the available-for-sale securities and, accordingly, there were no amounts reclassified out of accumulated other comprehensive income to earnings during the years ended December 31, 2015 and 2014.

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As of December 31, 2015 and 2014, the contractual maturity of all investments held was less than one year.

Fair Value Measurement

The Company's financial instruments consist of Level I and Level II assets and Level III liabilities. Level I securities include highly liquid money market funds and are valued based on quoted market prices. For Level II instruments, the Company estimates fair value by utilizing third party pricing services in developing fair value measurements where fair value is based on valuation methodologies such as models using observable market inputs, including benchmark yields, reported trades, broker/dealer quotes, bids, offers and other reference data. Such Level II instruments typically include U.S. treasury and U.S. government agency obligations. As of December 31, 2015 and December 31, 2014, the Company held, in addition to Level I and Level II assets, a contingent put option liability associated with the Company's Amended and Restated Loan and Security Agreement, or the Amended Loan Agreement, with Hercules Technology II, L.P. and Hercules Technology Growth Capital, Inc., collectively referred to as Hercules, which amends and restates the loan and security agreement with Hercules dated as of June 29, 2011, or the Original Loan Agreement, and which was classified as a Level III liability. See Note 7 "Long-Term Debt" for further description. The Company's estimate of fair value of the contingent put option liability was determined by using a risk-neutral valuation model, wherein the fair value of the underlying debt facility is estimated both with and without the presence of the default provisions, holding all other assumptions constant. The resulting difference between the two estimated fair values is the estimated fair value of the default provisions, or the contingent put option. Changes to the estimated fair value of these liabilities are recorded in interest income and other income (expense), net in the Consolidated Statements of Comprehensive Loss. The fair value of the underlying debt facility is estimated by calculating the expected cash flows in consideration of an estimated probability of default and expected recovery rate in default, and discounting such cash flows back to the reporting date using a risk-free rate. As of December 31, 2015 and 2014, the Company also held a Level III liability associated with warrants, or PIPE warrants, issued in connection with the Company's private placement equity offering, completed in June 2012. For a detailed description, see Note 11 "Stockholders' Equity." The PIPE warrants are considered a liability and are valued using the Black-Scholes option-pricing model, the inputs for which include exercise price of the PIPE warrants, market price of the underlying common shares, expected term, volatility based on a group of the Company's peers and the risk-free rate corresponding to the expected term of the PIPE warrants. Changes to any of these inputs can have a significant impact to the estimated fair value of the PIPE warrants. As of September 30, 2015, the Company remeasured on a non-recurring basis a portion of its leasehold improvements in its corporate offices using Level III valuation techniques. The write down to fair value of these long-lived assets resulted in an impairment charge of $0.5 million in the year ended December 31, 2015, which was recorded in interest income and other income (expense), net in the Consolidated Statements of Comprehensive Loss.

The following table sets forth the fair value of the Company's financial assets and liabilities by level within the fair value hierarchy (in thousands):

	As of December 31, 2015			
	Fair Value	Level I	Level II	Level III
Assets				
Money market funds	$2	$ 2	$—	$—
U.S. government agency obligations	30,352	—	30,352	—
Total assets measured at fair value	$30,354	$ 2	$30,352	$—
Liabilities				
PIPE warrant	$913	$ —	$—	$913
Contingent put option	266	—	—	266
Total liabilities measured at fair value	$1,179	$ —	$—	$1,179

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	As of December 31, 2014			
	Fair Value	**Level I**	**Level II**	**Level III**
Assets				
Money market funds	$33	$ 33	$—	$—
U.S. government agency obligations	15,312	—	15,312	—
Total assets measured at fair value	$15,345	$ 33	$15,312	$—
Liabilities				
PIPE warrant	$5,577	$ —	$—	$5,577
Contingent put option	282	—	—	282
Total liabilities measured at fair value	$5,859	$ —	$—	$5,859

The following table sets forth the assumptions used in the Black-Scholes option-pricing model to estimate the fair value of the PIPE warrants as of December 31, 2015 and 2014:

	As of December 31, 2015	**As of December 31, 2014**
Market Price	$3.85	$6.73
Exercise Price	$3.40	$3.40
Risk-free interest rate	1.06%	1.10%
Expected volatility	80.0%	61.0%
Expected life (in years)	1.92	2.92
Expected dividend yield	0.0%	0.0%

The following table sets forth a summary of the changes in the fair value of the Company's Level III financial liabilities for the years ended December 31, 2015 and 2014 (in thousands):

	Year Ended December 31, 2015
Fair value—beginning of period	$ 5,859

Change in fair value of PIPE warrants	(2,120)
Exercise of PIPE warrants	(2,544)
Change in fair value of contingent put option associated with Amended Loan Agreement with Hercules	(16)
Fair value—end of period	$ 1,179

	Year Ended December 31, 2014
Fair value—beginning of period	$ 13,445
Change in fair value of PIPE warrants	(6,988)
Exercise of PIPE warrants	(546)
Change in fair value of contingent put option associated with 2011 loan and security agreement with Hercules	(52)
Fair value—end of period	$ 5,859

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3. Inventories

Inventories consist of finished goods, raw materials and work in process and are stated at the lower of cost or market and consist of the following (in thousands):

	Balance as of December 31, 2015
Raw materials	$ 140
Work-in-process	181
Finished goods	145
Inventories	$ 466

4. Property and Equipment

Property and equipment consist of the following (in thousands):

	As of December 31,	
	2015	**2014**
Laboratory equipment	$3,522	$2,549
Leasehold improvements	4,609	4,469
Computer equipment and software	266	334
Construction in process	3,950	4,844
Tooling	1,062	527
Furniture and fixtures	55	50
	13,464	12,773
Less accumulated depreciation and amortization	(4,854)	(2,955)
Property and equipment, net	$8,610	$9,818

Depreciation and amortization expense was $2.0 million, $0.9 million and $0.6 million during the years ended December 31, 2015, 2014 and 2013, respectively. Property and equipment, net in the Consolidated Balance Sheets at December 31, 2015 and 2014, includes $3.0 million and $3.8 million, respectively, related to certain modifications the Company has made at Patheon Pharmaceutical Inc.'s, or Patheon's, Cincinnati facility under the terms of the Capital Expenditure and Equipment Agreement, or the Capital Agreement.

5. U.S. Department of Defense Funding

In May 2011, AcelRx received a grant from the USAMRMC in which the USAMRMC granted $5.6 million to the Company in order to support the development of investigational product candidate, ARX-04, for the treatment of moderate-to-severe acute pain. Under the terms of the grant, the USAMRMC will reimburse the Company for development, manufacturing and clinical costs necessary to prepare for and complete the planned Phase 2 dose-finding trial in a study of acute moderate-to-severe pain, and to prepare to enter Phase 3 development. The grant gives the USAMRMC the option to extend the term of the grant and provide additional funding for the research. As of December 31, 2013, the full amount of the grant, $5.6 million, had been recognized as revenue. There was no revenue recognized for years ended December 31, 2015 or 2014. Revenue attributable to the research and development performed under the USAMRMC grant, recorded as Contract and other revenue in the Consolidated Statements of Comprehensive Loss, was $2.1 million for the year ended December 31, 2013.

On May 11, 2015, the Company entered into a new award contract supported by the USAMRMC, within the U.S. Department of Defense, or the DoD, in which the DoD agreed to provide up to $17.0 million to the Company in order to support the development of the Company's product candidate, ARX-04 (sufentanil sublingual tablet, 30 mcg), a proprietary, non-invasive, single-use tablet in a disposable, pre-filled single-dose applicator, or SDA, for the treatment of moderate-to-severe acute pain, referred to as the DoD Contract. The DoD Contract supports development of ARX-04. Under the terms of the contract, the DoD will reimburse us for costs incurred for development, manufacturing, regulatory and clinical costs outlined in the contract in order to submit an NDA to the FDA, including reimbursement for certain personnel and overhead expenses. The period of performance under the contract began on May 11, 2015. The contract gives the DoD the option to extend the term of the contract and provide additional funding for the research. On March 2, 2016, the DoD Contract was amended to approve enrollment of additional patients in the SAP302 study, approve the addition of the SAP303 study, and extend the contract period of performance by four months from November 10, 2016 to March 9, 2017, to accommodate the increased SAP302 patient enrollment and the SAP303 study. The costs for these changes will be absorbed within the current contract value. If ARX-04 is approved by the FDA, the DoD has the option to purchase a certain number of units of commercial product pursuant to the terms of the contract.

Revenue attributable to the work performed under the DoD Contract, recorded as Contract and other revenue in the Consolidated Statements of Comprehensive Loss, was $4.4 million for the year ended December 31, 2015. There was no revenue recognized under the DOD Contract for years ended December 31, 2014 or 2013.

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6. Collaboration Agreement

On December 16, 2013, AcelRx and Grünenthal, entered into a Collaboration and License Agreement, or the License Agreement, and related Manufacture and Supply Agreement, or the MSA, and together with the License Agreement, the Agreements. The License Agreement grants Grünenthal rights to commercialize Zalviso, the Company's novel sublingual patient-controlled analgesia, or PCA, system, or the Product, in the countries of the European Union, Switzerland, Liechtenstein, Iceland, Norway and Australia, or the Territory, for human use in pain treatment within or dispensed by hospitals, hospices, nursing homes and other medically-supervised settings, or the Field. The Company retains rights with respect to the Product in countries outside the Territory, including the United States, Asia and Latin America. Under the MSA, the Company will exclusively manufacture and supply the Product to Grünenthal for the Field in the Territory. On July 22, 2015, the Company entered into amendments to the License Agreement, or the License Amendment, and together with the License Agreement, the Amended License Agreement, and the MSA, or the MSA Amendment, and together with the MSA, the Amended MSA, between the Company and Grünenthal, each effective as of July 17, 2015, and together, the Amended Agreements.

In the Amended Agreements, the parties amended the Product supply configurations and packaging of Product components and accessories, and associated pricing therefor, which the Company will manufacture and supply to Grünenthal for the Territory. The parties agreed to increase the pricing of the Product components and accessories in exchange for a reduction of $5.5 million in the total milestone payments due from Grünenthal contingent upon achieving specified net sales targets from a total of $171.5 million to $166.0 million. The parties also updated the development plan for the Product in the Territory, providing for additional near-term development services to be rendered by AcelRx in exchange for payments by Grünenthal of $0.7 million. In accordance with the terms of the Amended MSA, AcelRx also received a binding Product forecast from Grünenthal for approximately $3.7 million.

Amended License Agreement

Under the terms of the Amended License Agreement, Grünenthal has the exclusive right to commercialize the Product in the Field in the Territory. The Company retains control of clinical development, while Grünenthal and the Company will be responsible for certain development activities pursuant to a development plan as agreed between the parties. The Company will not receive separate payment for such development activities, apart from the $0.7 million included under the Amended Agreements. Grünenthal is exclusively responsible for marketing approval applications and other regulatory filings relating to the sufentanil sublingual tablet drug cartridge for the Product in the Field in the Territory, while the Company is responsible for the CE Mark and other regulatory filings relating to device portions of the Product. In July 2014, Grünenthal submitted an MAA to the European Medicines Agency, or EMA, for Zalviso™

(15 micrograms sufentanil sublingual tablets) for the management of acute moderate-to-severe post-operative pain in adult patients. A CE Mark for Zalviso was obtained in the fourth quarter of 2014 which specifies AcelRx as the device design authority and manufacturer. In September 2015, the European Commission approved the MAA for Zalviso for the 28 European Union member states as well as for the EEA.

The Company received an upfront non-refundable cash payment of $30.0 million in December 2013, and a milestone payment of $5.0 million related to the MAA submission in the third quarter of 2014, and an additional $15.0 million milestone payment upon the EC approval of the MAA for Zalviso, which was approved in September 2015. Under the Amended License Agreement, the Company is eligible to receive approximately $194.5 million in additional milestone payments, based upon successful regulatory and product development efforts ($28.5 million) and net sales target achievements ($166.0 million). Grünenthal will also make tiered royalty and supply and trademark fee payments in the mid-teens up to the mid-twenties percent range, depending on the level of sales achieved, on net sales of Zalviso. A portion of the tiered royalty payment, exclusive of the supply and trademark fee payments, will be paid to PDL in connection with the Royalty Monetization. For additional information on the Royalty Monetization with PDL, see Note 8 “Liability Related to Sale of Future Royalties.” Unless earlier terminated, the Amended License Agreement continues in effect until the expiration of the obligation of Grünenthal to make royalty and supply and trademark fee payments, which supply and trademark fee continues for so long as the Company continues to supply the Product to Grünenthal. The Amended License Agreement is subject to earlier termination in the event the parties mutually agree, by a party in the event of an uncured material breach by the other party, upon the bankruptcy or insolvency of either party, or by Grünenthal for convenience.

Amended MSA

Under the terms of the Amended MSA, the Company will manufacture and supply the Product for use in the Field for the Territory exclusively for Grünenthal. Grünenthal shall purchase from AcelRx, during the first five years after the effective date of the MSA, 100% and thereafter 80% of Grünenthal’s and its sublicensees’ and distributors’ requirements of Product for use in the Field for the Territory. The Product will be supplied at prices approximating the Company’s manufacturing cost, subject to certain caps, as defined in the MSA Amendment. The MSA Amendment requires the Company to use commercially reasonable efforts to enter stand-by contracts with third parties providing significant supply and manufacturing services and, under certain specified conditions, permits Grünenthal to use a third party back-up manufacturer to manufacture the Product for Grünenthal’s commercial sale in the Territory.

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Unless earlier terminated, the Amended MSA continues in effect until the later of the expiration of the obligation of Grünenthal to make royalty and supply and trademark fee payments or the end of any transition period for manufacturing obligations due to the expiration or termination of the Amended License Agreement. The Amended MSA is subject to earlier termination in connection with certain termination events in the Amended License Agreement, in the event the parties mutually agree, by a party in the event of an uncured material breach by the other party or upon the bankruptcy or insolvency of either party.

The Company identified the following four significant non-contingent performance deliverables under the original Agreements: 1) intellectual property (license), 2) the obligation to provide research and development services, 3) the significant and incremental discount on the manufacturing of Zalviso for commercial purposes, and 4) the obligation to participate on the joint steering committee.

At the time the Amended Agreements were executed, with the exception of the intellectual property license, these obligations remained partially undelivered. Additionally, the Company identified the following three performance deliverables under the License Amendment and the MSA Amendment: 1) the obligation to provide additional research and development services, 2) the obligation to provide Zalviso demonstration device systems, and 3) the obligation to manufacture and deliver Product under the binding forecast. The Company determined that the License Amendment and MSA Amendment are modifications to the original Agreements.

The Company considered the provisions of the multiple-element arrangement guidance in determining whether the deliverables outlined above have standalone value and thus should be treated as separate units of accounting. The Company’s management determined that the license under the original License Agreement had standalone value and represented a separate unit of accounting because the rights conveyed permitted Grünenthal to perform all efforts necessary to commercialize and begin selling the product upon regulatory approval. In addition, Grünenthal has the appropriate development, regulatory and commercial expertise with products similar to the product licensed under the agreement and has the ability to engage third parties to manufacture the product allowing Grünenthal to realize the value of the license without receiving any of the remaining deliverables. Grünenthal can also sublicense its license rights to third parties. Also, the Company’s management determined that the research and development services, Zalviso demonstration device systems, joint steering committee participation, the significant and incremental discount on the manufacturing of Zalviso, and the obligation to manufacture and deliver Products each represent individual units of accounting, as Grünenthal could perform such services and/or could acquire these on a separate basis.

The Company believes that none of the deliverables have vendor-specific objective evidence, or VSOE, or sufficient third-party evidence, or TPE, of selling price, as none of them have been sold separately by the Company, and as there is only limited information about third party pricing for similar deliverables. Accordingly, the Company developed best estimates of selling prices, or ESP, for each deliverable in order to allocate the noncontingent arrangement consideration to the units of accounting, based on current information available as of the modification date.

The Company's management determined the best estimate of selling price for the license based on Grünenthal's estimated future cash flows arising from the arrangement. Embedded in the estimate were significant assumptions regarding regulatory expenses, revenue, including potential customer market for the product and product price, costs to manufacture the product and the discount rate. The Company's management determined the best estimate of selling price of the research and development services and committee participation based on the nature and timing of the services to be performed and in consideration of personnel and other costs incurred in the delivery of the services. For the discount on manufacturing services, the Company's management estimated the selling price based on the market level of contract manufacturing margin it could have received if it were engaged to supply products to a customer in a separate transaction, the estimated cost of manufacturing, and the anticipated volume of Grünenthal's orders over the course of the agreement, to which the discount would apply. For the Zalviso demonstration devices and the obligation to manufacture and deliver Product, the Company's management estimated the selling price based on the binding volume of such devices and Products, the estimated cost of manufacturing, and the market level of contract manufacturing margin. ESP of the license, research and development and committee participation services and the discount on manufacturing services were updated at the time the Amended Agreements were executed for purposes of allocating the amended arrangement consideration.

The Amended Agreements entitle the Company to receive additional payments upon the achievement of certain development and sales milestones. Based on ASC Topic 605-28, *Revenue Recognition — Milestone Method*, the Company evaluates contingent milestones at inception or modification of the agreement, and recognizes consideration that is contingent upon the achievement of a milestone in its entirety as revenue in the period in which the milestone is achieved only if the milestone is considered substantive in its entirety. Milestones are events which have the following characteristics: (i) they can be achieved based in whole or in part on either the Company's performance or on the occurrence of a specific outcome resulting from the Company's performance, (ii) there was substantive uncertainty at the date the agreement was entered into that the event would be achieved and, (iii) they would result in additional payments due to the Company. A milestone is considered substantive if the following criteria are met: (i) the consideration is commensurate with either (1) the entity's performance to achieve the milestone, or (2) the enhancement of the value of the delivered item (s) as a result of a specific outcome resulting from the entity's performance to achieve the milestone, (ii) the consideration relates solely to past performance and, (iii) the consideration is reasonable relative to all of the other deliverables and payment terms, including other potential milestone consideration, within the arrangement.

The substantive milestone payments will be recognized as revenue in their entirety upon the achievement of each substantive milestone. Based on the criteria noted above, the identified substantive milestones in the original Agreements pertain to post approval product enhancements, expanded market opportunities and manufacturing efficiencies for Zalviso. Each of these potential achievements is based primarily on the Company's performance and involves substantive uncertainty as achievement of these milestones requires future research, development and regulatory activities, which are inherently uncertain in nature. The Company determined that the consideration for each milestone was commensurate with the Company's performance to achieve the milestone, including future research, development, manufacturing and regulatory activities and that the consideration is reasonable relative to all of the other deliverables and payments within the arrangement. Aggregate potential payments for these milestones total $28.5 million.

In addition to substantive milestones, two milestones associated with the original Agreements were deemed not to be substantive. These milestones pertain to regulatory developments for Zalviso in Europe, which the Company's management deemed to be not substantive due to the high likelihood of achievement, both at inception of the original Agreements and at the time the Amended Agreements were executed. Aggregate potential payments for these milestones totaled $20.0 million. In July 2014, Grünenthal submitted an MAA to the EMA for Zalviso for the management of acute moderate-to-severe post-operative pain in adult patients, triggering the first of these two milestones, a cash payment of $5.0 million. In September of 2015, the MAA was approved by the European Commission, triggering the second of these two milestones, a cash payment of $15.0 million. Amounts received under these non-substantive milestones were allocated to performance deliverables based on the relative selling price method and recognized as appropriate for such deliverables.

The Amended Agreements also include milestone payments related to specified net sales targets, totaling $166.0 million. These milestones do not meet the definition of a milestone under ASU 2010-17 because the achievement of these milestones is solely dependent on counter-party performance and not on any performance obligations of the Company.

At the time the Amended Agreements were executed, approximately $33.3 million of revenue had been recognized, and $1.7 million remained unrecognized from the aggregate to-date consideration of $35.0 million received under the original Agreements. Upon execution of the Amended Agreements, the Company updated the allocation of this arrangement consideration, along with the consideration owed under the Amended Agreements totaling $54.4 million, consisting of $0.7 million related to research and development services and the demonstration device systems, and $3.7 million related to the Product binding purchase forecast, to all of the identified deliverables in the arrangement (both delivered and undelivered) using their relative selling prices. Further, the $15.0 million non-substantive milestone achieved in September of 2015 was also allocated to the deliverables in the same manner. As a result of such allocations, additional amounts of $13.2 million and $0.5 million were allocated to the previously delivered license and research and development and committee participation services, respectively. A total of $4.4 million was allocated to the significant and incremental discount on manufacturing services, and is expected to be recognized over the period such discount is made available to Grünenthal, beginning in February 2016, on a straight-line basis over the estimated period through 2029. An additional $0.2 million has been allocated to committee participation services and is recognized on a straight-line basis over the performance obligation period extending through 2018. A total of $2.3 million was allocated to manufacturing services for the binding forecast of Products, and is expected to be recognized when the Products are delivered in the first quarter of 2016. The remaining $0.5 million was allocated to the additional research and development services under the Amended License Agreement and demonstration device systems, and manufacturing and delivery of the Products, and will be recognized as those services are performed or as the devices are delivered, as applicable.

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Below is a summary of revenue recognized under the Amended Agreements during the years ended December 30, 2015, 2014 and 2013 (in thousands):

	Years Ended December 31,		
	2015	2014	2013
License	$13,167	$4,560	$27,370
Joint steering committee, research and development services and demonstration devices	1,690	657	—
Total	$14,857	$5,217	$27,370

As of December 31, 2015, the Company had current and noncurrent portions of the deferred revenue balance under the Amended Agreements of $2.6 million and $0.6 million, respectively.

7. Long-Term Debt

Hercules Loan and Security Agreements

In June 2011, AcelRx entered into the Loan and Security Agreement, or the Loan Agreement, between the Company and with Hercules Technology II, L.P. and Hercules Technology Growth Capital, Inc., together, the Lenders, under which AcelRx borrowed $20.0 million in two tranches of $10.0 million each, represented by secured convertible term promissory notes.

The Company borrowed the first tranche of $10.0 million upon the closing of the transaction on June 29, 2011 and borrowed the second tranche of $10.0 million in December 2011. The Company used a portion of the proceeds from the first tranche to repay the remaining obligations under that certain loan and security agreement between the Company and Pinnacle Ventures, L.L.C., or Pinnacle Ventures, dated September 16, 2008. The interest rate for each tranche was 8.50%. In connection with the loan, the Company issued Hercules seven-year warrants to purchase an aggregate of 274,508 shares of common stock at a price of $3.06 per share. See Note 9 “Warrants” for further description.

On December 16, 2013, AcelRx entered into an Amended and Restated Loan and Security Agreement with the Lenders, or the Amended Loan Agreement, under which the Company may borrow up to $40.0 million in three tranches. The loans are represented by secured convertible term promissory notes, collectively, the Notes. The Amended Loan Agreement amends and restates the Loan Agreement between the Company and the Lenders dated as of June 29, 2011. The Company borrowed the first tranche of $15.0 million upon closing of the transaction on December 16, 2013, and the second tranche of $10.0 million on June 16, 2014. The Company used approximately $8.6 million of the proceeds from the first tranche to repay its obligations under the Loan and Security Agreement with the Lenders. The Company recorded the new debt at an estimated fair value of $24.9 million as of December 31, 2014.

In accordance with ASC Topic No. 470, “Debt – Modifications and Extinguishments” (Topic No. 470), the amendment noted above was determined to be an extinguishment of the existing debt and an issuance of new debt. The Company reached this conclusion based on a comparison of discounted remaining cash flows of the original loan agreement compared to the amended loan agreement, the result of which was a greater than 10% difference in discounted cash flows. The Company determined this difference to be significant and recorded the new debt at estimated fair value.

As a result of the extinguishment, the Company recorded a $1.2 million loss on extinguishment of debt which was recorded as interest income and other income (expense), net on the Consolidated Statements of Comprehensive Loss during the year ended December 31, 2013. The loss on extinguishment was a non-cash write off, consisting of deferred debt charges, the unamortized portion of the original issue discount related to the Loan Agreement and other fees associated with extinguishing the debt, including the estimated fair value of warrants issued in connection with the Amended Loan Agreement, facility and legal fees associated with the Amended Loan Agreement and the value of the contingent put option liability associated with the Loan Agreement at the time of the amendment.

On September 24, 2014, the Company entered into Amendment No. 1 to the Amended Loan Agreement with Hercules. Amendment No. 1 extended the time period under which the Company could draw down the third tranche, of up to $15.0 million, from March 15, 2015 to August 1, 2015, subject to the Company obtaining approval for Zalviso from the FDA. The Company did not receive FDA approval of Zalviso by August 1, 2015 and as such, will not have access to the third tranche.

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On September 18, 2015, concurrently with the closing of the Royalty Monetization, the Company entered into a Consent and Amendment No. 2, or Amendment No. 2, to the Amended Loan Agreement with the Lenders. Amendment No. 2 includes an interest only period from October 1, 2015 through March 31, 2016, with the potential for further extension to September 30, 2016 upon satisfaction of certain conditions, which have since been satisfied. Loans under the Amended Loan Agreement mature on October 31, 2017. In connection with Amendment No. 2, the Company reduced the exercise price of the warrants already held by the Lenders, which are exercisable for an aggregate of 176,730 shares of Common Stock, from the previous exercise price of $6.79 per share to $3.88 per share, or the Warrant Amendments. See Note 9 “Warrants” for further description.

The interest rate for each tranche will be calculated at a rate equal to the greater of either (i) 9.10% plus the prime rate as reported from time to time in The Wall Street Journal minus 5.25%, and (ii) 9.10%. Payments under the Amended Loan Agreement were interest only until April 1, 2015, followed by equal monthly payments of principal and interest through September 30, 2015, to be followed by an interest only period from October 1, 2015 through September 30, 2016, and by equal monthly payments of principal and interest from October 1, 2016 through the scheduled maturity date on October 1, 2017, or the Loan Maturity Date. In addition, a final payment equal to $1.7 million will be due on the Loan Maturity Date, or such earlier date specified in the Amended Loan Agreement. The Company’s obligations under the Amended Loan Agreement are secured by a security interest in substantially all of its assets, other than its intellectual property and those assets sold under the Royalty Monetization.

If the Company prepays the Amended Loan Agreement prior to maturity, it will pay Hercules a prepayment charge based on a percentage of the then outstanding principal balance, or 1% if the prepayment occurs after December 16, 2015.

Subject to certain conditions and limitations set forth in the Amended Loan Agreement, the Company has the right to convert up to $5.0 million of scheduled principal installments under the Notes into freely tradeable shares of the Company’s common stock, or Common Stock. The number of shares of Common Stock that would be issued upon conversion of the Amended Notes would be equal to the number determined by dividing (x) the product of (A) the principal amount to be paid in shares of Common Stock and (B) 103%, by (y) $9.30 (subject to certain proportional adjustments as provided for in the Amended Loan Agreement).

The Amended Loan Agreement includes customary affirmative and restrictive covenants, but does not include any financial maintenance covenants, and also includes standard events of default, including payment defaults, breaches of

covenants following any applicable cure period, a material impairment in the perfection or priority of Hercules' security interest or in the value of 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 Hercules may declare all outstanding obligations immediately due and payable and take such other actions as set forth in the Amended Loan Agreement.

Upon an event of default, including a change of control, Hercules has the option to accelerate repayment of the Amended Loan Agreement, including payment of any applicable prepayment charges, which range from 1%-3% of the outstanding loan balance and accrued interest, as well as a final payment fee of $1.7 million. This option is considered a contingent put option liability, as the holder of the loan may exercise the option in the event of default, and is considered an embedded derivative, which must be valued and separately accounted for in the Company's Consolidated Financial Statements. As the Amended Loan Agreement entered into on December 16, 2013 was considered an extinguishment, the contingent put option liability associated with the Loan Agreement, which had an estimated fair value of $32,000 at the time of the amendment, was written off as a part of the loss on extinguishment, and a new contingent put option liability was established. As of December 31, 2015 and 2014, the estimated fair value of the contingent put option liability was $266,000 and $282,000, respectively, which was determined by using a risk-neutral valuation model, wherein the fair value of the underlying debt facility is estimated both with and without the presence of the default provisions, holding all other assumptions constant. The resulting difference between the two estimated fair values is the estimated fair value of the default provisions, or the contingent put option. The fair value of the underlying debt facility is estimated by calculating the expected cash flows in consideration of an estimated probability of default and expected recovery rate in default, and discounting such cash flows back to the reporting date using a risk-free rate. The contingent put option liability was recorded as a debt discount to the loan and consequently a reduction to the carrying value of the loan. The contingent put option liability is revalued at the end of each reporting period and any change in the fair value is recognized in interest income and other income (expense), net in the Consolidated Statements of Comprehensive Loss.

The Company performed an analysis of Amendment No. 2 to determine if it was a modification or extinguishment of the debt under the Amended Loan Agreement. The Company assumed immediate prepayment of both the pre-modification debt and post-modification debt, including the change in the fair value due to the Warrant Amendments, and concluded that Amendment No. 2 was a modification rather than an extinguishment of the debt.

AcelRx Pharmaceuticals, Inc.

Notes to Consolidated Financial Statements

The principal balance due under the Amended Loan Agreement was $20.9 million at December 31, 2015, and $24.9 million at December 31, 2014. Interest expense related to the Amended Loan Agreement was $3.0 million, $0.8 million of which represented amortization of the debt discount, for the year ended December 31, 2015, and $2.6 million, $0.5 million of which represented amortization of the debt discount, for the year ended December 31, 2014. Amortization of the debt discount prior to amending the Hercules loan and security agreement in December 2013, which was recorded as interest expense, was $0.4 million for the year ended December 31, 2013.

Future Payments on Long-Term Debt

The following table summarizes our outstanding future payments associated with the Company's long-term debt as of December 31, 2015 (in thousands):

2016	$6,400
2017	18,305
Total payments	24,705
Less amount representing interest	(2,539)
Notes payable, gross	22,166
Unamortized portion of final payment	(1,224)
Unamortized discount on notes payable	(20)
	20,922
Less current portion of notes payable, including unamortized discount	4,541
Notes payable, less current portion	$16,381

8. Liability Related to Sale of Future Royalties

On September 18, 2015, the Company consummated the Royalty Monetization, in which it sold certain royalty and milestone payment rights to its newly formed wholly owned subsidiary, ARPI LLC, pursuant to a Purchase and Sale Agreement, or PSA. Subsequently, ARPI LLC sold the royalty and milestone payment rights to PDL for an upfront cash purchase price of $65.0 million, subject to a capped amount of $195.0 million pursuant to the Subsequent Purchase and Sale Agreement, or SPSA. Under the SPSA, PDL will receive 75% of the European royalties under the Amended License Agreement as well as 80% of the first four commercial milestones, worth $35.6 million (or 80% of

$44.5 million), subject to the capped amount. The Company is entitled to receive 25% of the royalties, 20% of the first four commercial milestones, 100% of the remaining commercial milestones and all remaining development milestones of $43.5 million, including the $15.0 million payment for the EC approval of the MAA for Zalviso.

The Company and ARPI LLC continue to retain certain duties and obligations under the Amended License Agreement. These include the collection of the royalty and milestones amounts due and enforcement of related provisions under the Amended License Agreement, among others. In addition, the Company must prepare a quarterly distribution report relating to the Amended License Agreement, containing among other items, the amount of royalty and milestone payments received, reimbursable expenses and set-offs. The Company and ARPI LLC must also provide PDL with notice of certain communications, events or actions with respect to the Amended License Agreement and infringement of any underlying intellectual property.

The Company has significant continuing involvement in the Royalty Monetization primarily due to an obligation to act as the intermediary for the supply of Zalviso to Grünenthal. Under the relevant accounting guidance, because of its significant continuing involvement, the Royalty Monetization has been accounted for as a liability that will be amortized using the interest method over the life of the arrangement. In order to determine the amortization of the liability, the Company is required to estimate the total amount of future royalty and milestone payments to be received by PDL and payments the Company is required to make to PDL, up to a capped amount of $195.0 million, over the life of the arrangement. The sum of the capped amount of $195.0 million, less the $61.2 million of net proceeds the Company received will be recorded as interest expense over the life of the liability. Consequently, the Company imputes interest on the unamortized portion of the liability and records interest expense. The Company’s estimate of the interest rate under the arrangement is based on the amount of royalty and milestone payments expected to be received by PDL over the life of the arrangement. The Company’s estimate of this total interest expense resulted in an effective annual interest rate of approximately 14%.

The Company will periodically assess the expected royalty and milestone payments using a combination of historical results, internal projections and forecasts from external sources. To the extent such payments are greater or less than our initial estimates or the timing of such payments is materially different than our original estimates, the Company will prospectively adjust the amortization of the liability and the interest rate.

The following table shows the activity within the liability account during the year ended December 31, 2015 (in thousands):

Liability related to sale of future royalties—beginning balance (as of December 31, 2014)	$—
Net proceeds from sale of future royalties	61,184
Non-cash interest expense recognized	2,428
Payments from AcelRx to PDL	—
Total liability related to sale of future royalties as of December 31, 2015	63,612
Less: current portion	118
Liability related to sale of future royalties, less current portion	$63,494

As royalties are remitted to PDL from ARPI LLC, as described in Note 1 “Organization and Summary of Significant Accounting Policies,” the balance of the liability will be effectively repaid over the life of the agreement. The Company will record non-cash royalty revenues and non-cash interest expense within its Consolidated Statements of Comprehensive Loss over the term of the Royalty Monetization.

9. Warrants

Series A Warrants

As of December 31, 2015, warrants to purchase 3,425 shares of common stock had not been exercised and were still outstanding. These warrants expire in March 2017.

Pinnacle Warrants

In February 2013, warrants to purchase 228,264 shares were net exercised, for 58,580 shares of common stock. As of December 31, 2015, no warrants to purchase shares of common stock issued to Pinnacle were outstanding.

Hercules Warrants

In connection with the Amended Loan Agreement, executed in December 2013, the Company issued warrants to Hercules which were exercisable for an aggregate of 176,730 shares of common stock with an exercise price of $6.79 per share, or the Warrants. In connection with Amendment No. 2 to the Amended Loan Agreement, the Company reduced the exercise price of the warrants already held by the Lenders from the previous exercise price of $6.79 per share to $3.88 per share, or the Warrant Amendments. Each Warrant may be exercised on a cashless basis. The Warrants are exercisable for a term beginning on the date of issuance and ending on the earlier to occur of five years from the date of issuance or the consummation of certain acquisitions of the Company as set forth in the Warrants. The number of shares for which the Warrants are exercisable and the associated exercise price are subject to certain proportional adjustments as set forth in the Warrants. The Company estimated the fair value of these Warrants as of the issuance date to be $1.1 million, which was used in the estimating the fair value of the amended debt instrument and was recorded as equity. The fair value of the Warrants was calculated using the Black-Scholes option-valuation model, and was based on the original strike price of $6.79, the stock price at issuance of $9.67, the five-year contractual term of the warrants, a risk-free interest rate of 1.55%, expected volatility of 71% and 0% expected dividend yield. The Company estimated the fair value of the modification of the Warrants, or the Warrant Amendments, as of the issuance date to be $0.1 million, which was used in estimating the fair value of the amended debt instrument and was recorded as equity.

As of December 31, 2015, warrants to purchase 176,730 shares of common stock issued to Hercules had not been exercised and were still outstanding. These warrants expire in December 2018.

In connection with the Loan Agreement with Hercules, executed in June 2011, the Company issued to Hercules warrants to purchase an aggregate of 274,508 shares of common stock at a price of $3.06 per share, which were net exercised for 183,404 shares of common stock during the year ended December 31, 2013.

2012 Private Placement Warrants

In connection with the Private Placement, completed in June 2012, the Company issued PIPE warrants to purchase up to 2,630,103 shares of common stock. The per share exercise price of the PIPE warrants was $3.40 which equals the closing consolidated bid price of the Company's common stock on May 29, 2012, the effective date of the Purchase Agreement. The PIPE warrants issued in the Private Placement became exercisable six months after the issuance date, and expire on the five year anniversary of the initial exercisability date. Under the terms of the PIPE warrants, upon certain transactions, including a merger, tender offer, sale of all or substantially all of the assets of the Company or if a person or group shall become the owner of 50% of the Company's issued and outstanding common stock, which is outside of the Company's control, each PIPE warrant holder may elect to receive a cash payment in exchange for the warrant, in an amount determined by application of the Black-Scholes option-pricing model. Accordingly, the PIPE warrants were recorded as a liability at fair value, as determined by the Black-Scholes option-pricing model, and then marked to fair value each reporting period, with changes in estimated fair value recorded through the Consolidated Statements of Comprehensive Loss in interest income and other income (expense), net. The Black-Scholes assumptions used to value the PIPE warrants are disclosed in Note 2 "Investments and Fair Value Measurement."

Upon execution of the Purchase Agreement, the fair value of the PIPE warrants was estimated to be $5.8 million, which was recorded as a liability. As of December 31, 2015, the fair value of the PIPE warrants was estimated to be $0.9 million. The change in fair value for the years ended December 31, 2015, and 2014, which was recorded as other income, was $2.1 million, and $7.0 million, respectively. The change in fair value for the year ended December 31, 2013, which was recorded as other expense, was $14.1 million.

During the year ended December 31, 2015, PIPE warrants to purchase 847,058 shares were net exercised for 527,101 shares of common stock. During the year ended December 31, 2014, PIPE warrants to purchase 135,000 shares were net exercised for 91,488 shares of common stock. During the year ended December 31, 2013, warrants to purchase 1,135,589 shares were net exercised, for 808,078 shares of common stock. As of December 31, 2015, PIPE warrants to purchase 512,456 shares of common stock issued in connection with the Private Placement had not been exercised and were outstanding. These warrants expire in November 2017.

10. Commitments and Contingencies

Operating Leases

In December 2011, the Company entered into a non-cancelable lease agreement for approximately 13,787 square feet of office and laboratory facilities in Redwood City, California, which serve as the Company headquarters, effective April 2012. The lease agreement expires in May 2016. Rent expense from the facility lease is recognized on a

straight-line basis from the inception of the lease in December 2011, the early access date, through the end of the lease.

In May 2014, the Company entered into an amendment, or the Lease Amendment, to that certain lease dated December 21, 2011, with Metropolitan Life Insurance Company, or the Existing Lease, for 13,787 square feet of space located at 301 Galveston Drive, Redwood City, California, or the Current Premises. Pursuant to the Lease Amendment, the term of the Existing Lease has been extended for a period of twenty (20) months and twenty-two (22) days and expiring January 31, 2018, or the Expiration Date, unless sooner terminated pursuant to the terms of the Existing Lease. In addition, the Lease Amendment included a new lease on an additional 12,106 square feet of office space, or the Expansion Space, which is adjacent to the current premises. The new lease for the Expansion Space has a term of 42 months commencing on August 1, 2014, and expiring on the Expiration Date. The Company has an option to extend the term of the Lease Amendment for an additional five years, which would commence upon the Expiration Date, at a market rate determined according to the Existing Lease.

On October 2, 2015, the Company executed an agreement to sublease 11,871 sq. of its Expansion Space located at 301 Galveston Drive, Redwood City, California for a term of 26 months commencing on December 1, 2015. The sublessee is entitled to abatement of the first two monthly installments of rent. Subsequent monthly installments of rent start at a rental rate of $2.05 per square foot (subject to agreed nominal increases). Upon the completion of the sublease, the Company has the option to take back the subleased space. Minimum rents expected to be received under this sublease are $0.3 million, $0.3 million and $0.0 million for the years ending December 31, 2016, 2017 and 2018, respectively.

Rent expense was $0.6 million, $0.5 million and $0.3 million during the years ended December 31, 2015, 2014 and 2013, respectively.

Future minimum payments under the lease agreement as of December 31, 2015, are as follows (in thousands):

Year Ending December 31:	
2016	$717
2017	737
2018	62
Total minimum payments	$1,516

In addition, the Company will pay the Landlord specified percentages of certain operating expenses and taxes related to the leased facility incurred by the Landlord.

Litigation

On October 1, 2014, a securities class action complaint was filed in the U.S. District Court for the Northern District of California against AcelRx and certain of its current and former officers. On April 17, 2015, lead plaintiff filed an amended complaint. The amended complaint alleged that between September 30, 2013 and July 25, 2014, AcelRx and certain of its current and former officers violated Sections 10(b) and 20(a) of the Securities Exchange Act of 1934 in connection with statements related to our lead drug candidate, Zalviso. On November 25, 2015, the Court granted the Company's Motion to Dismiss. Plaintiffs had the opportunity to file an amended complaint within 30 days' which they declined to do. On January 18, 2016, the Court issued an order dismissing the case with prejudice. From time to time the Company may be involved in additional legal proceedings arising in the ordinary course of business. The Company does not have contingent liabilities established for any litigation matters.

11. Stockholders' Equity

Common Stock

Public Offerings

On July 23, 2013, AcelRx completed an underwritten public offering of 4,370,000 shares of common stock, at a price of $11.65 per share to the public. The total gross proceeds of this offering were $50.9 million with net proceeds to AcelRx of $47.9 million after deducting underwriting discounts and commissions and other expenses payable by AcelRx.

Private Placement Offering

On June 1, 2012, or the Issuance Date, the Company issued an aggregate of 2,922,337 shares of common stock and warrants to purchase up to 2,630,103 shares of common stock, or the PIPE warrants, for aggregate gross proceeds of $10.0 million, or the Private Placement. Costs related to the offering were $0.9 million. The shares of common stock and PIPE warrants issued in the Private Placement were sold pursuant to a Securities Purchase Agreement, or Purchase Agreement, dated May 29, 2012, between the Company and certain purchasers, including certain entities affiliated with Mark Wan and Stephen J. Hoffman, members of the Company's board of directors. Pursuant to the Purchase Agreement, AcelRx sold shares of common stock and PIPE warrants to purchase common stock in immediately separable "Units," with each Unit consisting of (i) one share of common stock and (ii) a PIPE warrant to purchase 0.9 of a share of common stock. The per share exercise price of the PIPE warrants was $3.40. The offering price per Unit was $3.40 for non-affiliated investors, and $3.5125 for affiliated investors, which equals the sum of (i) $3.40, the closing consolidated bid price of the Company's common stock on May 29, 2012, plus (ii) $0.1125 (which is equal to $0.125 per PIPE warrant share, multiplied by 0.9), for an aggregate amount of $10.0 million. The PIPE warrants issued in the Private Placement became exercisable six months after the Issuance Date, and expire on the five year anniversary of the initial exercisability date.

In connection with the Private Placement, the Company filed a registration statement with the U.S. Securities and Exchange Commission, or SEC, registering for resale the shares of common stock and shares of common stock issuable upon exercise of the warrants sold in the Private Placement. The registration statement was declared effective by the SEC in July 2012.

Stock Plans

2006 Stock Plan

In August 2006, the Company established the 2006 Plan in which 342,000 shares of common stock were originally reserved for the issuance of incentive stock options, or ISOs, and nonstatutory stock options, or NSOs, to employees, directors or consultants of the Company. In February 2008, an additional 375,000 shares of common stock were reserved for issuance under the 2006 Plan and, in November 2009, an additional 1,376,059 shares of common stock were reserved for issuance under the 2006 Plan. Per the 2006 Plan, the exercise price of ISOs and NSOs granted to a stockholder who at the time of grant owns stock representing more than 10% of the voting power of all classes of the stock of the Company could not be less than 110% of the fair value per share of the underlying common stock on the date of grant. Effective upon the execution and delivery of the underwriting agreement for the Company's IPO, no additional stock options or other stock awards may be granted under the 2006 Plan.

2011 Equity Incentive Plan

In January 2011, the board of directors adopted, and the Company's stockholders approved, the 2011 Equity Incentive Plan, or 2011 Incentive Plan, as a successor to the 2006 Plan. The 2011 Incentive Plan became effective immediately upon the execution and delivery of the underwriting agreement for the IPO on February 10, 2011. As of February 10, 2011, no more awards may be granted under the 2006 Plan, although all outstanding stock options and other stock awards previously granted under the 2006 Plan will continue to remain subject to the terms of the 2006 Plan. The 51,693 shares reserved under the 2006 Plan that remained available for future grant at the time of the IPO were transferred to the share reserve of the 2011 Incentive Plan.

The initial aggregate number of shares of the Company's common stock that may be issued pursuant to stock awards under the 2011 Incentive Plan is 1,875,000 shares, which number was the sum of (i) 51,693 shares remaining available for future grant under the 2006 Plan at the time of the execution and delivery of the underwriting agreement for the Company's IPO, and (ii) an additional 1,823,307 new shares. Then, the number of shares of common stock reserved for issuance under the 2011 Incentive Plan will automatically increase on January 1st each year, starting on January 1, 2012 and continuing through January 1, 2020, by 4% of the total number of shares of the Company's common stock outstanding on December 31 of the preceding calendar year, or such lesser number of shares of common stock as determined by the board of directors. The term of the option is determined by the board of directors on the date of grant but shall not be longer than 10 years. Options under the 2011 Equity Incentive Plan generally vest over four years, and all options expire after 10 years. The Company issues new shares for settlement of vested restricted stock units and exercises of stock options. The Company does not have a policy of purchasing its shares relating to its share-based programs.

2011 Employee Stock Purchase Plan

Additionally, in January 2011, the board of directors adopted, and the Company's stockholders approved, the 2011 Employee Stock Purchase Plan, or the ESPP, which also became effective immediately upon the execution and delivery of the underwriting agreement for the IPO.

Initially, 250,000 shares of the Company's common stock were authorized for issuance under the ESPP pursuant to purchase rights granted to the Company's employees or to employees of any of its designated affiliates. The number of shares of the Company's common stock reserved for issuance will automatically increase on January 1st each year, starting January 1, 2012 and continuing through January 1, 2020, in an amount equal to the lower of (1) 2% of the total number of shares of the Company's common stock outstanding on December 31 of the preceding calendar year, or (2) a number of shares of common stock as determined by the board of directors. If a purchase right granted under the ESPP terminates without having been exercised, the shares of the Company's common stock not purchased under such purchase right will be available for issuance under the ESPP.

As of December 31, 2015, 350,148 shares have been issued to employees and there are 291,207 shares available for issuance under the ESPP. The weighted average fair value of shares issued under the ESPP in 2015, 2014 and 2013 was $4.48, $4.35 and $3.97 per share, respectively. In January 2016, an additional 904,953 shares were authorized for issuance under the 2011 Employee Stock Purchase Plan.

12. Stock-Based Compensation

The Company recorded total stock-based compensation expense for stock options, stock awards and the ESPP as follows
(in thousands):

	December 31, 2015	December 31, 2014	December 31, 2013
Cost of goods sold	$ 67	$ —	$ —
Research and development	2,587	2,252	1,657
General and administrative	2,356	2,188	1,822
Total	$ 5,010	$ 4,440	$ 3,479

The following table summarizes option activity under the 2011 Plan and 2006 Plan:

	Number of Stock Options Outstanding	Weighted-Average Exercise Price	Weighted-Average Remaining Contractual Life (Years)	Aggregate Intrinsic Value (in thousands)
December 31, 2014	6,366,763	$ 5.74		
Granted	560,500	4.28		
Forfeited	(997,099)	7.22		
Expired	(372,718)	6.19		
Exercised	(938,497)	2.95		
December 31, 2015	4,618,949	$ 5.77	7.3	$ 1,079
Vested and exercisable options—December 31, 2015	2,919,289	$ 5.14	6.5	$ 1,036
Vested and expected to vest—December 31, 2015	4,523,784	$ 5.75	7.2	$ 1,076

As of December 31, 2015, there were 2,654,302 shares available for future grant under the 2011 Plan. In January 2016, an additional 1,809,906 shares were authorized for issuance under the 2011 Incentive Plan.

Additional information regarding the Company’s stock options outstanding and vested and exercisable as of December 31, 2015 is summarized below:

	Options Outstanding			Options Vested and Exercisable	
Exercise Prices	Number of Stock Options Outstanding	Weighted-Average Remaining Contractual Life (Years)	Weighted-Average Exercise Price per Share	Shares Subject to Stock Options	Weighted-Average Exercise Price per Share
$1.20 - $2.56	463,444	4.1	$ 2.33	463,444	$ 2.33
$3.11 - $4.73	1,396,208	7.0	$ 3.67	1,033,204	$ 3.56
$5.31 - $8.18	1,820,297	7.7	$ 5.92	948,650	$ 5.64
$10.22 - $10.55	939,000	8.3	$ 10.33	473,991	$ 10.35
	4,618,949	7.3	$ 5.77	2,919,289	$ 5.14

The weighted average grant-date fair value of options granted during the years ended December 31, 2015, 2014 and 2013 was $2.69, $5.57 and $4.15 per share, respectively. As of December 31, 2015, total stock-based compensation expense related to unvested options to be recognized in future periods was $7.3 million which is expected to be recognized over a weighted-average period of 2.3 years. The grant date fair value of shares vested during the years ended December 31, 2015, 2014 and 2013 was $5.4 million, $3.2 million and $1.9 million, respectively. The total intrinsic value of options exercised during the years ended December 31, 2015, 2014 and 2013 was $1.3 million, $2.3 million and $3.6 million, respectively.

The Company used the following assumptions to calculate the fair value of each employee stock option:

	Year Ended December 31,		
	2015	2014	2013
Expected term (in years)	5.25 - 6.25	5.25 - 6.25	5.75 - 6.25
Risk-free interest rate	1.35% - 1.82%	1.76% - 1.92%	1.02% - 2.96%
Expected volatility	72%	69 - 72%	80%
Expected dividend rate	0%	0%	0%

Restricted Stock Units

In March 2011, the Company granted 343,815 Restricted Stock Units, or RSUs, to employees and directors under the 2011 Plan at a grant date fair value of $3.45. The fair value of the RSUs was determined on the date of grant based on the market price of the Company's common stock. RSUs are recognized as expense ratably over the vesting period and the Company's RSU's generally vest over three years as follows: 25% on the 6 month anniversary of the vesting commencement date, 25% on the 12 month anniversary of the vesting commencement date, 25% on the 24 month anniversary of the vesting commencement date and 25% on the 36 month anniversary of the vesting commencement date, so long as the RSU recipient continues to provide services to the Company. As of December 31, 2015 and 2014, there were no RSUs outstanding. The expense related to RSUs during the years ended December 31, 2015, 2014 and 2013 was $0, $56,000 and $290,000, respectively.

13. Restructuring Costs

On March 19, 2015, the Board of Directors of the Company, in connection with its efforts to reduce operating costs, conserve capital, focus the Company's financial and development resources on working with the FDA to seek marketing approval for Zalviso, and continuing development of ARX-04, implemented a cost reduction plan. The cost reduction plan reduced the Company's workforce by 19 employees, approximately 36% of total headcount, in the first quarter of 2015. Employee termination benefits related to this restructuring, are charged to restructuring costs in the Consolidated Statements of Comprehensive Loss.

The Company recorded restructuring costs as follows (in thousands):

	December 31, 2015
Employee termination benefits	$ 756
Total restructuring costs	$ 756

The following table presents activities related to the cost reduction plan for the year ended December 31, 2015 (in thousands):

	Employee severance and related

	costs
Balance of restructuring liability at December 31, 2014	$ —
Charges	756
Payments	(756)
Balance of restructuring liability at December 31, 2015	$ —

The restructuring liability has been fully disbursed as of December 31, 2015.

14. Net Loss per Share of Common Stock

The Company’s basic net loss per share of common stock is calculated by dividing the net loss by the weighted average number of shares of common stock outstanding for the period. The diluted net loss per share of common stock is computed by giving effect to all potential common stock equivalents outstanding for the period determined using the treasury stock method. For purposes of this calculation, options to purchase common stock and warrants to purchase common stock were considered to be common stock equivalents. In periods with a reported net loss, common stock equivalents are excluded from the calculation of diluted net loss per share of common stock if their effect is antidilutive.

During the years ended December 31, 2015 and 2014, the PIPE warrants had a dilutive impact to net loss per share due to a lower share price at December 31, 2015 and 2014, compared to the closing share price on December 31, 2014 and 2013, respectively. The decrease in share price created a lower Black-Scholes value and lower liability for the PIPE warrants, which resulted in other income during the years ended December 31, 2015 and 2014. The calculation of diluted net loss per share requires that, to the extent the average market price of the underlying shares for the reporting period exceeds the exercise price of the PIPE warrants and the presumed exercise of such securities are dilutive to loss per share for the period, adjustments to net loss used in the calculation are required to remove the change in fair value of the PIPE warrants for the period. Likewise, adjustments to the denominator are required to reflect the related dilutive shares.

The following table is a reconciliation of the numerators and denominators used in the calculation of basic and diluted net loss per share computations for the years ended December 31, 2015, 2014 and 2013:

	Years Ended December 31,		
	2015	2014	2013
	(in thousands, except share and per share amounts)		
Numerator:			
Net loss used to compute net loss per share			
Basic	$(24,399)	$(33,353)	$(23,426)
Adjustments for change in fair value of warrant liability	(2,120)	(6,988)	—
Diluted	$(26,519)	$(40,341)	$(23,426)
Denominator:			
Weighted average shares outstanding used to compute net loss per share:			
Basic	44,300,099	43,427,111	39,746,678
Dilutive effect of warrants	168,341	895,186	—
Diluted	44,468,440	44,322,297	39,746,678
Net loss per share—basic	$(0.55)	$(0.77)	$(0.59)
Net loss per share—diluted	$(0.60)	$(0.91)	$(0.59)

The following outstanding shares of common stock equivalents were excluded from the computation of diluted net loss per share of common stock for the periods presented because including them would have been antidilutive:

	Year Ended December 31,		
	2015	**2014**	**2013**
ESPP and stock options to purchase common stock	4,699,121	6,411,003	4,988,459
Restricted Stock Units	—	—	65,765
Convertible debt into common stock	553,763	553,763	553,763
Common stock warrants	180,155	180,155	1,674,669

15. Accrued Liabilities

Accrued liabilities consist of the following (in thousands):

	December 31,	
	2015	**2014**
Accrued compensation and employee benefits	$2,876	$2,540
Accrued liabilities associated with Grünenthal collaboration	—	499

Inventory and other contract manufacturing accruals	272	—
Other accrued liabilities	808	615
Total accrued liabilities	$3,956	$3,654

16. 401(k) Plan

The Company sponsors a 401(k) plan that stipulates that eligible employees can elect to contribute to the 401(k) plan, subject to certain limitations. Pursuant to the 401(k) plan, the Company makes a matching contribution of up to 4% of the related compensation. Under the vesting schedule, employees have ownership in the matching Employer Contributions based on the number of years of vesting service completed. Company contributions were $263,000, $201,000 and $143,000 for the years ended December 31, 2015, 2014 and 2013, respectively.

17. Related Party Transactions

Stephen Hoffman is a Senior Advisor to PDL and a member of the Company's Board of Directors, or the Board. The Board was aware of Dr. Hoffman’s status as an interested party in the Royalty Monetization and Dr. Hoffman recused himself from all deliberations and actions taken by the Board with respect to the Royalty Monetization. Dr. Hoffman’s consulting compensation from PDL is composed, in part, of a success fee which is formula driven based on a minimum dollar value of deals and the total dollar value of the deals, his relative contribution to each of the concluded deals and the total dollar value deployed in 2015. PDL estimates the amount attributable to the AcelRx transaction to be approximately $260,000.

18. Income Taxes

The Company did record a provision for income taxes of $0.8 million during the year ended December 31, 2015. The Company did not record a provision for income taxes during the years ended December 31, 2014 and 2013. Net deferred tax assets as of December 31, 2015 and 2014 consist of the following (in thousands):

	December 31, 2015	December 31, 2014
Deferred tax assets:		
Accruals and other	$ 3,162	$ 4,446
Research credits	5,105	4,413
Net operating loss carryforward	30,294	42,330
Section 59(e) R&D expenditures	12,785	17,083
Deferred revenue	21,677	—
AMT credit	742	—
Total deferred tax assets	73,765	68,272
Valuation allowance	(73,765)	(68,272)
Net deferred tax assets	$ —	$ —

Reconciliations of the statutory federal income tax to the Company’s effective tax during the years ended December 31, 2015, 2014 and 2013 are as follows (in thousands):

	Year Ended December 31,		
	2015	2014	2013

Tax at statutory federal rate	$(8,037)	$(11,392)	$(7,965)
State tax—net of federal benefit	2,853	(2,501)	(716)
PIPE Warrant liability	(726)	(2,393)	4,898
General Business credits	(455)	(628)	(1,326)
Stock Options	1,559	543	
Other	73	20	(80)
Change in valuation allowance	5,493	16,351	5,189
Provision for income taxes	$760	$—	$—

ASC 740 requires that the tax benefit of net operating losses, temporary differences and credit carryforwards be recorded as an asset to the extent that management assesses that realization is “more likely than not.” Realization of deferred tax assets is dependent on future taxable income, if any, the timing and the amount of which are uncertain. Accordingly, the deferred tax assets have been fully offset by a valuation allowance. The valuation allowance increased by $5.5 million, $16.4 million, and $4.8 million during the years ended December 31, 2015, 2014 and 2013, respectively.

As of December 31, 2015, the Company had federal net operating loss carryforwards of $73.8 million, which begin to expire in 2029. As of December 31, 2015, the Company had state net operating loss carryforwards of $108.9 million, which begin to expire in 2016.

As of December 31, 2015, approximately $2.9 million of federal and $2.8 million of state net operating loss is attributable to stock-based compensation deductions in excess of book expense. When realized, the benefit of the tax deduction related to these options will be accounted for as a credit to stockholders’ equity rather than as a reduction of the income tax provision.

As of December 31, 2015, the Company had a federal alternative minimum tax credit carryover of $0.7 million.

As of December 31, 2015, the Company had federal research credit carryovers of $5.0 million, which begin to expire in 2026. As of December 31, 2015, the Company had state research credit carryovers of $2.8 million, which will carryforward indefinitely.

Under Section 382 of the Internal Revenue Code of 1986, as amended, if a corporation undergoes an "ownership change," generally defined as a greater than 50% change (by value) in its equity ownership over a three year period, the corporation's ability to use its pre-change net operating loss carryforwards and other pre-change tax attributes, such as research credits, to offset its post-change income may be limited. Based on an analysis performed by the Company as of December 31, 2013, it was determined that two ownership changes have occurred since inception of the Company. The first ownership change occurred in 2006 at the time of the Series A financing and, as a result of the change, $1.4 million in federal and state net operating loss carryforwards will expire unutilized. In addition, $26,000 in federal and state research and development credits will expire unutilized. The second ownership change occurred in July 2013 at the time of the underwritten public offering; however, the Company believes the resulting annual imposed limitation on use of pre-change tax attributes is sufficiently high that the limit itself will not result in unutilized pre-change tax attributes.

Uncertain Tax Positions

A reconciliation of the beginning and ending balances of the unrecognized tax benefits during the years ended December 31, 2015, 2014 and 2013 is as follows (in thousands):

	Year Ended December 31,		
	2015	**2014**	**2013**
Unrecognized benefit—beginning of period	$1,667	$1,341	$810
Gross decreases—prior period tax positions	—	—	221
Gross increases—current period tax positions	272	326	310
Unrecognized benefit—end of period	$1,939	$1,667	$1,341

The entire amount of the unrecognized tax benefits would not impact the Company's effective tax rate if recognized.

Accrued interest and penalties related to unrecognized tax benefits are classified as income tax expense and were immaterial. The Company files income tax returns in the United States and in California. The tax years 2005 through 2015 remain open in both jurisdictions. The Company is not currently under examination by income tax authorities in federal, state or other foreign jurisdictions. The Company does not anticipate any significant changes within 12 months of this reporting date of its uncertain tax positions.

19. Subsequent Events

On March 2, 2016, the Company entered into an amendment to the award contract with the DoD in which the DoD agreed to approve enrollment of additional patients in the SAP302 study, approve the addition of the SAP303 study, and extend the contract period of performance by four months from November 10, 2016 to March 9, 2017, to accommodate the increased SAP302 patient enrollment and the SAP303 study. The costs for these changes will be absorbed within the current contract value. All other terms and conditions remain unchanged.

20. Unaudited Quarterly Financial Data (in thousands, except per share amounts)

The following table sets forth certain unaudited quarterly financial data for the eight quarters ended December 31, 2015. The unaudited information set forth below has been prepared on the same basis as the audited information and includes all adjustments necessary to present fairly the information set forth herein. The operating results for any quarter are not indicative of results for any future period. All data is in thousands except per share data.

	2015				**2014**			
	Q1	**Q2**	**Q3**	**Q4**	**Q1**	**Q2**	**Q3**	**Q4**
Revenues	$181	$1,924	$15,428	$1,730	$95	$71	$4,825	$226
Operating costs and expenses	$11,581	$10,047	$8,323	$9,266	$8,636	$12,331	$9,894	$12,005
Net income / (loss)	$(10,026)	$(8,896)	$5,069	$(10,546)	$(9,631)	$(10,575)	$671	$(13,818)
Net income / (loss) per share (basic)	$(0.23)	$(0.20)	$0.11	$(0.24)	$(0.22)	$(0.24)	$0.02	$(0.32)
Net income / (loss) per share (diluted)	$(0.27)	$(0.20)	$0.11	$(0.24)	$(0.22)	$(0.30)	$(0.13)	$(0.32)

EXHIBIT INDEX

Exhibit Number	Exhibit Description	Incorporation By Reference			
		Form	SEC File No.	Exhibit	Filing Date
3.1	Amended and Restated Certificate of Incorporation of the Registrant, currently in effect.	8-K	001-35068	3.1	2/28/2011
3.2	Amended and Restated Bylaws of the Registrant, currently in effect.	S-1	333-170594	3.4	1/7/2011
4.1	Reference is made to Exhibits 3.1 through 3.2.				
4.2	Specimen Common Stock Certificate of the Registrant.	S-1	333-170594	4.2	1/31/2011
4.3	Second Amended and Restated Investors' Rights Agreement, among the Registrant and certain of its security holders, dated as of November 23, 2009.	S-1	333-170594	4.3	11/12/2010
4.4	Warrant to Purchase Common Stock of the Registrant, issued to Hercules Technology II, L.P., dated as of December 16, 2013.	10-K	001-35068	4.4	3/17/2014
4.5	Warrant to Purchase Common Stock of the Registrant, issued to Hercules Technology Growth Capital, Inc., dated as of December 16, 2013.	10-K	001-35068	4.5	3/17/2014
4.6	Form of Warrant issued to certain purchasers pursuant to the Securities Purchase Agreement dated May 29, 2012, between the Registrant and the purchasers identified therein.	8-K	001-35068	4.8	5/30/2012
4.7	Warrant Modification Agreement to Purchase Common Stock of the Registrant, issued to Hercules Technology II, L.P. dated as of September 17, 2015.	10-Q	001-35068	4.7	11/3/2015
4.8	Warrant Modification Agreement to Purchase Common Stock of the Registrant, issued to Hercules Technology Growth Capital, Inc. dated as of September 17, 2015.	10-Q	001-35068	4.8	11/3/2015
10.1+	Form of Indemnification Agreement between the Registrant and each of its directors and executive officers.	S-1	333-170594	10.1	1/7/2011
10.2+	2006 Stock Plan, as amended.	S-1	333-170594	10.2	11/12/2010
10.3+		10-K	001-35068	10.3	3/30/2011

	Forms of Notice of Grant of Stock Option, Stock Option Agreement and Stock Option Exercise Notice under 2006 Stock Plan.				
10.4+	2011 Equity Incentive Plan.	S-8	333-172409	99.3	2/24/2011
10.5+	Forms of Stock Option Grant Notice, Notice of Exercise and Option Agreement under 2011 Equity Incentive Plan.	10-K	001-35068	10.5	3/30/2011
10.6+	Forms of Restricted Stock Unit Grant Notice and Restricted Stock Unit Agreement under 2011 Equity Incentive Plan.	10-K	001-35068	10.6	3/30/2011
10.7+	2011 Employee Stock Purchase Plan.	S-8	333-172409	99.6	2/24/2011
10.8	Lease between Metropolitan Life Insurance Company and the Registrant, dated December 15, 2011.	10-K	001-35068	10.9	3/23/2012
10.9	Amendment to Lease between Metropolitan Life Insurance and the Registrant, dated May 2, 2014	8-K	001-35068	10.1	5/7/2014
10.10	Amended and Restated Loan and Security Agreement among the Registrant, Hercules Technology II, L.P. and Hercules Technology Growth Capital, Inc., dated as of December 16, 2013.	10-K	001-35068	10.10	3/17/2014
10.11+	Amended and Restated Offer Letter between the Registrant and Larry Hamel, dated December 31, 2010.	S-1	333-170594	10.14	1/7/2011

Exhibit Number	Exhibit Description	Incorporation By Reference			
		Form	SEC File No.	Exhibit	Filing Date
10.12+	Amended and Restated Offer Letter between the Registrant and Badri (Anil) Dasu, dated December 30, 2010.	S-1	333-170594	10.15	1/7/2011
10.13+	Amended and Restated Offer Letter between the Registrant and Pamela Palmer, dated December 29, 2010.	S-1	333-170594	10.16	1/7/2011
10.14+	Amended and Restated Offer Letter between the Registrant and Richard King, dated December 31, 2010.	S-1	333-170594	10.17	1/7/2011
10.15+	Offer Letter between the Registrant and Timothy E. Morris, dated March 24, 2014.	10-Q	001-35068	10.3	5/8/2014
10.16+	Offer Letter between the Registrant and Jane Wright-Mitchell, dated June 13, 2014.	10-K	001-35068	10.3	5/8/2014
10.17+	Separation Agreement between the Registrant and Richard King, dated December 15, 2014.	8-K/A	001-35068	10.1	12/16/2014
10.18+	Offer Letter, effective as of April 1, 2015, between the Registrant and Howard B. Rosen.	8-K	001-35068	10.1	4/3/2015
10.19+	Non-Employee Director Compensation Policy.	10-K	001-35068	Item 11	3/12/2013
10.20+	2015 Cash Bonus Plan Summary.	8-K	001-35068	10.1	5/5/2015
10.21+	Supplemental Cash Bonus Plan.	8-K	001-35068	Item 5.02	11/10/2014
10.22+	Supplemental Retention Cash Bonus Plan.	8-K	001-35068	Item 5.02	12/8/2014
10.23	Supply Agreement between the Registrant and Mallinckrodt LLC, effective as of May 31, 2013.	10-Q	001-35068	10.1	11/5/2013
10.24#		10-K	001-35068	10.28	3/17/2014

	Manufacture and Supply Agreement between the Registrant and Grünenthal GmbH, effective as of December 16, 2013.				
10.25#	Collaboration and License Agreement between the Registrant and Grünenthal GmbH, effective as of December 16, 2013.	10-K	001-35068	10.29	3/17/2014
10.26#	First Amendment to the Manufacture and Supply Agreement between the Registrant and Grünenthal GmbH, effective as of July 17, 2015.	10-Q	001-35068	10.2	11/3/2015
10.27#	First Amendment to the Collaboration and License Agreement between the Registrant and Grünenthal GmbH, effective as of July 17, 2015.	10-Q	001-35068	10.1	11/3/2015
10.28	Manufacturing Services Agreement between Registrant and Patheon Pharmaceuticals, Inc., dated as of January 18, 2013	10-Q	001-35068	10.1	5/8/2013
10.29	Amended and Restated Capital Expenditure Agreement between Registrant and Patheon Pharmaceuticals, Inc., dated as of January 18, 2013	10-Q	001-35068	10.2	5/8/2013
10.30	Second Amendment to Amended and Restated Capital Expenditure and Equipment Agreement, between the Registrant and Patheon Pharmaceuticals, Inc. effective as of January 30, 2014.	10-Q	001-35068	10.4	5/8/2014
10.31#	Award/Contract between the Registrant and the U.S. Army Medical Research and Materiel Command, dated May 11, 2015.	10-Q	001-35068	10.2	8/4/2015
10.32	Modification of Contract W81XWH-15-C-0046 between the Registrant and the U.S. Army Medical Research and Materiel Command, effective August 6, 2015.	10-Q	001-35068	10.3	11/3/2015

Exhibit Number	Exhibit Description	Incorporation By Reference			
		Form	SEC File No.	Exhibit	Filing Date
10.33	Modification of Contract W81XWH-15-C-0046 between the Registrant and the U.S. Army Medical Research and Materiel Command, effective August 12, 2015.	10-Q	001-35068	10.4	11/3/2015
10.34	Modification of Contract W81XWH-15-C-0046 between the Registrant and the U.S. Army Medical Research and Materiel Command, effective September 4, 2015.	10-Q	001-35068	10.5	11/3/2015
10.35#	Purchase and Sale Agreement between Registrant and ARPI LLC, dated as of September 18, 2015.	10-Q	001-35068	10.6	11/3/2015
10.36#	Subsequent Purchase and Sale Agreement between ARPI LLC (a wholly owned subsidiary of the Registrant) and PDL BioPharma, Inc., dated as of September 18, 2015.	10-Q	001-35068	10.7	11/3/2015
10.37	Consent and Amendment No. 2 to Amended and Restated Loan and Security Agreement, dated as of December 16, 2013, and amended as of September 24, 2014, among the Registrant, Hercules Technology II, L.P. and Hercules Technology Growth Capital, Inc.	10-Q	001-35068	10.8	11/3/2015
21.2	Subsidiaries of the Registrant.				
23.1	Consent of OUM & Co., LLP, Independent Registered Public Accounting Firm.				
23.2	Consent of Ernst & Young, LLP, Independent Registered Public Accounting Firm.				
24.1	Power of Attorney (included in signature page).				
31.1	Certification of Principal Executive Officer pursuant to Rules 13a-14(a) and 15d-14(a) promulgated under the Securities Exchange Act of 1934, as amended.				
31.2	Certification of Principal Financial Officer pursuant to Rules 13a-14(a) and 15d-14(a) promulgated under the Securities Exchange Act of 1934, as amended.				
32.1	Certifications of Chief Executive Officer and Chief Financial Officer pursuant to 18 U.S.C. Section 1350, as adopted pursuant to Section 906 of the Sarbanes-Oxley Act of 2002.*				
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

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+ Indicates management contract or compensatory plan.

Material in the exhibit marked with a "***" has been omitted pursuant to a request for confidential treatment filed with the SEC. Omitted portions have been filed separately with the SEC.

* The certifications attached as Exhibit 32.1 accompany this Annual Report on Form 10-K pursuant to 18 U.S.C. Section 1350, as adopted pursuant to Section 906 of the Sarbanes-Oxley Act of 2002, and shall not be deemed "filed" by the Registrant for purposes of Section 18 of the Securities Exchange Act of 1934, as amended.