**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, 2021**

**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.)** |

**25821 Industrial Boulevard, Suite 400**
**Hayward, CA 94545**
**(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 | Trading Symbol(s) | Name of Each Exchange on Which Registered |
|---|---|---|
| **Common Stock, $0.001 par value** | **ACRX** | **The Nasdaq Global Market** |

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

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

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

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

Indicate by check mark whether the registrant has submitted electronically every Interactive Data File required to be submitted 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 such files). Yes ☑ No ☐

Indicate by check mark whether the registrant is a large accelerated filer, an accelerated filer, a non-accelerated filer, a smaller reporting company, or an emerging growth company. See the definitions of "large accelerated filer," "accelerated filer," "smaller reporting company," and "emerging growth company" in Rule 12b-2 of the Exchange Act.

| | | | |
|---|---|---|---|
| Large accelerated filer | ☐ | Accelerated filer | ☐ |
| Non-accelerated filer | ☑ | Smaller reporting company | ☑ |
| Emerging growth company | ☐ | | |

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

Indicate by check mark whether the registrant has filed a report on and attestation to its management's assessment of the effectiveness of its internal control over financial reporting under Section 404(b) of the Sarbanes-Oxley Act (15 U.S.C. 7262(b)) by the registered public accounting firm that prepared or issued its audit report. ☐

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, 2021 (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 $161,163,094. The calculation excludes 2,394,955 shares of the registrant's common stock held by current executive officers and directors 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 March 7, 2022, the number of outstanding shares of the registrant's common stock was 146,949,320.

**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, 2021 (the "2022 Proxy Statement"), are incorporated by reference into Part III of this report.

Unless the context indicates otherwise, the terms “AcelRx,” “AcelRx Pharmaceuticals,” “we,” “us” and “our” refer to AcelRx Pharmaceuticals, Inc., and its consolidated subsidiaries. “DZUVEO” and “Niyad” are trademarks, and “ACELRX,” “DSUVIA” and “Zalviso” are registered trademarks, all owned by AcelRx Pharmaceuticals, Inc. This report also contains trademarks and trade names that are the property of their respective owners.

## SPECIAL NOTE REGARDING FORWARD-LOOKING STATEMENTS

This Annual Report on Form 10-K, or Annual Report, contains statements that discuss future events or expectations, projections of results of operations or financial condition, trends in our business, business prospects and strategies and other “forward-looking” information. In some cases, you can identify “forward-looking statements” by words like “may,” “will,” “should,” “expects,” “plans,” “anticipates,” “believes,” “estimates,” “predicts,” “intends,” “potential” or “continue” or the negative of those words and other comparable words. These forward-looking statements are not guarantees of future performance or development and involve known and unknown risks, uncertainties and other factors that are in some cases beyond our control. These forward-looking statements may relate to, among other things, our expectations regarding the scope, progress, expansion, and costs of researching, developing and commercializing our product candidates; our opportunity to benefit from various regulatory incentives; expectations for our financial results, revenue, operating expenses and other financial measures in future periods; and the adequacy of our sources of liquidity to satisfy our working capital needs, capital expenditures, and other liquidity requirements. These are only some of the factors that may affect the forward-looking statements contained in this Annual Report. For a discussion identifying additional important factors that could cause actual results to vary materially from those anticipated in the forward-looking statements, see “Management’s Discussion and Analysis of Financial Condition and Results of Operations” and “Risk Factors” in this Annual Report. You should review these risk factors for a more complete understanding of the risks associated with an investment in our securities. However, we operate in a competitive and rapidly changing environment and new risks and uncertainties emerge, are identified or become apparent from time to time. It is not possible for us to predict all risks and uncertainties that could have an impact on the forward-looking statements contained in this Annual Report. You should be aware that the forward-looking statements contained in this Annual Report are based on our current views and assumptions. We undertake no obligation to revise or update any forward-looking statements made in this Annual Report to reflect events or circumstances after the date hereof or to reflect new information or the occurrence of unanticipated events, except as required by law.

**ACELRX PHARMACEUTICALS, INC.**

**2021 ANNUAL REPORT ON FORM 10-K**

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**PART I**

**Item 1. Business**

**Overview**

We are a specialty pharmaceutical company focused on the development and commercialization of innovative therapies for use in medically supervised settings.

**Our Portfolio**

Our portfolio of products and product candidates consists of sufentanil sublingual products and product candidates, pre-filled syringe product candidates and nafamostat mesylate product candidates, as further described below.

***Sufentanil Sublingual Products/Product Candidates***

| Product/Product Candidate | Description | Target Use | Status |
|---|---|---|---|
| DSUVIA® | Sufentanil sublingual tablet, 30 mcg | Moderate-to-severe acute pain in a medically supervised setting, administered by a healthcare professional | Received U.S. Food and Drug Administration, or FDA, approval in November 2018; commercial launch began first quarter of 2019. |
| DZUVEO® | Sufentanil sublingual tablet, 30 mcg | Moderate-to-severe acute pain in a medically monitored setting, administered by a healthcare professional | Granted European Commission, or EC, marketing approval in June 2018. Sunset date extended to December 31, 2022 by EC. To be commercialized in Europe by Laboratoire Aguettant, or Aguettant. |
| Zalviso® | Sufentanil sublingual tablet system, 15 mcg | Moderate-to-severe acute pain in the hospital setting, administered by the patient as needed | In the U.S., positive results from Phase 3 trial, IAP312, announced in August 2017. Currently evaluating the timing of the resubmission of the New Drug Application, or NDA, which is in part dependent on the finalization of the FDA's new opioid approval guidelines and process.<br>Approved in the European Union, where it was marketed commercially by Grünenthal GmbH, or Grünenthal, through May 12, 2021. |
| ARX-02 | Higher Strength Sufentanil Sublingual Tablet | Cancer breakthrough pain in opioid-tolerant patients | Phase 2 clinical trial and End of Phase 2 meeting completed. Investigational New Drug, or IND, application was inactivated.<br><br>Future development contingent upon identification of corporate partnership resources. |

| Product/Product Candidate | Description | Target Use | Status |
|---|---|---|---|
| 4ARX-03 | Combination Sufentanil/Triazolam 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. IND application was inactivated.<br><br>Future development contingent upon identification of corporate partnership resources. |

We have created a proprietary sublingual (under the tongue) formulation of sufentanil intended for the treatment of moderate-to-severe acute pain. We believe our non-invasive, proprietary sublingual sufentanil tablet potentially overcomes many of the limitations of current treatment options available for moderate-to-severe acute pain. The sufentanil pharmacokinetic profile when delivered sublingually avoids the high peak plasma levels and short duration of action observed with IV administration. 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 route of delivery used by DSUVIA and Zalviso provides a predictable 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, or IV line, DSUVIA and Zalviso may allow for ease of patient mobility.

We have chosen sufentanil as the therapeutic ingredient for DSUVIA and Zalviso. 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, a high-therapeutic index opioid, which has no active metabolites, 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. 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 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.

Drugs are classified or scheduled by the Drug Enforcement Agency, or DEA, according to their potential for abuse and addiction. Sufentanil is classified as a Schedule II controlled substance.

*DSUVIA®*

DSUVIA, known as DZUVEO in Europe, approved by the FDA in November 2018 (and by the European Medicines Agency, or EMA, in June 2018), is indicated for use in adults in certified medically supervised healthcare settings, such as hospitals, surgical centers, and emergency departments, for the management of acute pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate. DSUVIA was designed to provide rapid analgesia via a non-invasive route and to eliminate dosing errors associated with IV administration. DSUVIA is a single-strength solid dosage form administered sublingually via a single-dose applicator, or SDA, by healthcare professionals. Sufentanil is an opioid analgesic currently also marketed for IV and epidural anesthesia and analgesia. The sufentanil pharmacokinetic profile when delivered sublingually avoids the high peak plasma levels and short duration of action observed with IV administration.

Examples of potential patient populations and settings in which DSUVIA could be used include: emergency room patients; perioperative use for patients who are undergoing inpatient, short-stay or ambulatory surgery; inpatient use for up to 72 hours in patients with moderate-to-severe acute pain; procedural suite use for painful procedures such as oral surgery or cosmetic procedures; patients being treated and transported by paramedics; and for battlefield casualties. In the emergency room and in procedural suite environments, patients often do not have immediate IV access available, or may not require IV access. Moreover, IV dosing results in high peak plasma levels, thereby limiting the opioid dose and requiring frequent redosing intervals to titrate to satisfactory analgesia. Oral pills and liquids generally have slow and erratic onset of analgesia. Based on internal market research conducted to date, we believe that DSUVIA, a treatment option that provides timely analgesia without requiring an IV for moderate-to-severe acute pain, continues to be needed, in both civilian and military settings, as an alternative to other currently available opioids.

DSUVIA was approved with a REMS which restricts distribution to certified medically supervised healthcare settings in order to prevent respiratory depression resulting from accidental exposure. DSUVIA is only distributed to facilities certified in the DSUVIA REMS program following attestation by an authorized representative to comply with appropriate dispensing and use restrictions of DSUVIA. To become certified, a healthcare setting is required to train their healthcare professionals on the proper use of DSUVIA and have the ability to manage respiratory depression. DSUVIA is not available in retail pharmacies or for outpatient use. As part of the REMS program, we monitor distribution and audit wholesalers' data, evaluate proper usage within the healthcare settings and monitor for any diversion and abuse. We de-certify healthcare settings that are non-compliant with the REMS program.

On July 14, 2021, we entered into a License and Commercialization Agreement, or the DZUVEO Agreement, with Aguettant pursuant to which Aguettant obtained the exclusive right to develop and commercialize DZUVEO in the European Union, Norway, Iceland, Liechtenstein, Andorra, Vatican City, Monaco, Switzerland and the United Kingdom, or the DZUVEO Territory, for the management of acute moderate to severe pain in adults in medically monitored settings. We will supply Aguettant with primary packaged product and Aguettant will then complete secondary packaging of the finished product. We are entitled to receive up to €47.0 million in a combination of up-front and sales-based milestone payments, of which we received €2.5 million, or approximately $2.9 million, in 2021. Refer to Note 6 "Out-license Agreements—DZUVEO" in the accompanying notes to the Consolidated Financial Statements for additional information.

*Zalviso®*

While still under development in the United States, Zalviso is approved in the European Union, or EU. Zalviso is intended for the management of moderate-to-severe acute pain in hospitalized adult patients. Zalviso consists of a pre-filled cartridge of 40 sufentanil sublingual tablets, 15 mcg, delivered by the Zalviso System, a needle-free, handheld, patient-administered, pain management system. Zalviso is a pre-programmed non-invasive system that allows 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 IV patient-controlled analgesia, or PCA. Zalviso allows patients to self-administer sufentanil sublingual tablets via a pre-programmed, secure system designed in part to eliminate the risk of healthcare provider programming errors.

The Zalviso System consists of the following components: a disposable dispenser tip, a disposable dispenser cap, an adhesive thumb tag, a cartridge of 40 sufentanil sublingual 15 mcg tablets (approximately a two-day supply) in a disposable radio frequency identification and bar-coded cartridge, a reusable, rechargeable handheld controller, a tether, and an authorized access card.

The potential 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.

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.

We submitted an NDA for Zalviso in September 2013, or the Zalviso NDA, and on July 25, 2014, the Division of Anesthesia, Analgesia, and Addiction Products of the FDA issued a Complete Response Letter, or CRL, for the Zalviso NDA. The CRL contained 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 device errors, changes to address inadvertent dosing, among other items, and submission of additional data to support the shelf life of the product. 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 and mitigations put in place to reduce the risk of inadvertent dosing/misplaced tablets.

Our IAP312 study was designed to evaluate the effectiveness of changes made to the functionality and usability of the Zalviso device and to take into account comments from the FDA on the study protocol. In the IAP312 study, 320 hospitalized, post-operative patients used Zalviso to self-administer 15 mcg sublingual sufentanil tablets as often as once every 20 minutes for 24-to-72 hours to manage their moderate-to-severe acute pain. Throughout the study, for which top-line results were announced in August 2017, 2.2% of patients experienced a Zalviso device error, which was statistically less than the 5% limit specified in the study objectives. None of these device errors resulted in an over-dosing event. This 2.2% rate was lower ($p < 0.001$) than the 7.9% rate of device errors during patient use previously reported for the earlier version of the Zalviso device in the Phase 3 IAP311 study. In addition, results of this study supported earlier clinical findings, with favorable tolerability and a significant majority of “good” or “excellent” ratings provided by both patients and healthcare providers when assessing the method of pain control. These results will supplement those of our earlier Phase 3 studies (IAP309, IAP310 and IAP311), all of which met safety and efficacy endpoints, in the Zalviso NDA resubmission. The timing of the resubmission of the Zalviso NDA is in part dependent upon the finalization of the FDA’s new opioid approval guidelines and process.

Zalviso was approved for commercial sale in the European Union, or EU, in September 2015 and Grünenthal GmbH, or Grünenthal, began its commercial launch of Zalviso in the EU in April 2016. On May 18, 2020, we received a notice from Grünenthal that it was exercising its right to terminate the Collaboration and License Agreement, or, as amended, the License Agreement, which granted Grünenthal the European rights to commercialize Zalviso in the 28 EU member states at the time of the agreement, plus Switzerland, Liechtenstein, Iceland, Norway and Australia, or the Territory, for human use in pain treatment in medically supervised settings, and the related Manufacture and Supply Agreement, or, as amended, the MSA, under which AcelRx exclusively manufactured and supplied Zalviso to Grünenthal for commercial sales in the Territory. The MSA, together with the License Agreement, are referred to as the Grünenthal Agreements. Certain terms of the Grünenthal Agreements were extended to May 2021 to enable Grünenthal to sell down its Zalviso inventory, a right it had under the Grünenthal Agreements. The rights to market and sell Zalviso in the Territory reverted back to us in May 2021. Certain terms of the Grünenthal Agreements were further extended for a period of thirty days after the last Zalviso product distributed by Grünenthal prior to May 13, 2021 expires to enable the parties to manage applicable pharmacovigilance and other requirements.

On September 18, 2015, we sold a majority of the expected royalty stream and commercial milestones from the sales of Zalviso in Europe by Grünenthal to PDL BioPharma, Inc., or PDL, in a transaction referred to as the Royalty Monetization. On August 31, 2020, PDL announced it sold its royalty interest for Zalviso to SWK Funding, LLC, or SWK. Under the Royalty Monetization, we have a continuing obligation to use commercially reasonable efforts to negotiate a replacement license agreement for Zalviso, or New Arrangement; however, we have not yet entered into such an arrangement. For additional information regarding the Grünenthal Agreements, see Note 7 “Revenue from Contracts with Customers” in the accompanying notes to the Consolidated Financial Statements. For additional information on the Royalty Monetization, see Note 10 “Liability Related to Sale of Future Royalties” in the accompanying notes to the Consolidated Financial Statements.

***Pre-filled Syringe Product Candidates***

| Product/Product Candidate | Description | Target Use | Status |
|---|---|---|---|
| Ephedrine | Ephedrine pre-filled syringe, containing 10 ml of a solution of 3 mg/ml ephedrine hydrochloride for injection | Clinically important hypotension occurring in the setting of anesthesia | Product candidate licensed Aguettant; preparing NDA for submission to FDA.<br>Approved in the European Union; owned and marketed by Aguettant. |
| Phenylephrine | Phenylephrine pre-filled syringe containing 10 ml of a solution of 50 mcg/ml phenylephrine hydrochloride for injection | Clinically important hypotension resulting primarily from vasodilation in the setting of anesthesia | Product candidate licensed from Aguettant; preparing NDA for submission to FDA.<br>Approved in the European Union; owned and marketed by Aguettant. |

*Ephedrine and Phenylephrine*

On July 14, 2021, we entered into a License and Commercialization Agreement, or the PFS Agreement, with Aguettant pursuant to which we obtained the exclusive right to develop and, subject to FDA approval, commercialize in the United States (i) an ephedrine pre-filled syringe containing 10 ml of a solution of 3 mg/ml ephedrine hydrochloride for injection, and (ii) a phenylephrine pre-filled syringe containing 10 ml of a solution of 50 mcg/ml phenylephrine hydrochloride for injection. Aguettant will supply us with the products for use in commercialization, if they are approved in the U.S. Aguettant is entitled to receive up to $24 million in sales-based milestone payments. Refer to Note 5 “In-license Agreements” and Note 6 “Out-license Agreements—DZUVEO” in the accompanying notes to the Consolidated Financial Statements for additional information.

We are in dialogue with the FDA and have submitted a Briefing Book to the FDA supporting our proposed regulatory pathway for the ephedrine pre-filled syringe. We expect feedback from the FDA in the first quarter of 2022 that will direct our regulatory pathway for this product candidate, as well as the phenylephrine pre-filled syringe product candidate. We expect we will be able to submit NDA’s for both products in 2022.

These products are innovative ready-to-use formulations of active ingredients that are currently approved in the U.S. in concentrated formulations that must be diluted prior to administration to patients, and more recently in ready-to-use vial formulations. Hospitals currently purchase ready-to-use, pre-filled syringe presentations of these active ingredients from compounding facilities that have not obtained FDA approval for the products, or manually dilute the products in-house. Our product candidates have been developed in a ready-to-use strength and pre-filled into syringes that can be immediately administered to patients, eliminating the need for calculations and additional dilution and filling steps. We believe that, if approved, our pre-filled syringe products will offer significant benefits to hospitals and surgery centers over the current compounded products, including longer shelf-life, reduction of compounding errors, greater sterility assurance, and more consistent supply.

***Nafamostat Product Candidates***

| Product/Product Candidate | Description | Target Use | Status |
|---|---|---|---|
| Niyad | Lyophilized vial for injection | Regional anticoagulant for injection into the extracorporeal circuit | Submitted an investigational device exemption, or IDE, and received Breakthrough Device Designation from the FDA. |
| LTX-608 | Lyophilized vial for injection | IV infusion as an anti-viral treatment for COVID-19 | IND to be submitted following toxicology evaluation to enable Phase 2 study |
| LTX-608 | Lyophilized vial for injection | IV infusion for disseminated intravascular coagulation, or DIC | IND to be submitted following toxicology evaluation to enable Phase 2 study |
| LTX-608 | Lyophilized vial for injection | IV infusion for acute respiratory distress syndrome, or ARDS | IND to be submitted following toxicology evaluation to enable Phase 2 study |
| LTX-608 | Lyophilized vial for injection | IV infusion for acute pancreatitis | IND to be submitted following toxicology evaluation to enable Phase 2 study |

On January 7, 2022, we acquired Lowell Therapeutics, Inc., or Lowell, pursuant to the Agreement and Plan of Merger, dated as of November 14, 2021, or the Merger Agreement, in a transaction for consideration of approximately $32.5 million plus net cash acquired and certain other adjustments, and which includes up to approximately $26.0 million of contingent consideration payable in cash or stock at AcelRx's option, upon the achievement of regulatory and sales-based milestones, or the Merger Agreement. For additional information regarding the Merger Agreement, see Note 19. "Subsequent Events" in the accompanying notes to the Consolidated Financial Statements.

*Niyad™*

Niyad is being developed to become the first and only FDA-approved regional anticoagulant for injection into the extracorporeal circuit. Niyad is expected to be used during renal replacement therapy for acute kidney injury patients in the hospital and for end-stage renal disease patients receiving dialysis in outpatient clinics. Niyad is being studied under an investigational device exemption, or IDE, and has received Breakthrough Device Designation from the FDA. While not approved for commercial use in the U.S., the active drug component of Niyad, nafamostat, has been approved in Japan and South Korea as a regional anticoagulant for the extracorporeal circuit, disseminated intravascular coagulation, and acute pancreatitis. Niyad is a lyophilized formulation of nafamostat, a broad-spectrum, synthetic serine protease inhibitor, with anticoagulant, anti-inflammatory, and potential anti-viral activities.

The current standards of care being used today are heparin and citrate, neither of which are FDA approved for use in these patient procedures. The use of Niyad is expected to result in longer filter lifespan, less blood loss, fewer platelet transfusions, fewer bleeding events and less downtime. Niyad can be used in patients at risk of bleeding, whereas heparin cannot. The product is much easier to administer than citrate, which is not FDA-approved, and can be used in patients with liver failure (43% of the acute kidney injury patients on continuous dialysis), whereas citrate cannot. Amongst other potential indications, Niyad is expected to be used as an anticoagulant in continuous renal replacement therapy, or CRRT, for patients with acute kidney injury, or AKI, in the hospital, and for intermittent hemodialysis, or IHD, for patients with end-stage renal disease, or ESRD, undergoing treatment in outpatient dialysis clinics. The prevalence of patients with AKI and ESRD has been increasing every year since 2000.

*LTX-608*

LTX-608 is our proprietary nafamostat formulation for direct IV infusion being explored as an investigational product for: (a) antiviral treatment of COVID, (b) acute respiratory distress syndrome, or ARDS, (c) disseminated intravascular coagulation, or DIC, and (d) acute pancreatitis. Our initial focus for LTX-608 will be on its development as an antiviral treatment for COVID in combination with standard-of-care, or SOC. Studies are actively being conducted outside the U.S. where initial results demonstrate nafamostat's effectiveness in shortening time to clinical improvement, increasing the recovery rate and lowering the mortality rate when combined with SOC compared to SOC alone in the category of the sickest COVID patients. We have pending patent applications directed to the use of nafamostat as an antiviral agent, including use as a COVID treatment.

**Clinical Trials**

*Zalviso®*

We have completed three Phase 3 clinical trials for Zalviso: two placebo-controlled efficacy and safety trials and one open-label active comparator trial, in which Zalviso was compared to IV PCA morphine. Each of the three Phase 3 trials successfully achieved its primary endpoint. Based on FDA feedback, we completed a fourth study, IAP312, in a diverse post-surgical population to further evaluate the overall performance of the Zalviso System.

*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).

*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 321 patients randomized to sufentanil sublingual tablet treatment and 105 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 (+76.2 and -11.4, 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).

Four patients (three in the sufentanil sublingual tablet group and one in the placebo group) experienced a serious adverse event, or SAE, considered possibly or probably related to the study drug by the investigator. The SAEs observed in the patients in the sufentanil sublingual tablet group included severe oxygen saturation decrease, sinus tachycardia, and confusional state.

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 Events Occurring in ≥ 2% in Either Group

| Possibly or Probably Related Adverse Events<br>At least 2% in either group | Zalviso n=429<br>Two Placebo-Controlled Phase 3 Studies | Placebo n=162 |
|---|---|---|
| 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.

*Multi-center, single-arm, open-label study (IAP312)*

IAP312 was a Phase 3 study designed to evaluate the overall performance of the Zalviso System, in response to the CRL received from the FDA for Zalviso. Throughout the study in 320 enrolled patients, 2.2% of patients experienced a Zalviso device error, which was statistically less than the 5% limit specified in the study objectives. Importantly, none of these device errors resulted in an over-dosing event. This 2.2% rate was lower ($p < 0.001$) than the 7.9% rate of device errors during patient use previously reported for the earlier version of the Zalviso device in the Phase 3 IAP311 study.

In addition, as requested by FDA, the IAP312 study prospectively evaluated the number of inadvertently misplaced tablets which occurred during patient dosing. A small number of inadvertently misplaced tablets (less than 0.1% of total dispensed tablets) was observed in the original Phase 3 studies. However, the presence of inadvertently misplaced tablets had not been routinely assessed as part of the previous protocols. Throughout the IAP312 study, patients self-administered a total of 7,293 sufentanil tablets. Per the updated Zalviso training instructions electronically displayed on the hand-held device, 6 patients called the nurse when they failed to properly self-administer a single tablet to allow for proper retrieval and disposal of the tablet. Also, during inspection by the nurse, which occurred every two hours per protocol, a total of 7 misplaced tablets (<0.1% of total dispensed tablets) were discovered with 6 additional patients. No patient had a repeat incidence of an inadvertently misplaced tablet following re-training on the device. This combination of patient training and nurse inspection, along with the tracking features of the Zalviso device, could potentially address the FDA's concerns regarding drug accountability.

Finally, in this study, 86%, 89% and 100% of patients at the 24, 48 and 72-hour time points, respectively, recorded "good" or "excellent" ratings on the patient global assessment, or PGA, of the method of pain control, which measures a patient's satisfaction with their quality of analgesia. Healthcare professional global assessment, or HPGA, of the method of pain control was similarly strong, with 91%, 95% and 100% of nurses rating Zalviso as "good" or "excellent" over each respective 24-hour period. Zalviso was shown to be well tolerated by study participants, with nausea, hypotension and vomiting representing the most commonly reported adverse events. A total of 5 patients experienced serious adverse events, but all were considered unrelated to study drug by investigators.

*ARX-02(higher strength sufentanil sublingual tablet)*

A Phase 2 trial evaluating the efficacy and safety of ARX-02 for the treatment of cancer breakthrough pain in opioid-tolerant patients has been completed. The IND application for ARX-02 was inactivated as there is no ongoing clinical development.

*ARX-03(combination sufentanil/triazolam sublingual tablet)*

A Phase 2 trial which evaluated the efficacy and safety of this product for procedural anxiety and acute pain has been completed. The IND application for ARX-03 was inactivated as there is no ongoing clinical development.

ARX-02 and ARX-03 are investigational product candidates and are not approved by the FDA or any other regulatory agency. We do not intend to invest resources in these development stage product candidates; accordingly, any future development of these development stage product candidates is contingent on funding from a corporate partnership or other external funding source.

**The Market Opportunity for Sufentanil Sublingual Products**

Examples of potential patient populations and settings in which patients might require the short-term management of moderate-to-severe acute pain include emergency room patients; perioperative use for patients who are undergoing inpatient, short-stay or ambulatory surgery; inpatient use for up to 72 hours in patients with moderate-to-severe acute pain; procedural suite use for painful procedures such as oral surgery or cosmetic procedures; patients being treated and transported by paramedics; and for battlefield casualties.

While IV opioids are currently employed to control moderate-to-severe acute pain in many of these settings, the use of IV opioids suffers from the following:

- potential high peaks and troughs of plasma concentrations;
- infection risk associated with the invasive nature of IV delivery;
- consumption of hospital resources including an IV pump, a bed where the patient can be monitored, and nurse time; and
- possible impairment of a patient’s cognitive abilities, which can make it difficult to provide accurate medical history to physicians during evaluation.

We believe healthcare providers and hospital administrators caring for patients in moderate-to-severe acute pain in the aforementioned medically supervised settings could significantly benefit from the following items:

- a pharmacokinetic profile that avoids the high peak plasma levels and short duration of action observed with IV administration;
- non-invasively delivered analgesic that utilizes fewer hospital resources, thereby incurring less cost;
- effective and rapid-acting pain relief with sufficient duration of effect allowing efficient treatment while assuring patient satisfaction;
- pain relief that does not sacrifice cognitive function; and/or
- avoiding infection risks due to invasive routes of delivery, such as IV.

In our Phase 1 through Phase 3 clinical studies, sublingual sufentanil has demonstrated the following attributes:

- a pharmacokinetic profile that blunts peak plasma levels compared to IV administration;
- ease of administration;
- pain reduction (as much as 3-points on a validated 10-point scale) beginning as early as 15-to-30 minutes after administration;
- maintenance of cognitive function;
- adverse event types similar to IV opioids, such as nausea, headache, vomiting and dizziness; and
- lower percentage of patients with decreased oxygen saturation events compared to IV-PCA morphine.

We believe that sublingual sufentanil provides a safety, efficacy and tolerability profile enabling our products to potentially replace IV opioid use in patients with moderate-to-severe acute pain in the proposed medically supervised settings. This may be especially true for DSUVIA in the post-operative settings where, because of the unique pharmacokinetic profile, the healthcare practitioner may be able to manage patient-flow more efficiently in the recovery room after surgery, and in emergency medical settings. The number of emergency departments is decreasing in the United States, resulting in an increased focus on resource management to treat a growing number of patients in an efficient manner.

*United States Market*

Based on commissioned research conducted in 2016, we estimate that there are over 90 million patients who are treated in various medically supervised settings for their moderate-to-severe acute pain which is significant enough to warrant the use of an opioid. We believe these patients may be eligible for treatment with DSUVIA, and in some cases Zalviso, if approved in the United States. The target patient population for DSUVIA are those patients in a certified medically supervised healthcare setting, such as hospitals, surgical centers, and emergency departments, for less than 24 hours. The target patient population for Zalviso are patients in a hospital setting for greater than 24 hours. Our current estimate of patients in moderate-to-severe acute pain in medically supervised settings, by setting, is as follows:

| | |
|---|---|
| Emergency services (includes pre-hospital and Emergency Department treatment) | 52 million |
| Outpatient surgery | 11 million |
| Hospital/surgery center/office-based procedures | 20 million |
| Inpatient surgery/inpatient conditions | 10 million |

The market for Zalviso, given the target patients in a hospital setting for greater than 24 hours, is the approximately 10 million inpatient surgeries and inpatient conditions above. There can be no assurance that our estimates regarding the number of patients treated in the various settings will be accurate.

*European Market*

Based on commissioned research conducted in 2016, there are an estimated 142 million patients in the EU5 (France, Germany, Italy, Spain, and the United Kingdom) represented across DZUVEO target care settings annually. Each year, there are an estimated 110 million emergency attendances and 32 million surgical procedures performed each year. It is anticipated that there are 51 million patients in emergency medicine with moderate-to-severe acute pain and 16 million with moderate-to- severe acute pain following surgery each year.

**The Market Opportunity for Pre-Filled Syringe Products**

These products are innovative ready-to-use formulations of molecules that are currently approved in a concentrated formulation that must be diluted prior to administration to patients, and more recently in ready-to-use vial formulations. Hospitals currently purchase non-FDA approved ready-to-use, pre-filled syringe products from compounding facilities, or manually dilute the products in-house. Our product candidates have been developed in a ready-to-use strength and pre-filled into syringes that can be immediately administered to patients, eliminating the need for calculations and additional dilution and filling steps. We believe that, if approved, our products will offer significant benefits to hospitals and surgery centers over the current compounded products, including longer shelf-life, reduction of compounding errors, greater sterility assurance, and more consistent supply.

**The Market Opportunity for Nafamostat Products**

Niyad is being developed to become the first and only FDA-approved regional anticoagulant for the extracorporeal circuit. The current standards of care being used today are heparin and citrate, neither of which are FDA approved for use in these patient procedures. The use of Niyad is expected to result in longer filter lifespan, less blood loss, fewer platelet transfusions, fewer bleeding events and less downtime. Niyad can be used in patients at risk of bleeding, whereas heparin cannot. The product is much easier to administer than citrate, which is not FDA-approved, and can be used in patients with liver failure (43% of the acute kidney injury patients on continuous dialysis), whereas citrate cannot. Amongst other potential indications, Niyad is expected to be used as an anticoagulant in continuous renal replacement therapy, or CRRT, for patients with acute kidney injury, or AKI, in the hospital, and for intermittent hemodialysis, or IHD, for patients with end-stage renal disease, or ESRD, undergoing treatment in outpatient dialysis clinics. The prevalence of patients with AKI and ESRD has been increasing every year since 2000.

The second indication for our nafamostat product development candidate, LTX-608, on which we are focused is as an IV infusion for the treatment of COVID. Studies are actively being conducted outside the U.S. where initial results demonstrate nafamostat's effectiveness in shortening time to clinical improvement, increasing the recovery rate and lowering the mortality rate when combined with SOC compared to SOC alone in the category of the sickest COVID patients. We have pending patent applications directed to the use of nafamostat as an antiviral agent, including use as a COVID treatment.

**Our Strategy**

Our strategy is focused on the marketing of DSUVIA as well as the development, for approval by the FDA, of the recently acquired investigational products. Our commercial focus remains on sales of DSUVIA into the medically supervised healthcare settings market, such as hospitals, surgical centers, emergency departments and most recently, office-based procedural suites. The process of selling into hospital settings and obtaining approval for a product to be used within these types of institutions is complex and takes time, and particularly so since the COVID pandemic. Accordingly, our commercial focus on office-based procedural suites has increased, as they have been less impacted by the COVID pandemic, and obtaining approvals in these settings is often less complex.

Our four-pillar strategy for DSUVIA revenue growth is focused on delivering the most effective and efficient commercialization of DSUVIA through different channels, plus business development to expand the number of products in our portfolio.

The first pillar is concentrated on supporting broader use within the DoD after DSUVIA achieved U.S. Army Milestone C approval and was added to the Joint Deployment Formulary in 2020. We believe the opportunity for DSUVIA revenue growth includes deployed or deploying military troops, domestic-based military, military treatment facilities and Veterans Administration facilities. We are using a small internal commercial team focused on achieving our objectives within this first pillar.

The second pillar is centered around the launch of DSUVIA in the United States, focused on medically supervised settings, which includes promotion to hospitals, emergency departments, surgery centers, and more recently office-based procedural suites, with our internal commercial team.

The third pillar is focused on what we call specialty markets, which are typically large market opportunities, but more geographically dispersed with a lower concentration of patient visits than a hospital or surgery center. Examples of these specialty markets include oral/dental surgery, emergency medical services and plastic surgery. We intend to leverage the use of commercial partnerships with more established companies already serving customers in these specific markets. An example of an initiative in this pillar is our partnership with Zimmer Biomet Dental in oral/dental surgery, which was amended in February 2022 to become non-exclusive. Our objective is to focus on finding additional partners for these other specialties that align with our values and goals.

The fourth pillar involves identifying and licensing, or acquiring, complementary products to DSUVIA. We believe having a single product to market and sell into this setting is inherently inefficient and building a portfolio of products is important to mitigate such inefficiency. An example of actions performed in this pillar are the in-licensing of two pre-filled syringe products for the U.S. market, as well as our acquisition of Lowell. We continue to pursue ways to leverage our commercial and development infrastructure by identifying, evaluating and executing transactions to bring in additional products for healthcare institutions and will continue to be opportunistic on business development activities to increase the number of products in our portfolio.

Supporting the DSUVIA commercial strategy is the production strategy, focused on the completion of our transition to automated packaging equipment with our contract manufacturing organization in order to leverage improved technology to lower production cost.

Our strategy with respect to Zalviso is to (a) continue to use commercially reasonable efforts to negotiate a New Arrangement as required under the Royalty Monetization; and (b) upon the FDA providing further guidance about new opioid approval guidelines, evaluate resubmission of the Zalviso NDA to seek regulatory approval in the United States and, if successful, promote Zalviso as a follow-on product to DSUVIA, or potentially seek a commercial partner.

**Sales and Marketing**

Our four-pillar commercial strategy is focused on leveraging our internal commercial organization, plus collaboration partners, to commercialize DSUVIA. We have established and will continue developing our distribution capability and commercial organization in the United States to market and sell DSUVIA in the United States. In geographies where we decide not to commercialize ourselves, we will seek to out-license commercialization rights. In specialty areas that are not core to the hospital, ambulatory surgery centers, or ASCs, or emergency room settings, (e.g., plastic surgeries), we will seek commercialization partners that will support accessing these markets.

We are building commercial capability in the United States progressively to support the launch of DSUVIA in the United States market. We foresee two stages of commercial execution to support successful introduction of DSUVIA in the United States:

To date, we have:

- created and deployed a focused scientific support team to gather a detailed understanding of individual institutional and healthcare professional needs in order to present DSUVIA effectively;
- increased awareness of the clinical profile of sublingual administration of sufentanil through publication of our clinical data;
- engaged appropriate Advisory Boards that include representative physicians, including anesthesiologists and surgeons, nurses, pharmacy and therapeutics, or P&T, committee members and other related experts to provide us with input on appropriate commercial positioning for DSUVIA for each of these key audiences;
- built a sales and marketing organization that can define appropriate segmentation and positioning strategies and tactics for DSUVIA;
- established DSUVIA on hospital and ambulatory surgery center formularies as well as obtained approvals from individual physicians and practices of physicians performing office-based procedures, through deployment of an experienced team to explain the clinical and health economic attributes of DSUVIA; and
- gathered relevant clinical and health economic data identifying the limitations of IV opioids and other relevant treatments for moderate-to-severe acute pain in use today.

Next steps in our commercialization plan include:

- as needed, continuing to build and progressively deploy a high-quality, customer-focused and experienced sales organization in the United States dedicated to bringing innovative, highly valued healthcare solutions to patients, payers and healthcare providers;
- potentially expanding the label to include pediatric populations by conducting post-approval clinical trials for DSUVIA; and
- continuing to establish DSUVIA as a suitable choice for moderate-to-severe acute pain in certified medically supervised settings.

If we are unable to establish successful sales and marketing capabilities or enter into agreements with third parties to market and sell our products, we may be unable to generate any product revenue. For a more comprehensive discussion of the risks related to our commercialization, please see “Risk Factors—Risks Related to Commercialization of DSUVIA and Zalviso” appearing elsewhere in this Form 10-K.

**Distribution Agreement**

On July 17, 2020, we entered into a distribution agreement, or the Distribution Agreement, with Zimmer Biomet Dental, or ZB Dental, pursuant to which ZB Dental obtained the exclusive right to promote, market, sell, and arrange to distribute DSUVIA in the United States to clinicians, dentists, surgeons and other licensed health care practitioners that perform dental (including specialty dental), oral-maxillofacial, cranio-maxillofacial or oral surgery procedures, or Professionals, and their respective institutions and facilities that are permitted to use DSUVIA. ZB Dental’s distribution rights do not extend to ambulatory care centers outside the class of trade or into hospitals. On February 15, 2022, we amended the agreement with ZB Dental to remove the exclusivity provided to ZB Dental, now allowing us the right to promote, market, sell and distribute DSUVIA in the specified markets. The dental and oral-maxillofacial surgery markets have similar characteristics to the other office-based procedures on which we are currently focusing the majority of our commercial efforts.

**Intellectual Property**

We seek patent protection in the United States and internationally for our commercial products DSUVIA, DZUVEO and Zalviso. We also seek patent protection in the United States and internationally for our product candidates Niyad and LTX-608. Our policy is to pursue, maintain and defend patent rights developed internally or acquired externally 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 commercial products and 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 commercial products DSUVIA, DZUVEO and Zalviso, as well as for our product candidates ephedrine, phenylephrine, Niyad and LTX-608;
- defend our patents;
- preserve the confidentiality of our trade secrets; and
- operate our business without infringing or misappropriating patents and other third-party proprietary rights.

We have established and continue to build proprietary positions for our commercial products DSUVIA, DZUVEO and Zalviso and related technology, as well as for our product candidates ephedrine, phenylephrine, Niyad and LTX-608 in the United States and abroad.

As of December 31, 2021, we are the owner of record of 28 issued U.S. patents, which together provide coverage for sufentanil sublingual tablets, and the device components of Zalviso and DSUVIA. We have listed 18 of these U.S. patents in the Orange Book for DSUVIA. These patents have expiry dates extending to at least 2027. We also hold ten issued European patents, each validated and maintained in at least eight countries in Europe, seven patents in Japan, eight in China and seven in Korea, and a number of other international patents have expiry dates extending to at least 2027 excluding any potential patent term adjustments or extensions in those countries. 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 DSUVIA, DZUVEO and Zalviso commercial products. In particular, we are pursuing additional patent protection for our DSUVIA, DZUVEO and Zalviso formulations, our Zalviso device, and our Zalviso device, our DSUVIA and DZUVEO SDA, as well as to methods of treatment using such drug and device compositions. We will also seek to expand and develop new patent protection for our product candidates Niyad and LTX-608.

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 2036, 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, DSUVIA and Zalviso marks 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, DSUVIA and Zalviso marks are also registered in the European Union, as well as other countries. Our DZUVEO mark is also registered in the European Union.

**Competition**

*Sufentanil Sublingual Products*

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 products are the safety, efficacy and tolerability profile, the patient and healthcare professional satisfaction with using our products in relation to available alternatives and the reliability, convenience of dosing, price and reimbursement of our products. Over the past year, we have monitored changes in the pharmaceutical industry in response to opioid use in the United States. Pharmaceutical companies engaged in the distribution and sale of opioids, in particular for the treatment of chronic pain, are refocusing their efforts in order to support responsible opioid use. While our products are designed for the treatment of moderate-to-severe acute pain for use in medically supervised settings, rather than for the treatment of chronic pain or for outpatient use, these industry changes could impact the commercial success of DSUVIA, or Zalviso, if approved, in the United States.

DSUVIA competes, and Zalviso, if approved in the U.S., will compete, with a number of existing and future pharmaceuticals and drug delivery devices developed, manufactured and marketed by others. In particular, DSUVIA may compete with a wide variety of products and product candidates including (i) injectable opioid products, such as morphine, fentanyl, hydromorphone and meperidine; (ii) oral opioids such as oxycodone and hydrocodone; (iii) generic injectable local anesthetics, such as bupivacaine or branded formulations thereof; (iv) non-steroidal anti-inflammatory drugs, or NSAIDS, including ketorolac in intranasal or generic IV form, and IV meloxicam; and (v) transmucosal fentanyl products. Zalviso, if approved in the U.S., may compete with a number of opioid-based treatment options, including IV PCA pumps, oral PCA devices, and transdermal opioid PCAs.

*Pre-filled Syringe Products*

Hospitals currently purchase non-FDA approved ready-to-use, pre-filled syringe products from compounding facilities, or manually dilute the products in-house. Our product candidates have been developed in a ready-to-use strength and pre-filled into syringes that can be immediately administered to patients, eliminating the need for calculations and additional dilution and filling steps. We believe that, if approved, our products will offer significant benefits to hospitals and surgery centers over the current compounded products, including longer shelf-life, reduction of compounding errors, greater sterility assurance, and more consistent supply. In addition, our pre-filled syringe product candidates will also compete with existing generic versions of concentrated vial forms of product, ready-to-use diluted vial forms of product candidates will also compete with existing generic versions of concentrated vial forms of product, ready-to-use diluted vial forms of product, and for the ephedrine product, a recently FDA-approved pre-filled syringe with a different formulation and concentration than our product candidate.

*Nafamostat Products*

Niyad is the first nafamostat product candidate we are developing to be used as a regional anticoagulant for injection into the extracorporeal circuit. There are currently no products approved by the FDA for use as an anticoagulant in the extracorporeal circuit. Niyad would be the first and only product approved for this indication, if approved. The current standards of care being used today are heparin and citrate. Heparin is a systemic anticoagulant and cannot be used in patients at risk of bleeding. Citrate is complex to administer and requires significant human resource time and attention given the nature of the product, and cannot be used in patients with liver failure, which is approximately 43% of acute kidney injury patients.

The second nafamostat product development candidate on which we are focused is an IV infusion for the treatment of COVID. Studies are actively being conducted outside the U.S. where initial results demonstrate nafamostat’s effectiveness in shortening time to clinical improvement, increasing the recovery rate and lowering the mortality rate when combined with SOC compared to SOC alone in the category of the sickest COVID patients. We have pending patent applications directed to the use of nafamostat as an antiviral agent, including use as a COVID treatment.

**Pharmaceutical Manufacturing and Supply**

We currently rely on contract manufacturers to produce sufentanil sublingual tablets for commercial production of DSUVIA 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 products, if and when approved for marketing by the FDA. We currently rely on a single manufacturer for the commercial supplies of the active pharmaceutical ingredient, or API, for DSUVIA and Zalviso, and intend to qualify a second source. For DSUVIA, we currently package the finished goods under a manual process and would package DZUVEO in the same manner. We have purchased and installed an automated filling and packaging line to support increased capacity packaging for DSUVIA and DZUVEO; however, there can be no assurance that we will be able to successfully complete the qualification and validation of this line and obtain the necessary regulatory approvals to manufacture product on this line. We have identified other manufacturers that could satisfy our commercial supply and packaging requirements and we continue to evaluate those manufacturers.

**Device Manufacturing and Supply**

All contract manufacturers and component suppliers have been selected for their specific competencies in the manufacturing processes and materials that make up DSUVIA and Zalviso. We currently rely on single manufacturers for the commercial supplies of our drug components and packaging for DSUVIA and Zalviso, and do not currently have agreements in place for redundant supply or a second source for either DSUVIA or Zalviso. DSUVIA utilizes an SDA in the delivery of the tablets. FDA regulations require that materials be produced under cGMPs or Quality System Regulation, 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.

The device components of Zalviso are manufactured by contract manufacturers, component fabricators and secondary service providers. 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.

**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 pharmaceutical and medical device products, which must be approved by the FDA 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 and Manufacturing 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, annual program 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 approval 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.

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, the 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 a product candidate does 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. A REMS, which can include a medication guide, patient package insert, a communication plan, elements to assure safe use and implementation system, 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 approval 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 post marketing 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.

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.

**Medical Devices**

In the United States, absent certain limited exceptions, human clinical trials intended to support medical device clearance or approval require an investigational device exemption, or IDE, application. If the device presents a “significant risk” to human health, as defined by the FDA, the sponsor must submit an IDE application to the FDA and obtain IDE approval prior to commencing the human clinical trials. The IDE application must be supported by appropriate data, such as animal and laboratory testing results, showing that it is safe to test the device in humans and that the testing protocol is scientifically sound. Generally, clinical trials for a significant risk device may begin once the IDE application is approved by the FDA and the study protocol and informed consent are approved by appropriate IRBs at the clinical trial sites. Submission of an IDE will not necessarily result in the ability to commence clinical trials, and although the FDA’s approval of an IDE allows clinical testing to go forward for a specified number of subjects, it does not bind the FDA to accept the results of the trial as sufficient to prove the product’s safety and efficacy, even if the trial meets its intended success criteria.

Clinical trials must further comply with good clinical practice regulations for IRB approval and for informed consent and other human subject protections. Required records and reports are subject to inspection by the FDA for any clinical trials subject to FDA oversight. The results of clinical testing may be unfavorable, or, even if the intended safety and efficacy success criteria are achieved, may not be considered sufficient for the FDA to grant marketing approval or clearance of a product. The commencement or completion of any clinical trial may be delayed or halted, or be inadequate to support approval of a PMA application or clearance of a 510(k) premarket notification, for numerous reasons.

The Breakthrough Devices Program is a voluntary program intended to expedite the review, development, assessment and review of certain medical devices that provide for more effective treatment or diagnosis of life-threatening or irreversibly debilitating human diseases or conditions for which no approved or cleared treatment exists or that offer significant advantages over existing approved or cleared alternatives. All submissions for devices designated as breakthrough devices will receive priority review, meaning that the review of the submission is placed at the top of the appropriate review queue and receives additional review resources, as needed. Although breakthrough designation or access to any other expedited program may expedite the development or approval process, it does not change the standards for approval. Breakthrough designation may also be withdrawn by the FDA if it believes that the designation is no longer supported by data from our clinical development program. Additionally, breakthrough designation does not ensure that we will ultimately obtain FDA clearance or approval.

**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 June 2018, the European Commission, or EC, granted marketing approval of DZUVEO for the treatment of patients with moderate-to-severe acute pain in medically monitored settings. We intend to commercialize and promote DZUVEO in Europe with one or more strategic partners, and, in July 2021, we entered into a License and Commercialization Agreement with Laboratoire Aguettant, or Aguettant, for Aguettant to commercialize DZUVEO in the European Union, Norway, Iceland, Liechtenstein, Andorra, Vatican City, Monaco, Switzerland and the United Kingdom.

We are responsible for maintaining Zalviso device regulatory approval in the EU in order to support the manufacturing and supply of Zalviso for commercial sales. We completed the Conformité Européenne 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 Europe. 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. The CE Mark was originally issued by the British Standards Institution, or BSI, a Notified Body, or NB, located in the United Kingdom, or U.K., or BSI-U.K. The CE Mark file and certification has been transferred to the Netherlands NB of BSI, or BSI-NL, to mitigate the uncertainty with regards to Brexit. The ISO certification issued through BSI-U.K. was recently upgraded to the latest version of the standard, ISO 13485:2016 through BSI-U.K. and remains in effect. BSI ISO 13485:2016 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.

**Controlled Substances Regulations**

Sufentanil, a Schedule II controlled substance, is the API in DSUVIA and Zalviso. Controlled substances are governed by the DEA. Similarly, sufentanil is regulated as a controlled substance in Europe and other territories outside of the U.S. 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. Ephedrine is a scheduled listed chemical product under the Combat Methamphetamine Epidemic Act of 2005. Under this law, DEA applies strict controls and quotas on importation of ephedrine containing drug products.

The Drug Supply Chain Security Act of 2013, or DSCSA, imposes obligations on manufacturers of pharmaceutical products, among others, related to product tracking and tracing. Among the requirements are that manufacturers must 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 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, any person or entity from knowingly and willfully offering, paying, soliciting or receiving remuneration, directly or indirectly, overtly or covertly, in cash or in kind, to induce or in return for, purchasing, leasing, ordering or arranging for the purchasing, leasing or ordering of any item or service reimbursable under Medicare, Medicaid or other federal healthcare program. 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 exceptions and safe harbors are drawn narrowly, and practices involving remuneration that may be alleged to be intended to induce purchasing, leasing or ordering may be subject to scrutiny if they do not qualify for an exception or safe harbor. The failure to satisfy all of the requirements of an applicable exception or safe harbor do not make the conduct per se illegal under the Anti-Kickback Statute. Instead, the legality of the arrangement will be evaluated on a case-by-case basis based on a cumulative review of all of its facts and circumstances. Our practices may not in all cases meet all of the criteria for protection under an exception or safe harbor.

Additionally, the intent standard under the federal Anti-Kickback Statute was amended by the Patient Protection and Affordable Care Act of 2010, as amended by the Health Care and Education Reconciliation Act of 2010, collectively, the Affordable Care Act to a stricter standard such that a person or entity no longer needs to have actual knowledge of the federal Anti-Kickback Statute or specific intent to violate it in order to have committed a violation. Rather, if "one purpose" of the remuneration is to induce referrals, the federal Anti-Kickback Statute is violated. In addition, the Affordable Care Act codified case law that a claim that includes items or services resulting from a violation of the federal Anti-Kickback Statute also constitutes a false or fraudulent claim for purposes of the civil False Claims Act (discussed below).

The federal civil 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. 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, among others, a federal healthcare program that the person knows or should know is for a medical or other 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 their implementing regulations, imposes certain requirements relating to the privacy, security and transmission of individually identifiable health information primarily on covered entities, business associates and their covered subcontractors. Among other things, HITECH makes HIPAA's privacy and security standards directly applicable to business associates that are 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. International laws, such as the European Union General Data Protection Regulation, or GDPR, (EU 2016/679) and Swiss Federal Act on Data Protection, regulate the processing of personal data within the European Union and between countries in the European Union and countries outside of the European Union, including the United States. Failure to provide adequate privacy protections and maintain compliance with safe harbor mechanisms could jeopardize business transactions across borders and result in significant penalties.

Additionally, the federal Physician Payments Sunshine Act within the Affordable Care Act 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, (defined to include doctors, dentists, optometrists, podiatrists and chiropractors), other healthcare professionals (such as physician assistants and nurse practitioners), 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, certain states such as California require pharmaceutical companies to implement a comprehensive compliance program that includes a limit on expenditures for, or payments to, individual medical or health professionals. Moreover, several states have enacted legislation requiring pharmaceutical manufacturers to, among other things, file periodic reports with the state, make periodic public disclosures on sales and marketing activities, report information related to drug pricing, require the registration of sales representatives, and prohibit certain other sales and marketing practices.

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, imprisonment, exclusion of products from reimbursement under government programs, contractual damages, reputational harm, administrative burdens, diminished profits and future earnings, additional reporting requirements and/or oversight if we become subject to a corporate integrity agreement or similar agreement to resolve allegations of non-compliance with these laws 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 products. Such payers 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. Third-party payers and hospitals 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. For products administered under the supervision of a physician, obtaining coverage and adequate reimbursement may be particularly difficult because of the higher prices often associated with such products. Additionally, separate reimbursement for the product itself or the treatment or procedure in which the product is used may not be available, which may impact utilization. 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 and hospital 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 DSUVIA, or Zalviso, or any of our product candidates, if approved for commercial sale, will be considered medically necessary or 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 approved products 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. Third-party payers, government healthcare programs, wholesalers, group purchasing organizations, and hospitals frequently require that pharmaceutical companies negotiate agreements that provide discounts or rebates from list prices. We expect increasing pressure to offer larger discounts or discounts to a greater number of these organizations to maintain acceptable reimbursement levels for and access to our products. Net prices for drugs may be reduced by these mandatory discounts or rebates required by government healthcare programs, private payers, wholesalers, group purchasing organizations, hospitals, and by any future relaxation of laws that presently restrict imports of drugs from policy and payment limitations in setting their own reimbursement policies. In addition, if our competitors reduce the prices of their products, or otherwise demonstrate that they are better or more cost effective than our products, this may result in a greater level of reimbursement for their products relative to our products, which would reduce sales of our products and harm our results of operations.

There have been, and there will continue to be, legislative and regulatory proposals to change the healthcare system in ways that could impact our ability to commercialize our products profitably. We anticipate that the federal and state legislatures and the private sector will continue to consider and may adopt and implement healthcare policies, such as the Affordable Care Act, intended to curb rising healthcare costs. These cost containment measures may include: controls on government-funded reimbursement for drugs; new or increased requirements to pay prescription drug rebates to government health care programs; controls on healthcare providers; challenges to or limits on the pricing of drugs, including pricing controls, or limits or prohibitions on reimbursement for specific products through other means; requirements to try less expensive products or generics before a more expensive branded product; and public funding for cost effectiveness research, which may be used by government and private third-party payers to make coverage and payment decisions.

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 products 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 the United States, the Affordable Care Act 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 Affordable Care Act 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; and
- a Patient-Centered Outcomes Research Institute to oversee, identify priorities in, and conduct comparative clinical effectiveness research, along with funding for such research.

There have been judicial, executive branch and Congressional challenges to certain aspects of the Affordable Care Act. Congress has considered legislation that would repeal, or repeal and replace all or part of the Affordable Care Act. While Congress has not passed comprehensive repeal legislation, several bills affecting the implementation of certain taxes under the Affordable Care Act have been signed into law. The Tax Cuts and Jobs Act of 2017 includes a provision repealing, effective January 1, 2019, the tax-based shared responsibility payment imposed by the Affordable Care Act on certain individuals who fail to maintain qualifying health coverage for all or part of a year that is commonly referred to as the "individual mandate". Additionally, the 2020 federal spending package permanently eliminated, effective January 1, 2020, the Affordable Care Act's mandated "Cadillac" tax on high-cost employer-sponsored health coverage and medical device tax and, effective January 1, 2021, also eliminated the health insurer tax. . Further, the Bipartisan Budget Act of 2018, or the BBA, among other things, amends the Affordable Care Act, effective January 1, 2019, to increase from 50% to 70% the point-of-sale discount that is owed by pharmaceutical manufacturers who participate in Medicare Part D and to close the coverage gap in most Medicare drug plans, commonly referred to as the "donut hole". On June 17, 2021, the U.S. Supreme Court dismissed a challenge on procedural grounds that argued the Affordable Care Act is unconstitutional in its entirety because the "individual mandate" was repealed by Congress. Thus, the Affordable Care Act will remain in effect in its current form. Prior to the U.S. Supreme Court ruling, on January 28, 2021, President Biden issued an executive order that initiated a special enrollment period for purposes of obtaining health insurance coverage through the Affordable Care Act marketplace. The executive order also instructed certain governmental agencies to review and reconsider their existing policies and rules that limit access to healthcare, including among others, reexamining Medicaid demonstration projects and waiver programs that include work requirements, and policies that create unnecessary barriers to obtaining access to health insurance coverage through Medicaid or the Affordable Care Act. It is possible that the Affordable Care Act will be subject to judicial or Congressional challenges in the future. It is unclear how such challenges, and the healthcare reform measures of the Biden administration will impact the Affordable Care Act. We expect that the Affordable Care Act, as currently enacted or as it may be amended or repealed in the future, and other healthcare reform measures that may be adopted in the future, could have a material adverse effect on our industry generally and on our ability to successfully commercialize DSUVIA, and if approved in the United States, Zalviso.

In addition, other legislative changes have been proposed and adopted in the United States since the Affordable Care Act 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 2031 unless Congressional action is taken. However, COVID-19 relief legislation suspended the 2% Medicare sequester from May 1, 2020 through March 31, 2022. The American Taxpayer Relief Act further reduced Medicare payments to several providers, including hospitals. Under current legislation the actual reduction in Medicare payments will vary from 1% in 2022 to up to 3% in the final fiscal year of this sequester. Additionally, on March 11, 2021, President Biden signed the American Rescue Plan Act of 2021 into law, which eliminates the statutory Medicaid drug rebate cap, currently set at 100% of a drug's average manufacturer price, for single source and innovator multiple source drugs, beginning January 1, 2024.

Moreover, the DSCSA imposes additional 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. AcelRx is engaging Contract Manufacturing Organizations, or CMOs, and solution providers in serialization to implement the requirements of the DSCSA on our products. The acceptability of the approach that AcelRx is implementing will be ultimately subject to review by the FDA.

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 products, if any, may be.

We cannot predict the likelihood, nature or extent of government regulation that may arise from future legislation or administrative action, either in the United States or abroad. If we or our collaborators are slow or unable to adapt to changes in existing requirements or the adoption of new requirements or policies, or if we or our collaborators are not able to maintain regulatory compliance, our products may lose any regulatory approval that may have been obtained and we may not achieve or sustain profitability, which would adversely affect our business.

There has been increasing legislative and enforcement interest in the United States with respect to specialty drug pricing practices. Specifically, there have been several U.S. Congressional inquiries and proposed and enacted federal and state legislation designed to, among other things, bring more transparency to drug pricing and reform government program reimbursement methodologies for drugs. For example, at the federal level, the Trump administration used several means to propose or implement drug pricing reform, including through federal budget proposals, executive orders and policy. For example, on July 24, 2020 and September 13, 2020, the Trump administration announced several executive orders related to prescription drug pricing that attempt to implement several of the administration's proposals. On November 20, 2020, HHS finalized a regulation removing safe harbor protection for price reductions from pharmaceutical manufacturers to plan sponsors under Part D, either directly or through pharmacy benefit managers, unless the price reduction is required by law. The implementation of this rule has been delayed by the Biden administration from January 1, 2022 to January 1, 2023 in response to ongoing litigation. The rule also creates a new safe harbor for price reductions reflected at the point-of-sale, as well as a safe harbor for certain fixed fee arrangements between pharmacy benefit managers and manufacturers, the implementation of which has also been delayed until January 1, 2023. Further, on November 20, 2020, the Centers for Medicare & Medicaid Services, or CMS, issued an interim final rule implementing President Trump's Most Favored Nation executive order, which would tie Medicare Part B payments for certain physician-administered drugs to the lowest price paid in other economically advanced countries. As a result of litigation challenging the Most Favored Nation model, on December 27, 2021, CMS published a final rule that rescinded the Most Favored Nation interim final rule. In July 2021, the Biden administration released an executive order, "Promoting Competition in the American Economy," with multiple provisions aimed at prescription drugs. In response to Biden's executive order, on September 9, 2021, HHS released a Comprehensive Plan for Addressing High Drug Prices that outlines principles for drug pricing reform and sets out a variety of potential legislative policies that Congress could pursue to advance these principles. In addition, Congress is considering drug pricing as part of other health reform initiatives. At the state level, legislatures are increasingly passing legislation and implementing regulations designed to control pharmaceutical and biological product pricing, including price or patient reimbursement constraints, discounts, restrictions on certain product access and marketing cost disclosure and transparency measures, and, in some cases, measures designed to encourage importation from other countries and bulk purchasing.

Further, 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 other healthcare reform measures. Such policy actions could have a material adverse impact on our profitability.

**Employees and Human Capital Resources**

As of December 31, 2021, we employed 43 full-time employees, approximately half of whom work out of our corporate offices in Hayward, CA. The rest of our employees work remotely in various locations throughout the United States and are members of our commercial team. AcelRx is committed to pay equity, regardless of gender or race/ethnicity, and conducts pay equity analyses on an annual basis.

We invest in our workforce by offering competitive salaries, wages, and benefits. We endeavor to foster a strong sense of ownership by offering all employees stock options and restricted stock units under our broad-based stock incentive program. We also offer comprehensive and locally relevant benefits for all eligible employees. We recognize and support the growth and development of our employees.

We have implemented COVID-19 policies at our Hayward office designed to ensure the safety and well-being of all employees and the people associated with them. In addition, we have implemented COVID-19 policies for our sales force to ensure safe access to hospitals and other medically supervised settings, as appropriate. As a result of the COVID-19 pandemic, to reduce risk, our corporate employees have been asked to work remotely, and all employees have been asked to avoid all non-essential travel, adhere to good hygiene practices, and engage in physical distancing.

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. 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.

**Item 1A. Risk Factors**

*Our operations and financial results are subject to various risks and uncertainties. You should carefully consider the risks described below, together with all of the other information in this report, including our financial statements and notes thereto. If any of the following risks actually materialize, our business, financial condition, results of operations, liquidity, and future prospects could be materially harmed, the price of our common stock could decline, and you could lose part or all of your investment.*

*Summary Risk Factors*

*Our business is subject to numerous risks, as more fully described in this section below this summary. You should read these risks before you invest in our common stock. We may be unable, for many reasons, including those that are beyond our control, to implement our business strategy. In particular, our risks include:*

- Our business is being adversely impacted by the COVID-19 pandemic.
- We have incurred significant losses since our inception, anticipate that we will continue to incur significant losses in 2022 and may continue to incur losses in the future.
- We have not yet generated significant product revenue and may never be profitable.
- We will require additional capital and may be unable to raise capital, which would force us to delay, reduce or eliminate our commercialization efforts and product development programs and could cause us to cease operations.
- Positive clinical results obtained to date for Zalviso may be disputed in FDA review, do not guarantee regulatory approval and may not be obtained from future clinical trials.
- Existing and future legislation may increase the difficulty and cost for us to commercialize our products and affect the prices we may obtain.
- Guidelines and recommendations published by government agencies, as well as non-governmental organizations, and existing laws and regulations can reduce the use of DSUVIA, and Zalviso, if approved in the United States.
- Zalviso may cause adverse effects or have other properties that could delay or prevent regulatory approval or limit the scope of any approved label or market acceptance. DSUVIA may cause adverse effects or have other properties that could limit market acceptance.
- Although we have obtained regulatory approval for DSUVIA, and even if we obtain regulatory approval for 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.
- The commercial success of DSUVIA and, if approved, Zalviso and our other product candidates in the United States, as well as DZUVEO and Zalviso in Europe, will depend upon the acceptance of these products by the medical community, including physicians, nurses, patients, and pharmacy and therapeutics committees.
- If we are unable to maintain or grow our sales and marketing capabilities or enter into agreements with third parties to market and sell our products and, if approved, our product candidates, we may be unable to generate sufficient product revenue.
- The success of our merger agreement with Lowell Therapeutics, Inc, or Lowell, depends on our ability to realize the expected benefits and potential value creation related to the acquisition;
- A key part of our business strategy is to establish collaborative relationships to commercialize and fund development and approval of our products, 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.
- 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.
- The market price of our common stock may be highly volatile.
- Nasdaq may delist our securities from trading on its exchange, which could limit investors' ability to make transactions in our securities and subject us to additional trading restrictions.
- Litigation may substantially increase our costs and harm our business.
- Our involvement in securities-related class action litigation could divert our resources and management's attention and harm our business.

**Risks Related to COVID-19 Pandemic**

***Our business is being adversely impacted by the COVID-19 pandemic.***

Our business has been adversely affected by the COVID-19 outbreak. Federal, state, local and foreign government orders on account of the COVID-19 pandemic are preventing us from conducting certain activities. Following local and state government orders in California, where our corporate office is located and many of our employees live, we implemented work from home policies, which are limiting certain of our operations. If the COVID-19 outbreak continues, we may need to limit operations further and implement additional limitations, such as extending our work from home policies.

In response to the COVID-19 pandemic, some hospitals, ambulatory surgery centers and other healthcare facilities have barred visitors that are not caregivers or mission-critical and we have no visibility as to when these restrictions on access will be lifted for all of our customers. As a result, our commercial and medical affairs teams' educational and promotional efforts have been reduced, and in some cases, stopped. Furthermore, some governments, hospitals and doctors, as a measure to combat the further spread of COVID-19, reduced the number of procedures in which DSUVIA is administered as part of the pain treatment program, and temporarily halted performing elective surgeries, which adversely impacted the level of our sales relating to such procedures. We expect our near-term sales volumes to be adversely impacted for as long as access to healthcare facilities by our commercial and medical affairs personnel and the number of procedures in which DSUVIA is administered continues to be limited. The ultimate impact of the COVID-19 outbreak remains highly uncertain and subject to change. We do not yet know the full extent of potential delays or impacts on our business, healthcare systems or the global economy as a whole. However, these effects could have a material impact on our operations, and we will continue to monitor the COVID-19 situation closely.

**Risks Related to Commercialization**

***Our success is highly dependent on our ability to successfully commercialize DSUVIA.***

We invested a significant portion of our efforts and financial resources to develop and gain regulatory approval for DSUVIA and expect to continue making significant investments to commercialize DSUVIA. We believe our success is highly dependent on, and a significant portion of the value of our company relates to, our ability to successfully commercialize DSUVIA in the United States. The commercial success of DSUVIA depends heavily on numerous factors, including:

- our ability to market, sell, and distribute DSUVIA;
- our ability to establish and maintain commercial manufacturing with third parties;
- acceptance by the medical community, including physicians, nurses, patients and pharmacy and therapeutics committees;
- acceptance of pricing and placement on payers' formularies;
- our ability to effectively compete with other medications for the treatment of moderate-to-severe acute pain in medically supervised settings, including IV-opioids and any subsequently approved products;
- effective management of, and compliance with, the DSUVIA Risk Evaluation and Mitigation Strategy, or REMS, program;
- continued demonstration of an acceptable safety profile of DSUVIA; and
- our ability to obtain, maintain, enforce, and defend our intellectual property rights and claims.

If we are unable to successfully commercialize DSUVIA, our business, financial condition, and results of operations will be materially harmed.

***The commercial success of DSUVIA and, if approved, Zalviso and our other product candidates in the United States, as well as DZUVEO and Zalviso in Europe, 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 DSUVIA and, if approved, Zalviso and our other product candidates in the United States, as well as DZUVEO and Zalviso in Europe, by the medical community 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 payers;
- the use of our approved products by a healthcare professional for patient types that were not specifically studied in clinical trials;

- the prevalence and severity of any adverse events, or AEs, or serious adverse events, or SAEs;
- overcoming any perceptions of sufentanil as a potentially unsafe drug due to its high potency opioid status;
- limitations or warnings contained in the U.S. Food and Drug Administration, or FDA, -approved label for DSUVIA and, if approved, our other product candidates, or the European Medicines Agency, or EMA,-approved label for DZUVEO or Zalviso;
- restrictions or limitations placed on DSUVIA due to the REMS program or, if approved, on our product candidates;
- availability of alternative treatments;
- existing capital investment by hospitals in IV PCA technology;
- pricing and cost-effectiveness;
- the effectiveness of our current or any future collaborators' sales and marketing strategies;
- our ability to obtain formulary approvals; and
- our ability to obtain and maintain sufficient third-party coverage and reimbursement.

If our approved products do not achieve an adequate level of acceptance by the medical community, including physicians, nurses, patients and pharmacy and therapeutics committees, we may not generate sufficient revenue and become or remain profitable.

***If we are unable to maintain or grow our sales and marketing capabilities or enter into agreements with third parties to market and sell our products and, if approved, our product candidates, we may be unable to generate sufficient product revenue.***

In order to commercialize DSUVIA and, if approved, our product candidates in the United States, we must maintain or grow internal sales, marketing, distribution, managerial and other capabilities or make arrangements with third parties to perform these services. We have entered into agreements with third parties for the distribution of DSUVIA and may enter into such agreements for our product candidates, if approved, in the United States, including the product candidates we in-licensed from Laboratoire Aguettant, or Aguettant, in July 2021 pursuant to a License and Commercialization Agreement, or the PFS Agreement, and the product candidates we acquired through our acquisition of Lowell; however, if these third parties do not perform as expected or there are delays in establishing such relationships, our ability to effectively distribute products would suffer.

We have entered into strategic partnerships with third parties to commercialize our products outside of the United States. For example, in 2013 we entered into a collaboration with Grünenthal GmbH, or Grünenthal, for the commercialization of Zalviso in Europe and Australia, and in July 2021, we entered a License and Commercialization Agreement, or the DZUVEO Agreement, with Aguettant for the commercialization of DZUVEO in the European Union, Norway, Iceland, Liechtenstein, Andorra, Vatican City, Monaco, Switzerland and the United Kingdom, or the DZUVEO Territory. Grünenthal ceased commercializing Zalviso on May 12, 2021 and the rights to market and sell Zalviso reverted back to us. We intend to enter into additional strategic partnerships with third parties to commercialize our products outside of the United States, including a replacement license agreement for Zalviso in Europe. Per the terms of the royalty monetization arrangement with SWK Funding, LLC, or SWK (assignee of PDL BioPharma, Inc., or PDL), or the Royalty Monetization, we are obligated to use commercially reasonable efforts to negotiate a replacement license agreement, or New Arrangement. Accordingly, even if we are able to enter into a New Arrangement, and that licensee is successful in commercializing Zalviso in Europe, we will receive only a portion of any royalties until the capped amount owing to SWK is reached.

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 new 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 our products and 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 products to healthcare professionals and in geographical regions that will not be covered by our own marketing and sales force, or if our potential future collaboration partners do not successfully commercialize our products, our ability to generate revenues from product sales will be adversely affected.

If we are unable to maintain or grow adequate sales, marketing and distribution capabilities, whether independently or with third parties, we may not be able to generate sufficient product revenue and become profitable. We compete 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 products, 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 products. The process of establishing and maintaining collaborative relationships is difficult, time-consuming and involves significant uncertainty. For example:

- 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 or may be 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, including in connection with any contractual force majeure notices tied to the COVID-19 pandemic;
- 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 drugs, maintain regulatory approvals and our ability to successfully manufacture and achieve market acceptance of our products;
- 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 products; 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. For example, we have a continuing obligation, through the term of the Royalty Monetization with SWK, to use commercially reasonable efforts to negotiate a New Arrangement following Grünenthal's termination of our collaboration agreement for the commercialization of Zalviso in Europe. More generally, if we are unable to establish and maintain collaborative relationships on acceptable terms we may have to undertake development and commercialization activities at our own expense.

***We may experience difficulties in retaining our existing employees and managing our operations, including our continued commercialization of DSUVIA.***

We need to retain and maintain our existing sales, managerial, operational, finance and other personnel and resources in order to continue the commercialization of DSUVIA and manage our operations. Our current infrastructure may be inadequate to support our strategy and any future workforce reduction, such as the reduction that eliminated approximately 33% of our workforce in March 2020 in connection with a strategic transaction, may be disruptive to our operations, may negatively affect our productivity, and may constrain our commercialization activities. For example, a workforce reduction could yield unanticipated consequences, such as attrition beyond planned staff reductions, negatively impacting employee morale and our corporate culture, or increased difficulties in our day-to-day operations, and prevent us from successfully commercializing DSUVIA as rapidly as planned. If we encounter such unanticipated consequences, we may have difficulty retaining and attracting personnel. In addition, the implementation of any additional workforce or expense reduction programs may divert the efforts of our management team and other key employees, which could adversely affect our business. Furthermore, we may not realize, in full or in part, the anticipated benefits, savings and improvements in our cost structure from our cost reduction plan, due to unforeseen difficulties, delays or unexpected costs. If we are unable to realize the expected operational efficiencies and cost savings from the cost reduction plan, our operating results and financial condition would be adversely affected.

***Guidelines and recommendations published by government agencies, as well as non-governmental organizations, and existing laws and regulations can reduce the use of DSUVIA, and Zalviso, if approved in the United States.***

Government agencies and non-governmental organizations promulgate regulations and guidelines applicable to certain drug classes that may include DSUVIA and Zalviso, if approved in the United States. Recommendations of government agencies or non-governmental organizations may relate to such matters as maximum quantities dispensed to patients, dosage, route of administration, and use of concomitant therapies. Government agencies and non-governmental organizations have offered commentary and guidelines on the use of opioid-containing products. We are uncertain how these activities and guidelines may impact DSUVIA and our ability to gain marketing approval of Zalviso in the United States. Regulations or guidelines suggesting the reduced use of certain drug classes that may include DSUVIA or Zalviso, 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 DSUVIA or Zalviso, if approved, or negatively impact our ability to gain market acceptance and market share. The U.S. government and state legislatures have prioritized combatting the growing misuse and addiction to opioids and opioid overdose deaths and have enacted legislation and regulations as well as other measures intended to fight the opioid epidemic. Addressing opioid drug abuse is a priority for the current U.S. administration and the FDA and is part of a broader initiative led by the U.S. Department of Health and Human Services, or HHS. Overall, there is greater scrutiny of entities involved in the manufacture, sale and distribution of opioids. These initiatives, existing laws and regulations, and any negative publicity related to opioids may have a material impact on our business and our ability to manufacture opioid products.

***Governmental investigations, inquiries, and regulatory actions and lawsuits brought against us by government agencies and private parties with respect to our commercialization of opioids could adversely affect our business, financial condition, results of operations and cash flows.***

As a result of greater public awareness of the public health issue of opioid abuse, there has been increased scrutiny of, and investigation into, the commercial practices of opioid manufacturers by state and federal agencies. As a result of our manufacturing and commercial sale of DSUVIA in the United States and Zalviso in Europe, we could become the subject of federal, state and foreign government investigations and enforcement actions, focused on the misuse and abuse of opioid medications.

In addition, a significant number of lawsuits have been filed against opioid manufacturers, distributors, and others in the supply chain by cities, counties, state Attorney's General and private persons seeking to hold them accountable for opioid misuse and abuse. The lawsuits assert a variety of claims, including, but not limited to, public nuisance, negligence, civil conspiracy, fraud, violations of the Racketeer Influenced and Corrupt Organizations Act, or RICO, or similar state laws, violations of state Controlled Substance Acts or state False Claims Acts, product liability, consumer fraud, unfair or deceptive trade practices, false advertising, insurance fraud, unjust enrichment and other common law and statutory claims arising from defendants' manufacturing, distribution, marketing and promotion of opioids and seek restitution, damages, injunctive and other relief and attorneys' fees and costs. The claims generally are based on alleged misrepresentations and/or omissions in connection with the sale and marketing of prescription opioid medications and/or an alleged failure to take adequate steps to prevent abuse and diversion. While DSUVIA is designed for use solely in certified medically supervised healthcare settings and administered only by a healthcare professional in these settings, and is not distributed or available at retail pharmacies to patients by prescription, we can provide no assurance that parties will not file lawsuits of this type against us in the future. In addition, current public perceptions of the public health issue of opioid abuse may present challenges to favorable resolution of any potential claims. Accordingly, we cannot predict whether we may become subject to these kinds of investigations and lawsuits in the future, and if we were to be named as a defendant in such actions, we cannot predict the ultimate outcome. Any allegations against us may negatively affect our business in various ways, including through harm to our reputation.

If we were required to defend ourselves in these matters, we would likely incur significant legal costs and could in the future be required to pay significant amounts as a result of fines, penalties, settlements or judgments. It is unlikely that our current product liability insurance would fully cover these potential liabilities, if at all. Moreover, we may be unable to maintain insurance in the future on acceptable terms or with adequate coverage against potential liabilities or other losses. For more information about our product liability insurance and exclusions therefrom, please see the risk factor entitled "We face potential product liability claims, and, if such claims are successful, we may incur substantial liability" elsewhere in this section. The resolution of one or more of these matters could have a material adverse effect on our business, financial condition, results of operations and cash flows.

Furthermore, in the current climate, stories regarding prescription drug abuse and the diversion of opioids and other controlled substances are frequently in the media or advocated by public interest groups. Unfavorable publicity regarding the use or misuse of opioid drugs, the limitations of abuse-deterrent formulations, the ability of drug abusers to discover previously unknown ways to abuse opioid products, public inquiries and investigations into prescription drug abuse, litigation, or regulatory activity regarding sales, marketing, distribution or storage of opioids could have a material adverse effect on our reputation and impact on the results of litigation.

Finally, various government entities, including Congress, state legislatures or other policy-making bodies, or public interest groups have in the past and may in the future hold hearings, conduct investigations and/or issue reports calling attention to the opioid crisis, and may mention or criticize the perceived role of manufacturers, including us, in the opioid crisis. Similarly, press organizations have and likely will continue to report on these issues, and such reporting may result in adverse publicity for us, resulting in reputational harm.

***Approval of Zalviso and DZUVEO in Europe has resulted in a variety of risks associated with international operations that could materially adversely affect our business.***

Our collaborations with international partners, including Grünenthal and Aguettant, have required, and will require, us to supply product to support the commercialization of our products in Europe and it is likely that any New Arrangement would also include such a requirement. Entering into international business relationships subjects us to additional risks including:

- multiple, conflicting, and changing laws and regulations such as privacy and data regulations, transparency regulations, tax laws, export and import restrictions, employment laws, regulatory requirements, including for drug approvals, and other governmental approvals, permits, and licenses;
- EMA “sunset clause” requirements, which apply to DZUVEO, providing that the marketing authorization of a medicine will cease to be valid if it is not placed on the market within three years of the authorization being granted or if it is removed from the market for three consecutive years; however, the European Commission has extended this date to December 31, 2022 for DZUVEO;
- reduced protection for intellectual property rights;
- unexpected changes in tariffs, trade barriers and regulatory requirements;
- different payer reimbursement regimes, governmental payers, patient self-pay systems and price controls;
- economic weakness, including inflation, or political instability in particular foreign economies and markets;
- production shortages resulting from any events affecting raw material supply or manufacturing capabilities abroad; and
- business interruptions resulting from pandemics, geopolitical actions, including war and terrorism, or natural disasters including earthquakes, typhoons, floods and fires.

Any of these factors could have a material adverse effect on our business.

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

The U.S. biotechnology and pharmaceutical industries are characterized by intense competition and cost pressure. DSUVIA competes, and our product candidates, if approved in the U.S., will compete, with a number of existing and future pharmaceuticals and drug delivery devices developed, manufactured and marketed by others. In particular, DSUVIA may compete with a wide variety of products and product candidates including (i) injectable opioid products, such as morphine, fentanyl, hydromorphone and meperidine; (ii) oral opioids such as oxycodone and hydrocodone; (iii) generic injectable local anesthetics, such as bupivacaine or branded formulations thereof; (iv) non-steroidal anti-inflammatory drugs, or NSAIDS, including ketorolac in intranasal or generic IV form, and IV meloxicam; and (v) transmucosal fentanyl products. Zalviso, if approved in the U.S., may compete with a number of opioid-based treatment options, including IV PCA pumps, oral PCA devices, and transdermal opioid PCAs. The PFS product candidates, if approved in the U.S., may compete with other ready-to-use formulations of ephedrine and phenylephrine. The nafamostat product candidates, if approved in the U.S., may compete with heparin and citrate.

Key competitive factors affecting the commercial success of our approved products are likely to be efficacy, safety profile, reliability, convenience of dosing, price and reimbursement. Many of our competitors and 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 we may seek to commercialize. This may render our products obsolete or non-competitive. We anticipate that we will face intense and increasing competition as new drugs enter the market, additional technologies become available, and competitors establish collaborative or licensing relationships, which may adversely affect our competitive position. These and other competitive risks may materially adversely affect our ability to attain or sustain profitable operations.

***Hospital or other health care facility formulary approvals for DSUVIA or our product candidates, if approved, in the United States may not be achieved, or could be subject to certain restrictions, which could make it difficult for us to sell our products.***

Obtaining hospital or other health care facility formulary approvals can be an expensive and time-consuming process. We cannot be certain if and when we will obtain formulary approvals to allow us to sell our products into our target markets. In particular, the COVID-19-related restrictions on our commercial and medical affairs teams' access to hospitals and other health care facilities has adversely impacted the number of formulary approvals we achieved to date, and for as long as these restrictions remain in place, or new restrictions are implemented, we may have limited visibility or difficulties in obtaining these formulary approvals. Failure to obtain timely formulary approvals will limit our commercial success. In order to obtain formulary approvals, we often are required to complete evaluation programs whereby DSUVIA, or our product candidates, if approved, are used on a limited basis for certain patient types. The evaluation period may last several months and there can be no assurance that use during the evaluation period will lead to formulary approvals of DSUVIA, or our product candidates, if approved. Further, even successful formulary approvals are subject to certain restrictions based on patient type or hospital protocol. Failure to obtain timely formulary approvals for DSUVIA, or our product candidates, if approved, would materially adversely affect our ability to attain or sustain profitable operations.

***Coverage and adequate reimbursement may not be available for DSUVIA or our product candidates, if approved, in the United States, including Zalviso, or DZUVEO or Zalviso in Europe, which could make it difficult for us, or our partners, to sell our products profitably.***

Our ability to commercialize DSUVIA or our product candidates, if approved, in the United States, including Zalviso, and any collaboration partner's ability to commercialize DZUVEO or Zalviso in Europe successfully will depend, in part, on the extent to which coverage and adequate reimbursement will be available from government payer programs at the federal and state levels, authorities, including Medicare and Medicaid, private health insurers, managed care plans and other third-party payers.

No uniform policy requirement for coverage and reimbursement for drug products exists among third-party payers in the United States or Europe. Therefore, coverage and reimbursement can differ significantly from payer to payer. 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 payer separately, with no assurance that coverage and adequate reimbursement will be applied consistently or obtained in the first instance. For products administered under the supervision of a physician, obtaining coverage and adequate reimbursement may be particularly difficult because of the higher prices often associated with such products. Additionally, separate reimbursement for the product itself or the treatment or procedure in which the product is used may not be available, which may impact utilization. Our inability to promptly obtain and sufficiently maintain coverage and adequate reimbursement rates from third party payers could significantly harm our operating results, our ability to raise capital needed to commercialize our 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 payers 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 DSUVIA or Zalviso, if approved, in the United States, and DSUVIA/DZUVEO and Zalviso in Europe 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 our sales of DSUVIA and Zalviso, if approved, in the United States, and future product sales of Zalviso and DZUVEO in Europe, 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 products will depend on reimbursement policies and may be affected by future healthcare reform measures. Government authorities and third-party payers, 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 DSUVIA or our product candidates, if approved, in the United States, or DZUVEO or Zalviso in Europe. Also, reimbursement amounts may reduce the demand for, or the price of, our products. For example, studies of DZUVEO in Europe may be needed to ensure premium reimbursement in certain countries. If reimbursement is not available, or is available only to limited levels, we may not be able to successfully commercialize DSUVIA or our product candidates, if approved, in the United States, or DZUVEO or Zalviso in Europe.

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, separate pricing and reimbursement approvals may impact any future collaboration partners' ability to market and successfully commercialize our products in the 27 member states of the European Union. Adverse pricing limitations may hinder our ability to recoup our investment in DSUVIA in the United States, or our other product candidates, even after obtaining FDA marketing approval.

***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 products, including DSUVIA or our product candidates, 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. While we have received marketing approval for DSUVIA for our proposed indication, 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 and a requirement for corrective advertising, including Dear Doctor letters. 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 enforcement 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 DSUVIA or our product candidates, if approved, in the United States, we could become subject to significant liability, which would materially adversely affect our business and financial condition.

***If we are unable to establish and maintain 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 for DSUVIA and our product candidates, if approved. 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 DSUVIA and our product candidates, if approved, and related revenues could be negatively impacted.

***We intend to rely on a limited number of distributors and pharmaceutical wholesalers to distribute DSUVIA and our product candidates, if approved, in the United States.***

We intend to rely primarily upon distributors and pharmaceutical wholesalers in connection with the distribution of DSUVIA and our product candidates, if approved, in the United States. As part of the DSUVIA REMS program, we monitor distribution and audit wholesalers' data and will monitor such data from other distributors. If our distributors and wholesalers do not comply with the DSUVIA REMS requirements, or if we are unable to establish or maintain our business relationships with these distributors and pharmaceutical wholesalers on commercially acceptable terms, or if our distributors and wholesalers are unable to distribute our drugs for regulatory, compliance or any other reason, it could have a material adverse effect on our sales and may prevent us from achieving profitability.

**Risks Related to Clinical Development and Regulatory Approval**

***Our expectations for FDA approvability of our product candidates may be inaccurate, and we may be required to conduct additional manufacturing, nonclinical or clinical development work in order to obtain FDA approval for these products, which would add to our expenses and delay any associated revenue.***

On July 14, 2021, we entered into the PFS Agreement with Aguettant pursuant to which we obtained the exclusive right to develop and, subject to FDA approval, commercialize in the United States (i) an ephedrine pre-filled syringe containing 10 ml of a solution of 3 mg/ml ephedrine hydrochloride for injection, and (ii) a phenylephrine pre-filled syringe containing 10 ml of a solution of 50 mcg/ml phenylephrine hydrochloride for injection. Aguettant will supply us with the products for use in commercialization, if they are approved in the U.S. Our current expectation is that the PFS products will be approvable by the FDA without additional manufacturing, nonclinical or clinical development, but we have not met with the FDA yet to obtain their feedback on the available data to support the PFS products. If, after meeting with the FDA, we determine that additional development work will be needed for U.S. approval, we would incur additional expense and be delayed in obtaining any revenue from the PFS products.

Nafamostat is being developed for both medical device and drug indications for use. Although nafamostat is approved for certain uses in Japan, our ability to leverage that for an expedited development and approval pathway with the FDA may be limited, and we may be required to conduct additional unanticipated nonclinical studies and clinical trials in order to seek approval in the U.S. Niyad is being studied under an investigational device exemption, or IDE, and has received Breakthrough Device Designation from the FDA for regional anticoagulant for injection into the extracorporeal circuit. Niyad is expected to be used during renal replacement therapy for acute kidney injury patients in the hospital and for end-stage renal disease patients receiving dialysis in outpatient clinics. We expect that Niyad will require filing of a PMA; the Breakthrough Designation allows for more frequent and informal FDA communication regarding development plans, and allows for priority review once the marketing application is submitted.

The active drug component of Niyad, nafamostat, is also being developed for drug indications for which we expect to submit Investigational New Drug applications.

***Existing and future legislation may increase the difficulty and cost for us to commercialize our products and affect the prices we may obtain.***

In the United States and some foreign jurisdictions, the legislative landscape continues to evolve, including changes to the regulation of opioid-containing products. 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 of Europe. These changes will restrict or regulate post-approval activities for DSUVIA, DZUVEO and Zalviso, and affect our ability to profitably sell any products for which we obtain marketing approval. For example, in February 2016, the FDA announced a comprehensive action plan to take concrete steps towards reducing the impact of opioid abuse on American families and communities. As part of this plan, the FDA announced that it intended to review product and labeling decisions and re-examine the risk-benefit paradigm for opioids. In June 2019, the FDA issued draft guidance related to a new benefit/risk framework for new opioid analgesic products, which proposes that the new product candidate show some benefit over an existing product. In September 2019, the FDA held a public hearing to receive stakeholder input on the approval process for new opioids. In January 2020, FDA's Anesthetic and Analgesic Drug Products Advisory Committee recommended against the approval of a new opioid analgesic, oxycodegol, the NDA for which was subsequently withdrawn by its sponsor. The timing of the resubmission of the Zalviso NDA is in part dependent upon the finalization of the FDA's new opioid approval guidelines and process.

In the European Union, or EU, the pricing of prescription drugs is subject to government control. The EU also 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 addition, the EMA has a "sunset clause" which provides that the marketing authorization of a medicine will cease to be valid if it is not placed on the market within three years of the authorization being granted or if it is removed from the market for three consecutive years; however, the European Commission has extended this date to December 31, 2022 for DZUVEO.

In the United States, the Patient Protection and Affordable Care Act, as amended by the Health Care and Education Reconciliation Act of 2010, or collectively, the Affordable Care Act, 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 Affordable Care Act 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; and
- a Patient-Centered Outcomes Research Institute to oversee, identify priorities in, and conduct comparative clinical effectiveness research, along with funding for such research.

The Affordable Care Act continues to substantially change health care financing and delivery by both governmental and private insurers, which may increase our regulatory burdens and operating costs.

There have been executive, judicial and Congressional challenges to certain aspects of the Affordable Care Act. While Congress has not passed comprehensive repeal legislation, several bills affecting the implementation of certain taxes under the Affordable Care Act have been signed into law. The Tax Cuts and Jobs Act of 2017 includes a provision that repealed, effective January 1, 2019, the tax-based shared responsibility payment imposed by the Affordable Care Act on certain individuals who fail to maintain qualifying health coverage for all or part of a year that is commonly referred to as the "individual mandate". On June 17, 2021, the U.S. Supreme Court dismissed a challenge on procedural grounds that argued the Affordable Care Act is unconstitutional in its entirety because the "individual mandate" was repealed by Congress. Thus, the Affordable Care Act will remain in effect in its current form. Moreover, prior to the U.S. Supreme Court ruling, on January 28, 2021, President Biden issued an executive order that initiated a special enrollment period for purposes of obtaining health insurance coverage through the Affordable Care Act marketplace, which began on February 15, 2021 and remained open through August 15, 2021. The executive order instructed certain governmental agencies to review and reconsider their existing policies and rules that limit access to healthcare, including among others, reexamining Medicaid demonstration projects and waiver programs that include work requirements, and policies that create unnecessary barriers to obtaining access to health insurance coverage through Medicaid or the Affordable Care Act. It is possible that the Affordable Care Act will be subject to judicial or Congressional challenges in the future. It is also unclear how any such challenges and the healthcare reform measures of the Biden administration will impact the Affordable Care Act. We expect that the Affordable Care Act and other healthcare reform measures that may be adopted in the future, could have a material adverse effect on our industry generally and on our ability to successfully commercialize our products. We cannot predict the likelihood, nature or extent of government regulation that may arise from future legislation or administrative action, either in the United States or abroad. If we or our collaborators are slow or unable to adapt to changes in existing requirements or the adoption of new requirements or policies, or if we or our collaborators are not able to maintain regulatory compliance, our products may lose regulatory approval and we may not achieve or sustain profitability, which would adversely affect our business.

In addition, other legislative changes have been proposed and adopted in the United States since the Affordable Care Act was enacted. Aggregate reductions of Medicare payments to providers of 2% per fiscal year went into effect on April 1, 2013 and due to subsequent legislative amendments to the statute will stay in effect through 2031, with the exception of a temporary suspension from May 1, 2020 through March 31, 2022 due to the COVID-19 pandemic, unless Congressional action is taken. Under current legislation the actual reduction in Medicare payments will vary from 1% in 2022 to up to 3% in the final fiscal year of this sequester. The American Taxpayer Relief Act further reduced Medicare payments to several providers, including hospitals. Additionally, on March 11, 2021, President Biden signed the American Rescue Plan Act of 2021 into law, which eliminates the statutory Medicaid drug rebate cap, currently set at 100% of a drug's average manufacturer price, for single source and innovator multiple source drugs, beginning January 1, 2024. Congress is also considering additional health reform measures.

Moreover, the Drug Supply Chain Security Act of 2013 imposes additional obligations on manufacturers of pharmaceutical products, among others, related to product tracking and tracing. Among the requirements of this legislation, manufacturers are 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.

In the United States, there has been increasing legislative and enforcement interest with respect to specialty drug pricing practices. Specifically, there have been several recent U.S. Congressional inquiries and proposed and enacted federal and state legislation designed to, among other things, bring more transparency to drug pricing and reform government program reimbursement methodologies for drugs. At the federal level, the Trump administration used several means to propose or implement drug pricing reform, including through federal budget proposals, executive orders and policy initiatives. For example, on July 24, 2020 and September 13, 2020, President Trump announced several executive orders related to prescription drug pricing that attempt to implement several of the administration's proposals. The FDA concurrently released a final rule and guidance in September 2020, implementing a portion of the importation executive order providing pathways for states to build and submit importation plans for drugs from Canada. Further, on November 20, 2020, HHS finalized a regulation removing safe harbor protection for price reductions from pharmaceutical manufacturers to plan sponsors under Part D, either directly or through pharmacy benefit managers, unless the price reduction is required by law. The implementation of the rule has been delayed by the Biden administration from January 1, 2022 to January 1, 2023 in response to ongoing litigation. The rule also creates a new safe harbor for price reductions reflected at the point-of-sale, as well as a safe harbor for certain fixed fee arrangements between pharmacy benefit managers and manufacturers, the implementation of which has also been delayed until January 1, 2023. Further, on November 20, 2020, the Centers for Medicare & Medicaid Services, or CMS, issued an interim final rule implementing President Trump's Most Favored Nation, or MFN, executive order, which would tie Medicare Part B payments for certain physician-administered drugs to the lowest price paid in other economically advanced countries, effective January 1, 2021. As a result of litigation challenging the MFN model, on December 27, 2021, CMS published a final rule that rescinds the MFN Model interim final rule. In July 2021, the Biden administration released an executive order, "Promoting Competition in the American Economy," with multiple provisions aimed at prescription drugs. In response to Biden's executive order, on September 9, 2021, HHS released a Comprehensive Plan for Addressing High Drug Prices that outlines principles for drug pricing reform and sets out a variety of potential legislative policies that Congress could pursue to advance these principles. At the state level, legislatures are increasingly passing legislation and implementing regulations designed to control pharmaceutical and biological product pricing, including price or patient reimbursement constraints, discounts, restrictions on certain product access and marketing cost disclosure and transparency measures, and, in some cases, measures designed to encourage importation from other countries and bulk purchasing. 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 payers or authorities in other countries. In Europe, 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, revenue from sales of Zalviso and DZUVEO in Europe would be negatively affected.

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 products, 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. For instance, it is possible that additional governmental action is taken in response to the COVID-19 pandemic. The continuing efforts of the government, insurance companies, managed care organizations and other payers of healthcare services to contain or reduce costs of healthcare may adversely affect the demand for any drug products for which we have obtained or 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.

***We may experience market resistance, delays or rejections based upon additional government regulation from future legislation or administrative action, or changes in regulatory agency policy regarding opioids generally, and sufentanil specifically.***

In February 2016, the FDA announced a comprehensive action plan to take concrete steps towards reducing the impact of opioid abuse on American families and communities. As part of this plan, the FDA announced that it intended to review product and labeling decisions and re-examine the risk-benefit paradigm for opioids. In June 2019, the FDA issued draft guidance related to a new benefit/risk framework for new opioid analgesic products, which proposes that the new product candidate show some benefit over an existing product. In September 2019, the FDA held a public hearing to receive stakeholder input on the approval process for new opioids. The timing of the resubmission of the Zalviso NDA is in part dependent upon the finalization of the FDA's new opioid approval guidelines and process.

In May 2017, an Opioid Policy Steering Committee was established to address and advise regulators on opioid use. The Committee was charged with three initial questions: (i) should the FDA require mandatory education for healthcare professionals, or HCPs, who prescribe opioids; (ii) should the FDA take steps to ensure the number of prescribed opioid doses is more closely tailored to the medical indication; and (iii) is the FDA properly considering the risk of abuse and misuse of opioids during its drug review process. Zalviso has not been designed with an abuse-deterrent formulation and is not tamper-resistant. As a result, Zalviso has not undergone testing for tamper-resistance or abuse deterrence.

The FDA 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 candidate, Zalviso, as a result of such inspections. 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 FDA inspections could impact our ability to maintain FDA approval of DSUVIA, and our ability to expand and sustain commercial sales of DSUVIA in the United States.

Any delay in, or failure to receive or maintain, approval for Zalviso in the United States could prevent us from generating meaningful revenues or achieving profitability. Zalviso may not be approved even if we believe it has achieved its endpoints in clinical trials. Regulatory agencies, including the FDA, 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. Zalviso is being regulated as a drug product under the NDA process administered by the FDA. The FDA could in the future require additional regulation of Zalviso, or DSUVIA, under the medical device provisions of the Federal Food, Drug and Cosmetic Act, or 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. For example, DSUVIA is subject to a deferred post-marketing requirement for study in the pediatric population ages 6-17 years. As required in the DSUVIA FDA approval letter, a final protocol for this trial was submitted to the FDA in August 2020, in conjunction with a previously FDA approved request to defer initiation of pediatric studies until additional post-market safety data is obtained in adult patients using DSUVIA. 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 seek 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 the size of the commercial opportunity.

***The success of Zalviso relies, in part, on obtaining regulatory approval in the United States.***

The success of Zalviso relies, in part, upon our ability to develop and receive regulatory approval of this product candidate in the United States for the management of moderate-to-severe acute pain in adult patients in the hospital setting. Our Phase 3 program for Zalviso initially 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. In July 2014, the FDA issued a Complete Response Letter, or CRL, for our NDA for Zalviso, or the Zalviso CRL. The Zalviso CRL contained 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 device 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 Zalviso CRL, a clinical trial was needed to assess the risk of inadvertent dispensing and overall risk of dispensing failures. Based on the results of our Type C meeting with the FDA in September 2015, we completed the protocol review with the FDA and initiated this study, IAP312, in September 2016.

IAP312 was a Phase 3 study in post-operative patients designed to evaluate the effectiveness of changes made to the functionality and usability of the Zalviso device and to take into account comments from the FDA on the study protocol. The IAP312 study was designed to rule out a 5% device failure rate. The study design required a minimum of 315 patients. In the IAP312 study, sites proactively looked for tablets that were dispensed by the patient but failed to be placed under the tongue, known as dropped tablets. The FDA refers to dropped tablets as inadvertent dispensing. Correspondence from the FDA suggests that they may include the rate of inadvertent dispensing along with the device failures to calculate a total error rate. The IAP312 study evaluated all incidents of misplaced tablets; however, per the protocol, the error rate calculation does not include the rate of inadvertent dispensing. If the FDA includes the rate of inadvertent dispensing along with the device failures to calculate a total error rate, the resulting error rate may be unacceptable to the FDA. Further, the correspondence from the FDA suggests that we may need to modify the REMS program for Zalviso to address dropped tablets. The IAP312 results will supplement the three Phase 3 trials already completed in the Zalviso NDA resubmission. The timing of the resubmission of the Zalviso NDA is in part dependent upon the finalization of the FDA's new opioid approval guidelines and process.

There is no guarantee that the additional work we performed related to Zalviso, including the IAP312 trial, will result in our successfully obtaining FDA approval of Zalviso in a timely fashion, if at all. Although we believe the IAP312 study met safety, satisfaction and device usability expectations, there is no guarantee the IAP312 trial results will address the issues raised by the FDA. For example, the FDA may include the rate of inadvertent dispensing along with the device failures to calculate a total error rate and the resulting error rate may be unacceptable to the FDA, or the FDA may 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 resubmission or approval of the NDA and could require us to obtain significant additional funding. 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. We intend to seek a label indication for 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.

Upon resubmission of the Zalviso NDA, 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. Additionally, we may choose to engage in the dispute resolution process with the FDA.

Our proposed trade name of Zalviso has been approved by the EMA and is currently being used in Europe. It has also been conditionally 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, once 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.

***Positive clinical results obtained to date for Zalviso 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 each of our four Zalviso Phase 3 clinical trials completed to date, as well as our Phase 2 clinical trials for Zalviso. However, even if we believe that the data obtained 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. If the FDA were to require any additional clinical trials for Zalviso, our development efforts would be further delayed, which would have a material adverse effect on our business. Any such determination by the FDA would delay the timing of our commercialization plan for Zalviso and adversely affect our business operations.

***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 four Phase 3 clinical trials and several Phase 2 clinical trials for Zalviso, 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, we postponed the start of IAP312, originally planned for the first quarter of 2016, to September 2016. The postponement was due to a delay in the receipt and testing of final clinical supplies for this trial. As a result, the development timeline for Zalviso was further extended.

Our post-approval clinical trials for DSUVIA, or any future FDA-required clinical trials for Zalviso, 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, Institutional Review Board, or IRB, 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 IRB approval at each site;
- delays in recruiting suitable patients to participate in a trial;
- delays in the testing, validation, manufacture and delivery of the tablets and device components of DSUVIA or Zalviso;
- 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 FDA-required clinical trials are delayed for any reason, our development costs may increase, our approval process for Zalviso could be delayed, our ability to commercialize and commence sales of Zalviso could be materially harmed, and our ability to maintain FDA approval of DSUVIA could be jeopardized, which could have a material adverse effect on our business.

***Zalviso may cause adverse effects or have other properties that could delay or prevent regulatory approval or limit the scope of any approved label or market acceptance. DSUVIA may cause adverse effects or have other properties that could limit market acceptance.***

Adverse events, or AEs, caused by Zalviso could cause us, other reviewing entities, clinical trial sites or regulatory authorities to interrupt, delay or halt any future FDA-required clinical trials and could result in the denial of regulatory approval. Phase 2 clinical trials we conducted with Zalviso did generate some AEs, but no significant adverse events, or SAEs, related to the trial drug. In our Phase 3 active-comparator clinical trial (IAP309), 8% of Zalviso-treated patients dropped out of the trial prematurely due to an AE (11% in the IV patient-controlled morphine group), and we observed three SAEs that were assessed as possibly or probably related to study drug (one- respiratory depression in the Zalviso group and two- abdominal distension and ileus in the IV patient-controlled morphine group). In our Phase 3, double-blind, placebo-controlled, abdominal surgery trial (IAP310), 6% of Zalviso-treated patients dropped out of the trial prematurely due to an AE (9% in placebo group). There were no SAEs determined to be related to study drug. In our Phase 3, double-blind, placebo-controlled, orthopedic surgery trial (IAP311), 7% of Zalviso-treated patients dropped out of the trial prematurely due to an AE (7% in placebo group). Four patients (three in the Zalviso group and one in the placebo group) experienced an SAE considered possibly or probably related to the trial drug by the investigator. The SAEs possibly or probably attributed to Zalviso were severe oxygen saturation decrease, sinus tachycardia and confusional state. In our Phase 3 multicenter, open-label study of Zalviso (IAP312), 3% of patients dropped out prematurely due to an AE. Five patients experienced SAEs in the IAP312 study and none of these were considered possibly or probably related to the study drug by the investigator.

In our Phase 2 DSUVIA placebo-controlled bunionectomy study (SAP202), two patients in the DSUVIA 30 mcg group (5%) discontinued treatment due to an AE, one unrelated to study drug and the other probably related to study drug. There were no SAEs deemed related to study drug. In our Phase 3 placebo-controlled abdominal surgery study (SAP301), one DSUVIA-treated patient (1%) dropped out of the trial prematurely due to an AE (4% in placebo group). There were two SAEs determined to be related to study drug in the placebo-treated group and no related SAEs in the DSUVIA group. In our Phase 3 open-label, single-arm emergency room study (SAP302), no DSUVIA-treated patients dropped out of the trial prematurely due to an AE. One patient had an SAE – angina pectoris – possibly related to study drug. In our post-operative study in patients aged 40 years or older (SAP303), 3% of DSUVIA-treated patients dropped out of the trial prematurely due to an AE. There were no SAEs deemed related to study drug.

If DSUVIA or, if approved, Zalviso 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 REMS program;
- 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 DSUVIA or, if approved, Zalviso, and could substantially increase the costs of commercializing our products.

***Additional time may be required to obtain U.S. regulatory approval for Zalviso because it is a drug/device combination product candidate.***

DSUVIA and Zalviso are combination products 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 DSUVIA and Zalviso. As a result, we experienced delays in the development and commercialization of DSUVIA, and may experience future 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.

***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 our product candidate, Zalviso, 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 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. More generally, the FDA's comprehensive action plan to take concrete steps towards reducing the impact of opioid abuse on American families and communities may result in delays and challenges in obtaining NDA approval. 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.

***Although we have obtained regulatory approval for DSUVIA, and even if we obtain regulatory approval for our product candidates in the United States, we and our collaborators face extensive regulatory requirements, and our products may face future development and regulatory difficulties.***

Although we have obtained regulatory approval for DSUVIA, and even if we obtain regulatory approval for our product candidates in the United States, the FDA may impose significant restrictions on the indicated uses or marketing of our products or impose ongoing requirements for potentially costly post-approval trials or post-market surveillance. For example, DSUVIA is subject to a deferred post-marketing requirement for study in the pediatric population ages 6-17 years. A final protocol for this trial was submitted to the FDA in August 2020, in conjunction with a previously FDA approved request to defer initiation of pediatric studies until additional post-market safety data is obtained in adult patients using DSUVIA. Additionally, the labeling approved for DSUVIA includes restrictions on use due to the opioid nature of sufentanil. If approved, the labeling for Zalviso will likely include similar restrictions on use.

DSUVIA in the United States is also 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 concerning the advertising and promotion of DSUVIA and are subject to FDA review, in addition to other potentially applicable federal and state laws. Failure to comply with these regulations can result in the receipt of Warning Letters and further liability if off-label promotion is involved. For example, on February 11, 2021, we received a Warning Letter from the Office of Prescription Drug Promotion, or OPDP, of the FDA relating to a banner advertisement we submitted to the OPDP on December 6, 2019, and a tabletop display we submitted on February 28, 2020, and resubmitted to the OPDP at its request on September 23, 2020. We submitted the materials to the OPDP pursuant to the FDA requirement that sponsors submit all promotional materials to the FDA at the time of their initial dissemination or publication. The FDA's concerns identified in the letter include its view that the promotional material makes misleading claims and representations about the risks and efficacy of DSUVIA because the material does not reveal facts that are material in light of the representations made. As a result, we conducted a review of our marketing materials to identify any potential revisions in light of the letter. We responded to the FDA within the timeframe requested in the letter and, on March 23, 2021, held a teleconference with OPDP to seek guidance and clarification on the concerns raised in the letter. Following our meeting with OPDP, we conducted a further review of our marketing materials to identify any potential revisions in light of the letter and OPDP's guidance. We submitted a second response to FDA on April 7, 2021, and on June 17, 2021 we announced that the FDA agreed with our proposed plan to update certain promotional materials, including providing a letter to healthcare professionals, or the DHCP letter, explaining the corrections to the discontinued promotional materials. We included this DHCP letter on the DSUVIA.com website for a period of eight months. On February 18, 2022, in agreement with OPDP, the link to the corrective DCHP letter was removed from the DSUVIA.com website. Although we believe we have updated all promotional materials currently in use by our commercial team to address the FDA's concerns and we received word from FDA in mid-February that they are working on a Close-out Letter to the Warning Letter, we cannot give any assurances that we will receive such Close-out Letter or that we will not receive additional FDA Warning Letters in the future. If approved, our product candidates will be subject to these same requirements.

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 certain states we cannot apply for a license until a drug is approved by the FDA. The state licensing process may take several months which would delay commercialization in those states. 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 products, 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 DSUVIA, or, if approved, our product candidates, and generate revenues.

***Except for Zalviso and DZUVEO, which are both approved in Europe, we may never obtain additional regulatory approvals for our products and product candidates 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, 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 EC had granted marketing approval for Grünenthal's MAA for Zalviso for the management of acute moderate-to-severe post-operative pain in adult patients. In April 2016, Grünenthal completed the first commercial sale of Zalviso. Grünenthal terminated the collaboration, effective November 13, 2020. The terms of the Grünenthal Agreements were extended to May 12, 2021 to enable Grünenthal to sell down its Zalviso inventory, a right it had under the Grünenthal Agreements. Grünenthal's rights to market and sell Zalviso reverted back to us on May 12, 2021. We have not yet negotiated a New Arrangement and there can be no assurance that we will successfully enter into a New Arrangement. In June 2018, we announced that the EC had granted marketing approval of DZUVEO for the treatment of patients with moderate-to-severe acute pain in medically monitored settings. In July 2021, we entered into the DZUVEO Agreement with Aguettant.

Part of the foreign regulatory approval process includes compliance inspections of manufacturing facilities to ensure adherence to applicable regulations and guidelines. The foreign regulatory agency may delay, limit or deny marketing approval as a result of such inspections. 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 regulatory approval of DSUVIA and Zalviso in countries outside of the United States and Europe, or our ability to launch and successfully commercialize these products, once approved. In addition, results of EMA inspections could impact our ability to maintain EC approval of Zalviso and DZUVEO, and any future collaboration partner's ability to expand and sustain commercial sales of Zalviso or DZUVEO in Europe.

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 or premium reimbursement in all territories. For example, we anticipate we may need comparator studies for DZUVEO in Europe to ensure premium reimbursement in certain countries. While we have obtained approval of DZUVEO in Europe, we will be substantially dependent on Aguettant to comply with regulatory requirements. If we, or our commercial partners, 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.

***DSUVIA requires, and, if approved, Zalviso will require, a REMS program.***

DSUVIA was approved in the United States with a REMS program. If Zalviso is approved in the United States, it will also require a REMS program. The DSUVIA REMS program includes restrictions on product distribution and use only in certified medically supervised settings. Before DSUVIA is distributed, an authorized representative from each medically supervised setting must sign an attestation that they have the ability to manage acute opioid overdose and will train all relevant staff on administration of DSUVIA, including the importance of only dispensing the product in a medically supervised setting. Therefore, REMS-certification is a key gating item to generating product revenues for DSUVIA. In addition, the REMS program for DSUVIA may significantly increase our costs to commercialize this product. While we have received pre-clearance from the FDA regarding certain aspects of the proposed required REMS program for Zalviso, we cannot predict the final REMS program to be required as part of any FDA approval of Zalviso. Depending on the extent of the REMS requirements, any U.S. launch may be delayed, the costs to commercialize Zalviso may increase substantially and the potential commercial market could be restricted. Furthermore, risks of sufentanil that are not adequately addressed through the proposed REMS program for Zalviso may also prevent or delay its approval for commercialization.

**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 2022 and may continue to incur losses in the future.***

We have incurred significant net losses in each year since our inception in July 2005, and as of December 31, 2021, we had an accumulated deficit of $473.6 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 issuance of equity securities, borrowings, payments from Grünenthal, the monetization of certain future royalties and commercial sales milestones from the European sales of Zalviso by Grünenthal, funding from the Department of Defense, or DoD, and more recently with revenues from sales of DSUVIA since the commercial launch in the first quarter of 2019 and the upfront payment under the DZUVEO Agreement with Aguettant. 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 support commercialization activities for DSUVIA, manufacturing and supply activities for DZUVEO, and research and development activities for our product candidates, including the FDA regulatory review of the Zalviso NDA, once resubmitted. If DSUVIA is not successfully commercialized in the U.S., if our product candidates are not successfully developed or commercialized in the U.S., or if revenues are insufficient following marketing approval, we will not achieve profitability and our business may fail. Our success is also dependent on current and future collaborations to market our products outside of the United States, which may not materialize or prove to be successful.

***We have not yet generated significant product revenue and may never be profitable.***

Our ability to generate revenue from commercial sales and achieve profitability depends on our ability, alone and with collaborators, to successfully complete the development of, obtain the necessary regulatory approvals for, and commercialize our products. Although we received FDA approval of DSUVIA and began the commercial launch of DSUVIA in the United States, we may never generate enough revenues from sales of DSUVIA, or our product candidates, if approved, in the United States to become profitable. Although the EC granted marketing approval of DZUVEO in June 2018, we only recently entered into the DZUVEO Agreement with Aguettant to commercialize DZUVEO in Europe and there can be no assurance that Aguettant will successfully commercialize DZUVEO. Although we had a collaboration agreement with Grünenthal for commercialization of Zalviso in Europe and Australia, Grünenthal was unable to achieve a level of commercial sales of Zalviso to trigger sales milestone payments that would have been payable to us. The Grünenthal Agreements have been terminated and Grünenthal's rights to market and sell Zalviso reverted back to us on May 12, 2021.

In September 2015, we consummated a monetization transaction with 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 Amended License Agreement, subject to a capped amount. PDL sold its royalty interest for Zalviso to SWK in 2020. As mentioned above, Grünenthal has terminated the Grünenthal Agreements and the rights reverted back to us on May 12, 2021. Per the terms of the Royalty Monetization, we are obligated to use commercially reasonable efforts to negotiate a New Arrangement. Accordingly, even if we are able to enter into a New Arrangement, and that licensee is successful in commercializing Zalviso in Europe, we will receive only a portion of any royalties until the capped amount owing under the Royalty Monetization is reached. We do not anticipate generating significant near-term revenues from DSUVIA or our product candidates, if approved, in the United States. Our ability to generate future revenues from product sales depends heavily on our success in:

- maintaining regulatory approval for DSUVIA and obtaining and maintaining regulatory approval for our product candidates in the United States; and

- launching and commercializing DSUVIA and our product candidates, if approved, in the United States by building, internally or through collaborations, an institutionally focused sales force, and launching and commercializing DZUVEO and Zalviso internationally through collaborations, which may require additional funding.

Because of the numerous risks and uncertainties associated with launching a commercial pharmaceutical product, 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 for our product candidates 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.

We anticipate continuing to incur significant costs associated with commercializing DSUVIA in the United States. Even if we are able to generate revenues from the sale of DSUVIA or our product candidates, if approved, in the United States, we may not become profitable and may need to obtain additional funding to continue operations.

***Future sales of DSUVIA to the DoD are not predictable, may occur on an irregular basis and may not meet our expectations due to various U.S. government-related factors that are beyond our control and into which we have little to no visibility, including the timing and extent of future U.S. military deployments. If DoD spending on DSUVIA does not meet our expectations, it could adversely affect our expected results of operations, financial condition and liquidity.***

In April 2020, DSUVIA achieved Milestone C approval by the DoD, a decision that clears the path for the DoD to begin placing orders for DSUVIA to fulfill its updating requirements for all Army Sets, Kits, and Outfits, or SKOs, for deployed/deploying troops. Completion of this SKO fulfillment process is dependent on the Army's completion of their product information package including instructions on fulfillment and training which remains in process. In September 2020, we announced that DSUVIA was added to the DoD Joint Deployment Formulary, a core list of pharmaceutical products that are designated for deploying military units across all service branches. Future sales of DSUVIA to the DoD are not predictable, may occur on an irregular basis, and may not meet our expectations due to various U.S. government-related factors that are beyond our control and into which we have little to no visibility, including the timing and extent of future U.S. military deployments. Even if we do generate revenue from such sales, we may never generate revenue that is significant or predictable, which could impair our value and our ability to raise capital, expand our business or continue our operations. The placement of new orders by the DoD is, among other things, contingent upon overall U.S. government policies, budget and appropriation decisions and processes which are driven by numerous factors, including geo-political events, deployment of military units, macroeconomic conditions, and the ability of the U.S. government to enact relevant legislation, such as appropriations bills and accords on the debt ceiling. Our expectations about the timing and size of initial stocking orders for the SKOs and other orders by the DoD are based on our understanding of troop deployment schedules. If DoD spending on DSUVIA does not meet our expectations, it could have a material adverse effect on our expected results of operations, financial condition and liquidity.

***We have been substantially dependent on Grünenthal to successfully commercialize Zalviso in Europe and they have terminated their collaboration agreement with us.***

Under our agreements with Grünenthal, we granted Grünenthal rights to commercialize Zalviso in Europe for human use in pain treatment within, or dispensed by, hospitals, hospices, nursing homes and other medically supervised settings. In September 2015, the EC granted marketing approval for Grünenthal's MAA for Zalviso for the management of acute moderate-to-severe post-operative pain in adult patients, and Grünenthal began its European launch of Zalviso with the first commercial sale occurring in April 2016. Grünenthal terminated the collaboration, effective November 13, 2020. The terms of the Grünenthal Agreements were extended to May 12, 2021 to enable Grünenthal to sell down its Zalviso inventory, a right it had under the Grünenthal Agreements. Grünenthal's rights to market and sell Zalviso reverted back to us on May 12, 2021.

During the pilot and launch phases in the various European countries, Grünenthal reported certain issues from HCPs with the initial set up of the Zalviso controllers before being given to patients for use. To address the issues, we assisted Grünenthal with implementing additional training for HCPs and revised the controller software. Controllers with the revised software, which were delivered in December 2016, underwent extensive bench testing and we believe we successfully addressed the issues presented. Additional devices were delivered beginning in early 2017. Controllers with the U.S. version of the revised software were also used in the IAP312 clinical study that was initiated in September 2016. There can be no assurance that the issues identified in the initial pilot and launch phases by Grünenthal will not have a material adverse impact on future sales of Zalviso in Europe under a New Arrangement. Further, if new issues occur, there may be a material adverse impact on the future sales of Zalviso in Europe under a New Arrangement which may have a negative impact on future revenues received and recognized by us.

We did not realize the expected benefits from our collaboration with Grünenthal, and may not realize the expected benefits from any New Arrangement, due to a number of important factors, including:

- The timing and amount of any payments we may receive under our agreements will depend on, among other things, the efforts, allocation of resources, and successful commercialization of Zalviso by any future collaboration partner in Europe;
- Grünenthal changed the focus of its commercialization efforts to pursue higher-priority programs and any future collaboration partner may do the same;
- Grünenthal stopped its commercialization efforts in countries where it had the sole right to commercialize Zalviso, requiring us to find another collaboration partner for Zalviso in Europe; and
- Grünenthal terminated its agreements with us, and any future collaboration partner may also terminate any future agreement with us, adversely affecting our potential revenue from Zalviso;

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 commercialization of DSUVIA or the development of 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 Grünenthal Agreements under our agreements with PDL, and, if we breach those representations or covenants, we may become subject to indemnification claims by SWK (assignee of PDL) and liable to SWK 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 will be substantially dependent on Aguettant to successfully commercialize DZUVEO in Europe.***

In June 2018, the EC granted marketing approval for DZUVEO and in July 2021 we entered into the DZUVEO Agreement with Aguettant to commercialize DZUVEO in Europe. We will be substantially dependent on Aguettant to successfully commercialize DZUVEO in Europe. Any failures in the commercialization of DZUVEO in Europe could have a significant adverse impact on our revenues and operating results.

The DZUVEO Agreement requires us to support the manufacturing and supply of DZUVEO for Aguettant. In addition, we anticipate we may need comparator studies in Europe to ensure premium reimbursement in certain countries. Our inability to profitably manufacture and supply DZUVEO to Aguettant, or to successfully complete these additional comparator studies and obtain premium reimbursement in certain countries, may prevent, limit or delay commercialization and any associated future revenues from DZUVEO in Europe.

***We have limited experience commercializing DSUVIA, which may make it difficult to predict our future performance or evaluate our business and prospects.***

Since inception, our operations have been primarily focused on developing our technology and undertaking pharmaceutical development and clinical trials for DSUVIA and Zalviso, understanding the market potential for DSUVIA and Zalviso, and preparing for the commercialization of DSUVIA and the potential commercialization of Zalviso in the United States. We launched commercialization efforts for DSUVIA in February 2019. As a result of our limited commercialization experience, any predictions that are made about our future performance, 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 commercialization efforts and product development programs and could cause us to cease operations.***

Launch of a commercial pharmaceutical product and pharmaceutical development activities can be time consuming and costly. We expect to incur significant expenditures in connection with supporting our ongoing commercialization activities for DSUVIA, manufacturing and supply activities for DZUVEO, and research and development activities for our product candidates, including the FDA regulatory review of the Zalviso NDA, once resubmitted. While we believe we have sufficient capital resources to continue planned operations for at least the next twelve months, we will need additional capital to pursue full commercialization of DSUVIA and our product candidates, if approved.

Clinical trials, regulatory reviews, and the launch of commercial product are expensive activities. In addition, commercialization costs for DSUVIA and our product candidates, if approved, in the United States may be significantly higher than estimated as a result of technical difficulties or otherwise. Revenues may be lower than expected and 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. In the future, we may seek to sell additional equity securities, including under the Sales Agreement with Cantor, and debt securities, monetize or securitize certain assets including future royalty streams and milestones, refinance our loan agreement, obtain a revolving credit facility, enter into product development, license or distribution agreements with third parties, or divest DSUVIA, DZUVEO, Zalviso in Europe, or any of our product candidates. Such arrangements may not be available on favorable terms, if at all.

Future events and circumstances, including those beyond our control, may cause us to consume capital more rapidly than we currently anticipate. 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, reduce the scope of, or cease, the commercial launch of DSUVIA, or the development of our product candidates 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 commercialize DSUVIA or develop 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 scale back or discontinue the commercialization of DSUVIA, or the development of our product candidates;
- seek additional corporate partners for Zalviso on terms that might be less favorable than might otherwise be available;
- seek corporate partners for DSUVIA/DZUVEO on terms that might be less favorable than might otherwise be available; or
- relinquish, or license on unfavorable terms, our rights to technologies, products or product candidates that we otherwise would seek to develop or commercialize ourselves.

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

We expect that significant additional capital will be needed in the future to continue our planned operations. In order to raise additional funds to support our operations, we may sell additional equity securities, including under the Controlled Equity Offering$^{SM}$ Sales Agreement, or the ATM Agreement, with Cantor Fitzgerald & Co., or Cantor, as agent. 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. Selling additional equity securities may result in dilution to our existing stockholders and new investors may be materially diluted by subsequent sales. Incurring additional indebtedness, including through the sale of debt securities, would result in increased fixed payment obligations and could also result in additional 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. Sales of equity or debt securities may also provide new investors with rights superior to our existing stockholders. 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.

In addition, worsening economic conditions and other adverse effects or developments relating to the ongoing COVID-19 pandemic may negatively affect the market price of our stock, regardless of our actual operating performance. The market price for our common stock is likely to continue to be volatile, particularly due to the ongoing COVID-19 pandemic, and subject to significant price and volume fluctuations in response to market, industry and other factors. If additional funding is not available on favorable terms, if at all, due to these factors, we may not be able to obtain sufficient additional funding to support our operations.

***The terms of our loan agreement with Oxford may restrict our current and future operations, particularly our ability to respond to changes in business or to take certain actions, including to pay dividends to our stockholders.***

On May 30, 2019, we entered into the Loan Agreement with Oxford Finance LLC, or Oxford, a Delaware limited liability company, as the Lender. The Loan Agreement contains, and any future indebtedness we incur will likely contain, a number of restrictive covenants that impose operating restrictions, including restrictions on our ability to engage in acts that may be in our best long-term interests. The Loan Agreement includes covenants that, among other things, restrict our ability to (i) declare dividends or redeem or repurchase equity interests; (ii) incur additional liens; (iii) make loans and investments; (iv) incur additional indebtedness; (v) engage in mergers, acquisitions, and asset sales; (vi) transact with affiliates; (vii) undergo a change in control; (viii) add or change business locations; and (ix) engage in businesses that are not related to our existing business. The Loan Agreement also requires that we at all times maintain unrestricted cash of not less than $5.0 million.

A breach of any of these covenants could result in an event of default under the Loan Agreement. Upon the occurrence of such an event of default, a default interest rate of an additional 5% may be applied to the outstanding loan balances and all outstanding obligations under the Loan Agreement can be declared to be immediately due and payable If our indebtedness is accelerated, we cannot assure you that we will have sufficient assets to repay the indebtedness. The restrictions and covenants in the Loan Agreement and any future financing agreements may adversely affect our ability to finance future operations or capital needs or to engage in other business activities.

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

As of December 31, 2021, we had approximately $13.3 million of outstanding debt under the Loan Agreement. The Loan Agreement has a scheduled maturity date of June 1, 2023 and is secured by 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, the Lender could elect to declare all amounts outstanding, together with accrued and unpaid interest, and other payments, to be immediately due and payable. Additional capital may not be available on terms acceptable to us, or at all. 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, the Lender will have a first claim on our assets pledged under the Loan Agreement. If the lender 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 Loan Agreement and resulting foreclosure would have a material adverse effect on our financial condition and our ability to continue our operations.

**Risks Related to Our Reliance on Third Parties**

***We rely on third party manufacturers to produce commercial supplies of DSUVIA in the United States, commercial supplies of Zalviso in Europe, and clinical supplies of Zalviso in the United States, and will rely on third party manufacturers to produce DZUVEO for Aguettant and on Aguettant to produce commercial supplies of our product candidates, if approved, in the United States. The failure of third-party manufacturers to provide us with adequate commercial and clinical supplies could result in a material adverse effect on our business.***

Third party manufacturers produce commercial and clinical supplies of our products and product candidates. Reliance on third party manufacturers entails many risks including:

- the inability to meet our product specifications and quality requirements consistently;
- the inability to procure raw materials in a timely fashion due to ongoing challenges in the global supply chain;
- 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 or supply agreements with third parties under commercially reasonable terms;
- termination or nonrenewal of manufacturing or supply 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 products 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, or government orders related to the COVID-19 pandemic;
- 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.

In addition, the DZUVEO Agreement requires us to manufacture and supply DZUVEO to Aguettant. As mentioned above, we were obligated to manufacture and supply Zalviso under the Grünenthal Agreements for use in Europe and their other licensed territories and will likely be required to do so under any New Arrangement. If we are unable to establish a reliable commercial supply of DZUVEO for Aguettant, and, if a New Arrangement is entered into, Zalviso for Europe, we may be unable to satisfy our obligations under the DZUVEO Agreement or any New Arrangement in a timely manner or at all, and we may, as a result, be in breach of such agreements. If any such breach, or other breach, were to be material and remain uncured, it could result in termination of the agreement, which in turn could, in the case of a New Arrangement, result in us being responsible for indemnification of losses suffered by SWK under the Royalty Monetization. If any of these events were to occur, our business would be materially adversely affected.

***We rely on limited sources of supply for the active pharmaceutical ingredient, or API, of DSUVIA and Zalviso and any disruption in the chain of supply may cause a delay in supplying DSUVIA and Zalviso.***

Currently we only have one supplier qualified as a vendor for the manufacture of DSUVIA, known as DZUVEO in Europe, and Zalviso with the FDA and EMA, respectively. If supply from the approved vendor is interrupted, there could be a significant disruption in commercial supply. Any alternate vendor would need to be qualified through an NDA supplement and/or an MAA variation which could result in delays. 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 controlled substance. 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 or our partners need to use dedicated equipment throughout development and commercial manufacturing to avoid the possibility of cross-contamination. If our or our partners' 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. Any problems with our or our partners' facilities or equipment may impair our ability to successfully commercialize DSUVIA or Zalviso, if approved, and to complete our clinical trials, and increase our cost.

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

We have relied, and will continue to rely, on contract manufacturers, component fabricators and third-party service providers to produce the necessary DSUVIA single-dose applicator, or SDA, and Zalviso devices for the commercial marketplace. We currently outsource manufacturing and packaging of the DSUVIA SDA and the controller, dispenser and cartridge components of the Zalviso device to third parties and intend to continue to do so. Some of these component purchases 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 DSUVIA, DZUVEO or Zalviso devices with each of the 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 scale-up and automating processes, which could adversely impact our ability to supply our customers with DSUVIA, Zalviso and DZUVEO in Europe, and, if approved, Zalviso in the U.S. and any other foreign territories.

As we scale up manufacturing of DSUVIA and Zalviso, if approved, and conduct required production and stability testing, these processes may require refinement or resolution. For example, as we scale up, we may identify significant issues which could result in failure to maintain regulatory approval of DSUVIA, increased scrutiny by regulatory agencies, delays in clinical program and regulatory approval, increases in our operating expenses, or failure to obtain approval for our product candidates in the United States.

We have built out a suite within our CMO's production facility in Cincinnati, Ohio that serves 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 this location. While we produced a number of commercial lots to support Grünenthal's launch in Europe, our experience is limited, which impacted our ability to deliver commercial supplies to Grünenthal on a timely basis, and may in the future impact our ability to deliver commercial supplies under any New Arrangement, if required, on a timely basis.

In January 2013, we entered into an agreement with a CMO 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. On August 22, 2017, we entered into an amendment to this agreement to manufacture, supply, and provide certain validation and stability services with respect to DSUVIA for sales in the United States, and potential sales in Canada and Mexico, and other countries. There is no guarantee that our CMO's services will be satisfactory or that they will continue to meet the strict regulatory guidelines of the FDA or other foreign regulatory agencies. If our CMO 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 the 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 approval for Zalviso, and other foreign regulatory agency approval of DSUVIA/DZUVEO and Zalviso outside Europe. These challenges may have a material adverse impact on our business, results of operations, financial condition and prospects.

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 facilities, 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 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 Europe, we may be unable to satisfy our obligations under any New Arrangement, if required, in a timely manner or at all, and we may, as a result, be in breach of any New Arrangement.

For DSUVIA, we currently package the finished goods under a manual process and would package DZUVEO in the same manner. The capacity and cost to package the goods under this manual process are not optimal to support successful future sales of DSUVIA and DZUVEO. We have purchased and installed an automated filling and packaging line to support increased capacity packaging for DSUVIA and DZUVEO. We have experienced delays to final implementation of our automated line due to the impact of COVID-19, in addition to testing requirements of our vendor. While we have now completed the acquisition and installation of this line; there can be no assurance that we will be able to successfully complete the qualification and validation of this line and obtain the necessary regulatory approvals to manufacture commercial product on this line. Due to the recent strains on the global supply chain, the lead time for many components used in our production are getting longer and may impact our ability to manufacture our products in a timely manner.

***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 the Phase 2 and 3 clinical trials of DSUVIA, as well as our Phase 3 clinical program for Zalviso. 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 post-approval clinical programs for DSUVIA and any FDA-required clinical programs for our 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 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 our product candidates. As a result, our financial results and the commercial prospects for Zalviso, if approved, would be harmed, our costs could increase, and our ability to generate revenues could be delayed.

**Risks Related to Our Business Operations and Industry**

***Failure to receive required quotas of controlled substances or comply with the Drug Enforcement Agency 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 classified as a Schedule II controlled substance, 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. In addition, our contract manufacturers are required to maintain relevant licenses and registrations. This high degree of regulation can result in significant compliance costs, which may have an adverse effect on the commercialization of DSUVIA and the development and commercialization of Zalviso, if approved.

The DEA limits the availability and production of all Schedule II controlled 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 apply for quotas on our behalf. We will need significantly greater amounts of sufentanil to successfully commercialize DSUVIA, to support European commercialization of DZUVEO and Zalviso, and to commercialize Zalviso, if approved in the United States. Any delay by the DEA in establishing the procurement quota, reduction in our quota for sufentanil, failure to increase our quota over time to meet anticipated increases in demand, or refusal by the DEA to establish the procurement quota could delay or stop the commercial sale of our approved products or the clinical development of Zalviso in the United States. This, in turn, could have a material adverse effect on our business, results of operations, financial condition and prospects.

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

Healthcare providers, including 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 payers 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. Applicable federal and state healthcare laws include, but are not limited to, the following:

- the federal healthcare Anti-Kickback Statute, which 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, 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 payer (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, which impose certain obligations, including mandatory contractual terms, on covered healthcare providers, health plans and clearinghouses, and their respective business associates that perform services for them that involve the use, or disclosure of, individually identifiable health information, as well as their covered subcontractors with respect to safeguarding the privacy, security and transmission of individually identifiable health information;

- foreign laws, regulations, standards and regulatory guidance which govern the collection, use, disclosure, retention, security and transfer of personal data, including the European Union General Data Privacy Regulation, or GDPR, which introduces strict requirements for processing personal data of individuals within the European Union;

- the federal transparency law, enacted as part of the Affordable Care Act, and its implementing regulations, which requires certain manufacturers of drugs, devices, biologicals and medical supplies to report annually to the CMS information related to payments and other transfers of value provided to physicians, (defined to include, doctors, dentists, optometrists, podiatrists and chiropractors), other healthcare professionals (such as physician assistants and nurse practitioners), 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, state and local laws that require the registration of pharmaceutical sales representatives, and state laws governing the privacy and security of health information in certain circumstances, many of which differ from each other in significant ways, with differing effects; and

- the federal Foreign Corrupt Practices Act of 1977, United Kingdom Bribery Act 2010 and other similar anti-bribery laws in other jurisdictions which 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 SEC. 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 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, imprisonment, exclusion from government funded healthcare programs, such as Medicare and Medicaid, contractual damages, reputational harm, increased losses and diminished profits, additional oversight and reporting obligations if we become subject to a corporate integrity agreement or other agreement to resolve allegations of non-compliance with these laws, 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.

***In order to supply the Zalviso device to any future collaborator for commercial sales in Europe, we must maintain conformity of our quality system to applicable ISO standards and must comply with applicable European laws and directives.***

We underwent a Conformité Européenne 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 Europe. 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. The CE Mark was originally issued by the British Standards Institution, or BSI, a Notified Body, or NB, located in the United Kingdom, or U.K., or BSI-U.K. The CE Mark file and certification has been transferred to the Netherlands NB of BSI, or BSI-NL, to mitigate the uncertainty with regards to Brexit. The ISO certification issued through BSI-U.K. was recently upgraded to the latest version of the standard, ISO 13485:2016 through BSI-U.K. and remains in effect. BSI ISO 13485:2016 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 European Economic Area (which includes the 27 EU member states as well as Norway, Iceland and Liechtenstein), or EEA, as well as to meet equivalent requirements in other international markets. The certification applies to the Hayward, California location which designs, manufactures and distributes finished medical devices, and includes critical suppliers. If we fail to remain in compliance with applicable European laws and directives, we would be unable to continue to affix the CE Mark to our Zalviso device, which would prevent any future collaboration partner from selling these devices within the EU and EEA.

***Significant disruptions of our information technology systems or data security incidents could result in significant financial, legal, regulatory, business and reputational harm to us.***

We are increasingly dependent on information technology systems and infrastructure, including mobile technologies, to operate our business. In the ordinary course of our business, we collect, store, process and transmit large amounts of sensitive information, including intellectual property, proprietary business information, personal information and other confidential information. It is critical that we do so in a secure manner to maintain the confidentiality, integrity and availability of such sensitive information. We have also outsourced elements of our operations (including elements of our information technology infrastructure) to third parties, and as a result, we manage a number of third-party vendors who may or could have access to our computer networks or our confidential information. In addition, many of those third parties in turn subcontract or outsource some of their responsibilities to third parties. While all information technology operations are inherently vulnerable to inadvertent or intentional security breaches, incidents, attacks and exposures, the accessibility and distributed nature of our information technology systems, and the sensitive information stored on those systems, make such systems potentially vulnerable to unintentional or malicious internal and external attacks on our technology environment. Potential vulnerabilities can be exploited from inadvertent or intentional actions of our employees, third-party vendors, business partners, or by malicious third parties. Attacks of this nature are increasing in their frequency, levels of persistence, sophistication and intensity, and are being conducted by sophisticated and organized groups and individuals with a wide range of motives (including, but not limited to, industrial espionage) and expertise, including organized criminal groups, "hacktivists," nation states and others. In addition to the extraction of sensitive information, such attacks could include the deployment of harmful malware, ransomware, denial-of-service attacks, social engineering and other means to affect service reliability and threaten the confidentiality, integrity and availability of information. In addition, the prevalent use of mobile devices increases the risk of data security incidents.

Significant disruptions of our third-party vendors' and/or business partners' information technology systems or other similar data security incidents could adversely affect our business operations and result in the loss, misappropriation, and/or unauthorized access, use or disclosure of, or the prevention of access to, sensitive information, which could result in financial, legal, regulatory, business and reputational harm to us. In addition, information technology system disruptions, whether from attacks on our technology environment or from computer viruses, natural disasters, terrorism, war and telecommunication and electrical failures, could result in a material disruption of our development programs and our business operations. For example, the loss of clinical trial data from completed or future clinical trials could result in delays in our regulatory approval efforts and significantly increase our costs to recover or reproduce the data.

There is no way of knowing with certainty whether we have experienced any data security incidents that have not been discovered. While we have no reason to believe this to be the case, attackers have become very sophisticated in the way they conceal access to systems, and many companies that have been attacked are not aware that they have been attacked. Any event that leads to unauthorized access, use or disclosure of personal information, including but not limited to personal information regarding our patients or employees, could disrupt our business, harm our reputation, compel us to comply with applicable federal and state breach notification laws and foreign law equivalents, subject us to time consuming, distracting and expensive litigation, regulatory investigation and oversight, mandatory corrective action, require us to verify the correctness of database contents, or otherwise subject us to liability under laws, regulations and contractual obligations, including those that protect the privacy and security of personal information. This could result in increased costs to us, and result in significant legal and financial exposure and/or reputational harm. In addition, any failure or perceived failure by us or our vendors or business partners to comply with our privacy, confidentiality or data security-related legal or other obligations to third parties, or any further security incidents or other inappropriate access events that result in the unauthorized access, release or transfer of sensitive information, which could include personally identifiable information, may result in governmental investigations, enforcement actions, regulatory fines, litigation, or public statements against us by advocacy groups or others, and could cause third parties, including clinical sites, regulators or current and potential partners, to lose trust in us or we could be subject to claims by third parties that we have breached our privacy- or confidentiality-related obligations, which could materially and adversely affect our business and prospects. Moreover, data security incidents and other inappropriate access can be difficult to detect, and any delay in identifying them may lead to increased harm of the type described above. While we have implemented security measures intended to protect our information technology systems and infrastructure, there can be no assurance that such measures will successfully prevent service interruptions or security incidents.

***Business interruptions could delay our operations and sales efforts.***

Our headquarters is located in the San Francisco Bay Area, near known earthquake fault zones and is vulnerable to significant damage from earthquakes. Our contract manufacturers, suppliers, clinical trial sites and local and national transportation vendors are all subject to business interruptions due to weather, outbreaks of pandemic diseases, natural disasters, or man-made incidents. We are also vulnerable to other types of natural disasters and other events that could disrupt our operations. If any of these events occurred and prevented us or third parties on which we rely from using all or a significant portion of our or their facilities, it may be difficult or, in certain cases, impossible for us to continue our business and operations for a substantial period of time.

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 qualified scientific, manufacturing, and commercial personnel will also be critical to our success. We may not be able to attract and retain these personnel on acceptable terms given the competition among numerous pharmaceutical and biotechnology companies for similar personnel. We also experience competition for the hiring of scientific and clinical personnel from universities and research institutions. 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. 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.

***We may fail to realize the benefits expected from our acquisition of Lowell, which could adversely affect our stock price.***

Our acquisition of Lowell is our largest acquisition to date. The anticipated benefits we expect from this acquisition are, necessarily, based on projections and assumptions about the combined businesses of our company and Lowell, which may not materialize as expected or which may prove to be inaccurate. The value of our common stock could be adversely affected if we are unable to realize the anticipated benefits from the acquisition on a timely basis or at all. Achieving the benefits of the acquisition of Lowell will depend, in part, on our ability to integrate the business, operations and products of Lowell successfully and efficiently with our business. The challenges involved in this integration include, but are not limited to, (i) difficulties entering new markets and integrating new product candidates with which we have no or limited direct prior experience; and (ii) successfully managing relationships with our combined supplier base.

The financial results of the combined company may be adversely affected by cash expenses and non-cash accounting charges incurred in connection with our integration of the business and operations of Lowell. The amount and timing of these possible charges are not yet known. Further, our failure to identify or accurately assess the magnitude of certain liabilities we assumed in the acquisition could result in unexpected litigation or regulatory exposure, unfavorable accounting charges, unexpected increases in taxes due, a loss of anticipated tax benefits or other adverse effects on our business, operating results or financial condition. The price of our common stock could decline to the extent the combined company's financial results are materially affected by any of these events.

***We may acquire companies, product candidates or products or engage in strategic transactions, which could divert our management's attention and cause us to incur various costs and expenses.***

We may acquire or invest in companies, product candidates or products that we believe could complement or expand our business or otherwise offer growth opportunities. The pursuit of potential acquisitions or investments may divert the attention of management and has caused, and in the future may cause, us to incur various costs and expenses in identifying, investigating, and pursuing them, whether or not they are consummated. We may not be able to identify desirable acquisitions or investments or be successful in completing or realizing anticipated benefits from such transactions. In addition, the acquisition of product candidates and products is a highly competitive area, and many other companies are pursuing the same or similar product candidates to those that we may consider attractive. Larger companies with more well-established and diverse revenue streams may have a competitive advantage over us due to their size, financial resources and more extensive clinical development and commercialization capabilities.

In addition, we receive inquiries relating to potential strategic transactions, including collaborations, licenses, and acquisitions. Such potential transactions may divert the attention of management and may cause us to incur various costs and expenses in investigating and evaluating such transactions, whether or not they are consummated.

***We face potential product liability claims, and, if such claims are successful, we may incur substantial liability.***

Commercial sales of DSUVIA and Zalviso expose us to the risk of product liability claims. Product liability claims might be brought against us by patients, 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;
- 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 products; and
- decreased demand for our products.

Our current product liability insurance coverage may not be sufficient to reimburse us for any expenses or losses we may suffer. In addition, our current product liability insurance contains an exclusion related to any claims related to our products from a governmental body, or payer, or those claims arising from a multi-plaintiff action for bodily injury or property damage. Multi-plaintiff claims caused by product defects are covered. This exclusion does not apply to any bodily injury claim related to our products made by an individual. 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 are excluded from our insurance coverage or exceed our insurance coverage, could adversely affect our results of operations and business. 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.

Our insurance coverage included the sale of Zalviso to our former commercial partner, Grünenthal, and will likely include the sale of Zalviso by any future commercial partner. We intend to commercialize and promote DZUVEO in Europe with a strategic partner which may result in further expansion of our insurance coverage to include sales of DZUVEO in Europe. There can be no assurance that such coverage will be adequate to protect us against any future losses due to liability.

***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) regulations implemented by the FDA and similar foreign regulatory bodies; (2) laws requiring the reporting of true, complete and accurate information to such regulatory bodies; (3) healthcare fraud and abuse laws of the United States and similar foreign fraudulent misconduct laws; and (4) laws requiring the reporting of financial information or data accurately. 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 significant civil, criminal and administrative penalties, damages, monetary fines, disgorgement, imprisonment, additional oversight and reporting obligations if we become subject to a corporate integrity agreement or similar agreements to resolve allegations of non-compliance with these laws, 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, 2021, we are the owner of record of 93 issued patents worldwide drawn to AcelRx's sufentanil sublingual tablets, medication delivery devices and other platform technologies. These issued patents include 18 patents that we have listed in the FDA's Orange Book for DSUVIA, some of which have expiration dates that extend into 2031. These issued patents also include a European patent drawn to the DZUVEO device that has an expiration date that extends into 2036.

Because sufentanil is not a new chemical entity, potential regulatory (data) exclusivity periods for new formulation, dosage form and/or dosage strength sufentanil products in the United States is limited to three years under the Hatch-Waxman Act. While the FDA was not able to approve a 505(b)(2) NDA or an abbreviated new drug application, or ANDA, using DSUVIA as its reference listed drug prior to November 2, 2021, we may now be subject to a third party's Paragraph IV or other patent certification based on the patents we have listed in the FDA's Orange Book for DSUVIA and engage in litigation against such a 505(b)(2) or ANDA applicant at any time.

In addition, we are pursuing a number of U.S. patent applications and foreign national applications directed to DSUVIA, Zalviso, Niyad, and LTX-608. 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.

As we continue to develop our product candidates ephedrine, phenylephrine, Niyad and LTX-608, we expect to pursue 505(b)(2) NDA application pathways since all of the base pharmacological agents are not new chemical entities. As a result of this filing avenue, we will need to include patent certifications regarding the reference listed drugs that our applications are based upon. These patent certifications could trigger patent litigation by the patent holders that we have certified against.

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 ours, 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 or post-issuance proceedings such as opposition, *inter partes* review, post-grant review, *ex parte* re-examination or other post-issuance proceedings. In addition, there is no assurance that the relevant patent office court or agency in such adversarial proceedings would not make unfavorable decisions, such as reducing the scope of a patent of ours, invalidating issued claims 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 products to market and interfere with our business.***

Our commercial success depends in part on our not infringing patents or trademarks, or misappropriating other third-party intellectual property. Although we are not currently aware of litigation or other proceedings or third-party claims of intellectual property infringement related to DSUVIA or Zalviso, the pharmaceutical industry is especially prone to extensive litigation proceedings between competitors regarding their 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 or misappropriate 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 our products, or may include composition or method claims that encompass our technology, allowing them to assert that our continued use of our own technologies infringes such newly emerging patent rights.

In the event that a patent infringement claim is asserted against us, we may counter, as an affirmative defense, that we do not infringe the relevant patent claims, that the patent is invalid or otherwise unenforceable or any combination thereof. The strength of our defenses will depend on the patents asserted, the interpretation of those patents, and our ability to establish the invalidity of the asserted patents. However, we could be unsuccessful in advancing non-infringement, invalidity or unenforceability 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 a court in a final and non-appealable decision were to hold that we have infringed someone else's valid patent claim, we could be prevented from using that third-party patented technology and may also be required to pay the owner of the patent for damages for past sales and need to seek license access to the patented technology for future sales. If we decide to pursue such 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 to avoid the third-party patent claims, we may not be able to do so in a timely or cost-effective manner, if at all.

In addition, because patent applications remain unpublished for 18 months from their initial filing date and some applications may be afforded confidentiality during prosecution that can take years to issue, there may currently be pending applications that are unknown to us and that may later result in issued patents that could cover one or more of our products.

It is possible that we may in the future receive communications from competitors and other companies alleging that we may be infringing their patents, misappropriating their trade secrets or otherwise violating their intellectual property rights, where they may offer license access to such intellectual property or threaten litigation. In addition to patent infringement claims, third parties may assert copyright, trademark or other intellectual property rights against us. We may need to expend considerable resources to counter such claims and may not be successful in our defense. Our business may suffer if a finding of infringement or misappropriation 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 just as 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 estate.

We cannot predict the breadth of claims that may be allowed or enforced in the patents that may issue from the applications that we currently have pending, or may in the future acquire or license from third parties. Claims could be brought regarding the validity of our patents by third parties. Further, if any patent right that 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 assert patent infringement claims against such entities, 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 intellectual property rights, particularly in countries outside the United States where national laws and court systems are less robust, making patent rights more difficult to enforce, and very expensive to pursue. 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 intellectual property 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 DSUVIA, DZUVEO and Zalviso in Europe or any of our ephedrine, phenylephrine, Niyad or LTX-608 product opportunities, if approved, 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 without misappropriating our rights. 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 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 our intellectual property rights.

***We have not yet registered our trademarks in all 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 EU and India. In early 2014, the FDA accepted the Zalviso mark and, in November 2018, the FDA accepted the DSUVIA mark. 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, such as securing the registration of DSUVIA in Canada, 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.***

The trading price of our common stock has experienced significant volatility and is likely to be volatile in the future. For example, the closing price of our common stock ranged between $0.49 and $2.77 during the year ended December 31, 2021, and between $0.76 and $2.07 during the year ended December 31, 2020. Our stock price could be subject to wide fluctuations in response to a variety of factors, including the following:

- failure to successfully commercialize DSUVIA in the United States or to successfully develop and commercialize our product candidates in the United States;
- inability to obtain additional funding needed to conduct our planned business operations;
- inability to satisfactorily comply with FDA regulations concerning the advertising and promotion of DSUVIA, including receiving a Close-out Letter resolving the concerns raised by FDA in the Warning Letter delivered to us on February 11, 2021;
- the integration and performance of any assets or businesses we acquire;
- our inability to develop and commercialize products and product candidates that we in-license;
- uncertainties regarding the magnitude and duration of impacts we are experiencing due to COVID-19;
- the perception of limited market sizes or pricing for our products;
- further delays in resubmitting the NDA for Zalviso, and any additional adverse developments or perceived adverse developments with respect to the FDA's review of the Zalviso NDA, upon resubmission;
- inability to enter into, or unfavorable terms associated with, a New Arrangement for the commercialization of Zalviso in Europe;
- safety issues;
- adverse results or delays in future clinical trials;
- changes in laws or regulations applicable to our products;
- inability to obtain adequate product supply for our products, or the inability to do so at acceptable prices;
- adverse regulatory decisions;
- changes in the structure of the healthcare payment systems;
- inability to maintain regulatory approvals for DZUVEO and Zalviso in the European Union, including ISO 13485 certification and CE Mark approval for Zalviso;
- 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;
- decisions by our collaboration partners regarding market access, pricing, and commercialization efforts in countries where they have the right to commercialize our products;
- failure to maintain our existing collaborations or enter into new collaborations;
- the perception of the pharmaceutical industry generally, and of opioid manufacturers more specifically, 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 employment matters, business development efforts, proprietary rights, including patents, litigation matters and our ability to obtain patent protection for our technologies;
- additions or departures of key management or scientific personnel;
- costs associated with potential governmental investigations, inquiries, regulatory actions or lawsuits that may be brought against us as a result of us being an opioid manufacturer;

- other types of significant lawsuits, including patent, stockholder, securities class action and derivative 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.

***Our common stock may be delisted from The Nasdaq Global Market if we cannot regain compliance with Nasdaq's continued listing requirements.***

In order to maintain our listing on Nasdaq, we are required to comply with the Nasdaq requirements, which includes maintaining a minimum bid price and a minimum public float. In particular, we are required to maintain a minimum bid price of $1.00 per share. On December 2, 2021, we received a notice from Nasdaq stating that we were not in compliance with Nasdaq Listing Rule 5450(a)(1) (the "Minimum Bid Price Rule") because our common stock failed to maintain a minimum closing bid price of $1.00 for 30 consecutive business days. This notice had no immediate effect on the Nasdaq listing or trading of our common stock.

We have a compliance period for the Minimum Bid Price Rule of 180 calendar days, or until May 31, 2022, in which to regain compliance, pursuant to Nasdaq Marketplace Rule 5810(c)(3)(A). If, at any time before that date the bid price of our common stock closes at $1.00 per share or more for a minimum of 10 consecutive business days, Nasdaq will notify us that we have achieved compliance with the Rule.

If we do not achieve compliance with the Minimum Bid Price Rule during the initial 180 calendar day period, we may be eligible for an additional 180 calendar day compliance period. To qualify, we would need to transfer the listing of our common stock to the Nasdaq Capital Market, provided that it meets the continued listing requirement for market value of publicly held shares and all other initial listing standards of the Nasdaq Capital Market, with the exception of the Minimum Bid Price Rule. In addition, the Company would also be required to notify Nasdaq of its intent to cure the minimum bid price deficiency, which may include, if necessary, implementing a reverse stock split. However, if it appears to Nasdaq that we will not be able to cure the deficiency, or if we do not meet the other listing standards, Nasdaq could provide notice that the common stock will become subject to delisting. In the event we receive notice that our common stock is being delisted, Nasdaq rules permit us to appeal any delisting determination by Nasdaq to a Hearings Panel (the "Panel"). We expect that our common stock would remain listed pending the Panel's decision. However, there can be no assurance that, if we do appeal the delisting determination by Nasdaq to the Panel, that such appeal would be successful, or that we will be able to regain compliance with the Minimum Bid Price Rule or maintain compliance with the other listing requirements.

If we fail to effect a reverse stock split, thus regaining compliance with the Minimum Bid Price Rule, our common stock may be delisted. Delisting from the Nasdaq Global Market or any Nasdaq market could make trading our common stock more difficult for investors, potentially leading to declines in our share price and liquidity. In addition, without a Nasdaq market listing, stockholders may have a difficult time getting a quote for the sale or purchase of our common stock, the sale or purchase of our common stock would likely be made more difficult and the trading volume and liquidity of our common stock could decline. Delisting from Nasdaq could also result in negative publicity and could also make it more difficult for us to raise additional capital. The absence of such a listing may adversely affect the acceptance of our common stock as currency or the value accorded by other parties. Further, if we are delisted, we would also incur additional costs under state blue sky laws in connection with any sales of our securities. These requirements could severely limit the market liquidity of our common stock and the ability of our stockholders to sell our common stock in the secondary market. If our common stock is delisted by Nasdaq, our common stock may be eligible to trade on an over-the-counter quotation system, such as the OTCQB market, where an investor may find it more difficult to sell our common stock or obtain accurate quotations as to the market value of our common stock. We cannot assure you that our common stock, if delisted from Nasdaq, will be listed on another national securities exchange or quoted on an over-the counter quotation system. If our common stock is delisted, it may come within the definition of "penny stock" as defined in the Exchange Act, and would be covered by Rule 15g-9 of the Exchange Act. That Rule imposes additional sales practice requirements on broker-dealers who sell securities to persons other than established customers and accredited investors. For transactions covered by Rule 15g-9, the broker-dealer must make a special suitability determination for the purchaser and receive the purchaser's written agreement to the transaction prior to the sale. Consequently, Rule 15g-9, if it were to become applicable, would affect the ability or willingness of broker-dealers to sell our securities, and accordingly would affect the ability of stockholders to sell their securities in the public market. These additional procedures could also limit our ability to raise additional capital in the future.

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

Because we will continue to need additional capital in the future to continue to expand our business and our research and development activities, among other things, we may conduct additional equity offerings. For example, under the universal shelf registration statement filed by us in June 2020 and declared effective by the SEC in July 2020, we may offer and sell any combination of common stock, preferred stock, debt securities and warrants in one or more offerings, up to a cumulative value of $150 million. To date, we have approximately $54.5 million remaining under such universal shelf registration statement. 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. Our management is authorized to grant stock options and other equity-based awards to our employees, directors and consultants under our equity incentive plans. Grants under our equity incentive plans may also cause our stockholders to experience additional dilution, which could cause our stock price to fall. We may also issue shares of our common stock as consideration in mergers, acquisitions and other business development transactions. 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.

***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 the Loan Agreement. Regardless of the restrictions in the Loan Agreement 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.

**Risks of a General Nature**

***Litigation may substantially increase our costs and harm our business.***

We have been, are, and may in the future become, party to lawsuits including, without limitation, actions and proceedings in the ordinary course of business relating to our directors, officers, stockholders, intellectual property rights, employment matters and the safety or efficacy of our products, which will cause us to incur legal fees and other costs related thereto, including potential expenses for the reimbursement of legal fees of officers and directors under indemnification obligations. The expense of defending against such litigation may be significant and there can be no assurance that we will be successful in any defense. Further, the amount of time that may be required to resolve such lawsuits is unpredictable, and these actions may divert management's attention from the day-to-day operations of our business, which could adversely affect our business, results of operations, and cash flows. Our insurance carriers may deny coverage, may be inadequately capitalized to pay on valid claims, or our policy limits may be inadequate to fully satisfy any damage awards or settlements. If this were to happen, the payment of any such awards could have a material adverse effect on our consolidated operations, cash flows and financial position. Additionally, any such claims, whether or not successful, could damage our reputation and business. Litigation is subject to inherent uncertainties, and an adverse result in such matters that may arise from time to time could have a material adverse effect on our business, results of operations, and financial condition. Please see "Part I.—Item 3. Legal Proceedings" for additional information about pending legal proceedings.

***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 Complete Response Letters, Warnings Letters, such as the Warning Letter we received from the FDA on February 11, 2021, negative clinical results, a negative vote or decision by an FDA advisory committee, or other negative feedback from the FDA, EMA, 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. Following receipt of the FDA's Warning Letter, a securities class action complaint was filed against us and two of our officers on June 8, 2021 in the United States District Court for the Northern District of California. The amended securities class action complaint, which was filed on March 7, 2022, named a third officer as a defendant. On July 6, 2021, September 30, 2021, October 26, 2021 and November 17, 2021, four purported shareholder derivative complaints were filed in the United States District Court for the Northern District of California asserting state and federal claims based on the same alleged misstatements as the securities class action complaint. On December 6, 2021, the Court entered an order consolidating all four actions and staying the consolidated action pending the outcome of any motion to dismiss the securities class action. Please see "Part I.—Item 3. Legal Proceedings" for additional information about these pending legal proceedings. Securities-related class action litigation often is expensive and diverts management's attention and our financial resources, which could harm our business. Additional lawsuits related to the pending litigation may follow. Moreover, if AcelRx experiences a decline in its stock price, we could face additional securities class action lawsuits.

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

As of December 31, 2021, we had federal net operating loss carryforwards of $308.5 million, of which $114.9 million federal net operating losses generated before January 1, 2018 will begin to expire in 2029. Federal net operating losses of $193.6 million generated after January 1, 2018 will carryforward indefinitely but are subject to the 80% taxable income limitation. As of December 31, 2021, we had state net operating loss carryforwards of $154.7 million, which begin to expire in 2028. Our ability to use our federal and state net operating losses to offset potential future taxable income and related income taxes that would otherwise be due is dependent upon our generation of future taxable income before the expiration dates of the net operating losses, and we cannot predict with certainty when, or whether, we will generate sufficient taxable income to use all of our net operating losses. Federal net operating losses generated prior to 2018 will continue to be governed by the net operating loss tax rules as they existed prior to the adoption of the Tax Cuts and Jobs Act of 2017, or Tax Act, which means that generally they will expire 20 years after they were generated if not used prior thereto. Many states have similar laws. Accordingly, our federal and state net operating losses could expire unused and be unavailable to offset future income tax liabilities. Under the newly enacted Tax Act as modified by CARES Act, federal net operating losses incurred in tax years beginning after December 31, 2017 and before January 1, 2021 may be carried back to each of the five tax years preceding such loss, and federal net operating losses arising in tax years beginning after December 31, 2020 may not be carried back. Moreover, federal net operating losses generated in tax years ending after December 31, 2017 may be carried forward indefinitely, but the deductibility of such federal net operating losses is limited to 80% of current year taxable income for tax years beginning after December 31, 2020.

In addition, 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 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.

***Our effective tax rate may fluctuate, and we may incur obligations in tax jurisdictions in excess of accrued amounts.***

We are subject to taxation in numerous U.S. states and territories. As a result, our effective tax rate is derived from a combination of applicable tax rates in the various places that we operate. In preparing our financial statements, we estimate the amount of tax that will become payable in each of such places. Nevertheless, our effective tax rate may be different than experienced in the past due to numerous factors, including passage of the newly enacted federal income tax law, changes in the mix of our profitability from state to state, the results of examinations and audits of our tax filings, our inability to secure or sustain acceptable agreements with tax authorities, changes in accounting for income taxes and changes in tax laws. Any of these factors could cause us to experience an effective tax rate significantly different from previous periods or our current expectations and may result in tax obligations in excess of amounts accrued in our financial statements.

**Item 1B. Unresolved Staff Comments**

None.

**Item 2. Properties**

We lease approximately 13,322 square feet of office space in Hayward, California under a sublease agreement that expires on January 30, 2023. We believe that our facilities are adequate to meet our current needs.

**Item 3. Legal Proceedings**

From time to time we may be involved in legal proceedings relating to intellectual property, commercial, employment and other matters arising in the ordinary course of business. Such matters are subject to uncertainty and there can be no assurance that such legal proceedings will not have a material adverse effect on our business, results of operations, financial position or cash flows. Please see the matters under the caption "Part II.—Item 8. Financial Statements and Supplementary Data—Note 12. Commitments and Contingencies—Litigation."

**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 traded on The Nasdaq Global Market since February 11, 2011 under the symbol "ACRX". As of March 7, 2022, there were 40 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 Agreement. Regardless of the restrictions in our Loan Agreement 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. Reserved

**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 and analysis generally covers our financial condition and results of operations for the year ended December 31, 2021, including year-over-year comparisons versus the year ended December 31, 2020. Our Annual Report on Form 10-K for the year ended December 31, 2020 includes a discussion and analysis of our financial condition and results of operations for the year ended December 31, 2019 in Item 7 of Part II, "Management's Discussion and Analysis of Financial Condition and Results of Operations." This discussion and other parts of this Annual Report on Form 10-K contain forward-looking statements that involve risks and uncertainties, such as statements regarding our plans, objectives, expectations, intentions, and projections. Our actual results could differ materially from those discussed in these forward-looking statements. Factors that could cause or contribute to such differences include, but are not limited to, those discussed in "Part I, Item 1A - Risk Factors" of this Annual Report on Form 10-K.*

**Overview**

We are a specialty pharmaceutical company focused on the development and commercialization of innovative therapies for use in medically supervised settings. Our portfolio of products and product candidates consists of sufentanil sublingual products and product candidates, pre-filled syringe product candidates, and nafamostat product candidates as further described in "Item 1. Business."

On July 14, 2021, we entered into a License and Commercialization Agreement, or the PFS Agreement, with Laboratoire Aguettant, or Aguettant, pursuant to which we obtained the exclusive right to develop and, subject to FDA approval, commercialize in the United States (i) an ephedrine pre-filled syringe containing 10 ml of a solution of 3 mg/ml ephedrine hydrochloride for injection, and (ii) a phenylephrine pre-filled syringe containing 10 ml of a solution of 50 mcg/ml phenylephrine hydrochloride for injection. Aguettant is entitled to receive up to $24 million in sales-based milestone payments.

On July 14, 2021, we also entered into a License and Commercialization Agreement, or the DZUVEO Agreement, with Aguettant pursuant to which Aguettant obtained the exclusive right to develop and commercialize DZUVEO in the European Union, Norway, Iceland, Liechtenstein, Andorra, Vatican City, Monaco, Switzerland and the United Kingdom, or the DZUVEO Territory, for the management of acute moderate to severe pain in adults in medically monitored settings. We are entitled to receive up to €47.0 million in a combination of up-front and sales-based milestone payments, of which we received €2.5 million, or approximately $2.9 million, in 2021. Refer to Note 5 "In-license Agreements" and Note 6 "Out-license Agreements—DZUVEO" in the accompanying notes to the Consolidated Financial Statements for additional information.

On January 7, 2022, we acquired Lowell Therapeutics, Inc., or Lowell, in a transaction for consideration of approximately $32.5 million plus net cash acquired and certain other adjustments, and includes approximately $26.0 million of contingent consideration payable in cash or stock at AcelRx's option, upon the achievement of regulatory and sales-based milestones. For additional information regarding the acquisition of Lowell, see Note 19. "Subsequent Events" in the accompanying notes to the Consolidated Financial Statements.

We are further developing a distribution capability and commercial organization to continue to market and sell DSUVIA in the United States. In geographies where we decide not to commercialize ourselves, we may seek to out-license commercialization rights. We currently intend to commercialize and promote DSUVIA/DZUVEO outside the United States and Europe with one or more strategic partners.

***Product Development Programs***

Our product development portfolio features two innovative therapies for the treatment of acute pain, two ready-to-use pre-filled syringe product candidates (ephedrine and phenylephrine), Niyad (a regional anticoagulant for the dialysis circuit) and LTX-608 (a proprietary nafamostat formulation for direct IV infusion as an anti-viral treatment for COVID-19, for disseminated intravascular coagulation, or DIC, for acute respiratory distress syndrome, or ARDS, and for acute pancreatitis). Please refer to "Part I. Item 1. Business—Our Portfolio" for a detailed discussion of our approved products and product candidates.

***Distribution Agreement***

Our distribution agreement, or the Distribution Agreement, with Zimmer Biomet Dental, or ZB Dental, provided ZB Dental the exclusive right to promote, market, sell, and arrange to distribute DSUVIA in the United States to clinicians, dentists, surgeons and other licensed health care practitioners that perform dental (including specialty dental), oral-maxillofacial, cranio-maxillofacial or oral surgery procedures, or Professionals, and their respective institutions and facilities that are permitted to use DSUVIA. On February 15, 2022, we amended the Distribution Agreement to remove the exclusivity provided to ZB Dental, allowing us to promote, market, sell and distribute DSUVIA in the specified classes of trade. The dental and oral-maxillofacial surgery markets have similar characteristics to the other office-based procedures on which we are currently focusing the majority of our commercial efforts.

**General Trends and Outlook**

***COVID-19-related***

Government-mandated orders and related safety policies on account of the COVID-19 pandemic continue to prevent us from operating our business in the normal course. Beginning in early 2020, state and local officials issued orders in response to the pandemic which included, among other things, requirements for residents to shelter in place and for non-essential businesses to cease activities at facilities within certain cities, counties, and states. State and local officials have taken different approaches to these orders, and some have not issued any such orders. Once issued, the orders have been relaxed and then tightened, depending on the rate of COVID-19 cases. As a result of these orders, we implemented a work from home policy for our California-based employees and we continue to adhere to the various and diverse orders issued by government officials in the jurisdictions in which we operate. In addition, some hospitals, ambulatory surgery centers and other healthcare facilities have barred visitors that are not caregivers or mission-critical and otherwise restricted access to such facilities. As a result, the educational and promotional efforts of our commercial and medical affairs personnel have been substantially reduced, and in some cases, stopped. Cancellation or delays of formulary committee meetings and delays of elective surgeries have also affected the pace of formulary approvals and, consequently, the rate of adoption and use of DSUVIA. We expect our near-term sales volumes to continue to be adversely impacted as long as access to healthcare facilities by our commercial and medical affairs personnel continues to be limited, especially in light of the rise in COVID-19 cases associated with the emerging variants. We will continue to evaluate the impact on our revenues and related metrics and operating expenses during this period and assess the need to adjust our expenses and expectations.

As a result of COVID-19 and related international travel restrictions, in addition to the testing requirements of our vendor, the timing for testing and acceptance of our DSUVIA fully automated packaging line, and subsequent FDA approval, has been delayed. Based on our best estimate, now that the line has been installed, we expect FDA approval in the first half of 2023.

We will continue to engage with various elements of our supply chain and distribution channel, including our customers, contract manufacturers, and logistics and transportation providers, to meet demand for products and to remain informed of any challenges within our supply chain. We continue to monitor demand and intend to adapt our plans as needed to continue to drive our business and meet our obligations during the evolving COVID-19 pandemic. However, if the COVID-19 pandemic continues and persists for an extended period of time, we may face disruptions to our supply chain and operations, and associated delays in the manufacturing and supply of our products. Such supply disruptions may adversely impact our ability to generate sales of and revenues from our products and our business, financial condition, results of operations and growth prospects could be adversely affected.

As the global pandemic of COVID-19 continues to rapidly evolve, it could result in a significant long-term disruption of global financial markets, reducing our ability to access capital, which could in the future negatively affect our liquidity. The extent to which the COVID-19 pandemic impacts our business, our ability to generate sales of and revenues from our approved products, and our future clinical development and regulatory efforts will depend on future developments that are highly uncertain and cannot be predicted with confidence, such as the ultimate geographic spread of the disease, the duration of the outbreak, travel restrictions, quarantines and social distancing requirements in the United States and other countries, business closures or business disruptions and the effectiveness of actions taken in the United States and other countries to contain and treat the virus.

***Department of Defense***

In April 2020, DSUVIA achieved Milestone C approval by the Department of Defense, or DoD, a decision that clears the path for the DoD to begin placing orders for DSUVIA for inclusion in all Army Sets, Kits, and Outfits, or SKOs, for deployed/deploying troops. This SKO fulfillment is dependent on the Army’s completion of their product information package including instructions on fulfillment and training which remains in process. In September 2020, we announced that DSUVIA was added to the DoD Joint Deployment Formulary, a core list of pharmaceutical products that are designated for deploying military units across all service branches. Also in September 2020, the U.S. Army awarded AcelRx with an initial contract of up to $3.6 million over the next four years for the purchase of DSUVIA to support a DoD-sponsored study to aid the development of clinical practice guidelines. We believe that study will initiate clinically in 2022. Since the fourth quarter of 2020, DSUVIA orders are being fulfilled for the Army Prepositioned Stock Program, or APS. The aforementioned clinical and APS orders are separate from the planned SKO fulfillment.

**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 commercialization activities to support the U.S. launch of DSUVIA, support European sales of DZUVEO by Aguettant, and of Zalviso by any replacement partner, and fund any future research and development activities needed to support the FDA regulatory review of our product candidates.

We will incur capital expenditures related to our fully automated packaging line for DSUVIA, which has now been installed, and for which we expect FDA approval in the first half of 2023. We anticipate that the fully automated line for DSUVIA will contribute to a significant decrease in costs of goods sold in 2023 and beyond.

Our net losses were $35.1 million and $40.4 million for the years ended December 31, 2021 and 2020, respectively. As of December 31, 2021, we had an accumulated deficit of $473.6 million. As of December 31, 2021, we had cash, cash equivalents and short-term investments totaling $51.6 million compared to $42.9 million as of December 31, 2020.

**Critical Accounting Estimates**

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 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 from Contracts with Customers***

We follow the provisions of ASC Topic 606, *Revenue from Contracts with Customers*. The guidance provides a unified model to determine how revenue is recognized. We recognize revenue upon transfer of control of promised products or services to customers in an amount that reflects the consideration we expect to receive in exchange for those products or services. We sell our products primarily through wholesale and specialty distributors.

In determining the appropriate amount of revenue to be recognized as we fulfill our obligations under our agreements, we perform the following steps: (i) identification of the promised goods or services in the contract; (ii) determination of whether the promised goods or services are performance obligations, including whether they are distinct in the context of the contract; (iii) measurement of the transaction price, including the constraint on variable consideration; (iv) allocation of the transaction price to the performance obligations based on estimated selling prices; and (v) recognition of revenue when (or as) we satisfy each performance obligation.

Product sales revenue

We sell our product primarily through distributors. Revenues from product sales are recognized when distributors obtain control of our product, which occurs at a point in time, upon delivery to such distributors. These distributors subsequently resell the product to certified medically supervised healthcare settings. In addition to distribution agreements with these customers, we enter into arrangements with group purchasing organizations, or GPOs, and other certified medically supervised healthcare settings that provide for privately negotiated discounts with respect to the purchase of our products. For revenue recognition under bill-and-hold arrangements, wherein the customer agrees to buy product from us but requests delivery at a later date, we deem that control passes to the customer when the product is ready for delivery. We recognize revenue under these types of arrangements when a signed agreement is in place, the transaction is billable, the customer has significant risk and rewards for the product and the ability to direct the asset, the product has been set aside specifically for the customer, and the product cannot be redirected to another customer. Revenue from product sales is recorded at the transaction price, net of estimates for variable consideration consisting of chargebacks, government rebates, returns, distribution fees and GPO fees. Variable consideration is recorded at the time product sales are recognized resulting in a reduction in product revenue. The amount of variable consideration that is included in the transaction price may be constrained and is included in the net sales price only to the extent that it is probable that a significant reversal in the amount of the cumulative revenue recognized will not occur in a future period. Variable consideration is estimated using the most-likely amount method, which is the single-most likely outcome under a contract and is typically at the stated contractual rate. Where appropriate, these estimates take into consideration a range of possible outcomes that are probability-weighted in accordance with the expected value method under ASC Topic 606 for relevant factors. These factors include current contractual and statutory requirements, specific known market events and trends, industry data, and/or forecasted customer buying and payment patterns. Actual amounts of consideration ultimately received may differ from our estimates. If actual results vary materially from our estimates, we will adjust these estimates, which will affect revenue from product sales and earnings in the period such estimates are adjusted. These estimates include:

Chargebacks - Our customers subsequently resell our product to qualified healthcare providers. In addition to distribution agreements with customers, we enter into arrangements with qualified healthcare providers that provide discounts with respect to the purchase of our product. Chargebacks represent the estimated obligations resulting from contractual commitments to sell product to qualified healthcare providers at prices lower than the list prices charged to customers who directly purchase the product from us. Customers charge us for the difference between what they pay for the product and the ultimate selling price to the qualified healthcare providers. These reserves are established in the same period that the related revenue is recognized, resulting in a reduction of product revenue-related accrued liabilities on the Consolidated Balance Sheets. Chargeback amounts are determined at the time of resale to the qualified healthcare providers by customers, and we issue credits for such amounts generally within a few weeks of the customer's notification to us of the resale. Reserves for chargebacks consists of credits that we expect to issue for units that remain in the distribution channel inventories at each reporting period end that we expect will be sold to the qualified healthcare providers, and chargebacks for units that our customers have sold to the qualified healthcare providers, but for which credits have not been issued.

Government Rebates - We are subject to discount obligations under state Medicaid programs. We estimate our Medicaid rebates and record them in the same period the related product revenue is recognized, resulting in a reduction of product revenue and the establishment of a current liability that is included in accrued liabilities on the Consolidated Balance Sheets.

Returns - We allow our distributors to return product for credit 6 months prior to, and up to 12 months after, the product expiration date. As such, there may be a significant period of time between the time the product is shipped and the time the credit is issued on returned product.

Distribution Fees - Distribution fees include fees paid to certain customers for sales order management, data and distribution services. Distribution fees are recorded as a reduction of revenue in the period the related product revenue is recognized.

GPO Fees - We pay administrative fees to GPOs for services and access to data. These fees are based on contracted terms and are paid after the quarter in which the product was purchased by the GPOs' members.

Trade Discounts and Allowances - We provide our customers with discounts which include early payment incentives that are explicitly stated in our contracts and are recorded as a reduction of revenue in the period the related product revenue is recognized.

We believe our estimated allowances for chargebacks, government rebates and product returns require a high degree of judgment and are subject to change based on our limited experience and certain quantitative and qualitative factors. We believe our estimated allowances for distribution fees, GPO fees and trade discounts and allowances do not require a high degree of judgment because the amounts are settled within a relatively short period of time. We will continue to assess our estimates of variable consideration as we accumulate additional historical data and will adjust these estimates accordingly. Changes in product revenue allowance estimates could materially affect our results of operations and financial position.

Contract and other collaboration revenue

We entered into award contracts with the DoD to support the development of DSUVIA. These contracts provided for the reimbursement of qualified expenses for research and development activities. Revenue under these arrangements was recognized when the related qualified research expenses were incurred. We were entitled to reimbursement of overhead costs associated with the study costs under the DoD arrangements. We estimated this overhead rate by utilizing forecasted expenditures. Final reimbursable overhead expenses were dependent on direct labor and direct reimbursable expenses throughout the life of each contract, which increased or decreased based on actual expenses incurred.

We also generate revenue from collaboration agreements. These agreements typically include payments for upfront signing or license fees, cost reimbursements for development and manufacturing services, milestone payments, product sales, and royalties on licensee's future product sales. Product sales related revenue under these collaboration agreements is classified as product sales revenue, while other revenue generated from collaboration agreements is classified as contract and other collaboration revenue.

*Performance Obligations*

A performance obligation is a promise in a contract to transfer a distinct good or service to the customer and is the unit of account in ASC Topic 606. Our performance obligations include delivering product to our distributors, commercialization license rights, development services, services associated with the regulatory approval process, joint steering committee services, demonstration devices, manufacturing services, material rights for discounts on manufacturing services, and product supply.

We have optional additional items in contracts, which are considered marketing offers and are accounted for as separate contracts when the customer elects such options. Arrangements that include a promise for future commercial product supply and optional research and development services at the customer's or our discretion are generally considered as options. We assess if these options provide a material right to the licensee and if so, such material rights are accounted for as separate performance obligations. If we are entitled to additional payments when the customer exercises these options, any additional payments are recorded in revenue when the customer obtains control of the goods or services.

*Transaction Price*

We have both fixed and variable consideration. Non-refundable upfront fees and product supply selling prices are considered fixed, while milestone payments are identified as variable consideration when determining the transaction price. Funding of research and development activities is considered variable until such costs are reimbursed at which point, they are considered fixed. We allocate the total transaction price to each performance obligation based on the relative estimated standalone selling prices of the promised goods or services for each performance obligation.

At the inception of each arrangement that includes milestone payments, we evaluate whether the milestones are considered probable of being achieved and estimate the amount to be included in the transaction price using the most likely amount method. If it is probable that a significant revenue reversal would not occur, the value of the associated milestone (such as a regulatory submission by us) is included in the transaction price. Milestone payments that are not within our control, such as approvals from regulators, are not considered probable of being achieved until those approvals are received.

For arrangements that include sales-based royalties, including milestone payments based on the level of sales, and the license is deemed to be the predominant item to which the royalties relate, we recognize revenue at the later of (a) when the related sales occur, or (b) when the performance obligation to which some or all of the royalty has been allocated has been satisfied (or partially satisfied).

*Allocation of Consideration*

As part of the accounting for these arrangements, we must develop assumptions that require judgment to determine the stand-alone selling price of each performance obligation identified in the contract. Estimated selling prices for license rights and material rights for discounts on manufacturing services are calculated using an income approach model and can include the following key assumptions: the development timeline, sales forecasts, costs of product sales, commercialization expenses, discount rate, the time which the manufacturing services are expected to be performed, and probabilities of technical and regulatory success. For all other performance obligations, we use a cost-plus margin approach.

*Timing of Recognition*

Significant management judgment is required to determine the level of effort required under an arrangement and the period over which we expect to complete our performance obligations under the arrangement. We estimate the performance period or measure of progress at the inception of the arrangement and re-evaluate it each reporting period. This re-evaluation may shorten or lengthen the period over which revenue is recognized. Changes to these estimates are recorded on a cumulative catch-up basis. If we cannot reasonably estimate when our performance obligations either are completed or become inconsequential, then revenue recognition is deferred until we can reasonably make such estimates. Revenue is then recognized over the remaining estimated period of performance using the cumulative catch-up method. Revenue is recognized for products at a point in time when control of the product is transferred to the customer in an amount that reflects the consideration we expect to be entitled to in exchange for those product sales, which is typically once the product physically arrives at the customer, and for licenses of functional intellectual property at the point in time the customer can use and benefit from the license. For performance obligations that are services, revenue is recognized over time proportionate to the costs that we have incurred to perform the services using the cost-to-cost input method.

***Inventories***

Inventories are valued at the lower of cost or net realizable value. 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. DSUVIA was approved by the FDA in November 2018. Prior to FDA approval, all manufacturing costs for DSUVIA were expensed to research and development. Upon FDA approval, manufacturing costs for DSUVIA manufactured for commercial sale have been capitalized.

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 net realizable value approach as that used to value the inventory. Because the predetermined, contractual transfer prices we received from Grünenthal GmbH, or Grünenthal, were less than the direct costs of manufacturing, all Zalviso inventories were carried at net realizable value.

***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 former commercial partner, Grünenthal pursuant to the Collaboration and License Agreement, dated as of December 16, 2013, as amended, to PDL BioPharma, Inc., or PDL, for an upfront cash purchase price of $65.0 million. 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 effective 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 ARPI LLC and paid to PDL, up to a capped amount of $195.0 million, over the life of the arrangement. The aggregate future estimated royalty and milestone payments (subject to the capped amount), less the $61.2 million of net proceeds we received, are 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 related to the Royalty Monetization accordingly.

During the three months ended June 30, 2020, Grünenthal notified us that it was terminating the Amended License Agreement, effective November 13, 2020. The terms of the Grünenthal Agreements were extended to May 2021 to enable Grünenthal to sell down its Zalviso inventory, a right it had under the Grünenthal Agreements. The rights to market and sell Zalviso in the Territory reverted back to us in May 2021.

There is a continuing obligation on our part, through the term of the Royalty Monetization, to use commercially reasonable efforts to negotiate a replacement license agreement, or New Arrangement. However, without a New Arrangement to commercialize Zalviso in Europe, we are currently unable to reliably estimate the future payments to SWK Funding LLC, or SWK, (assignee of PDL) over the remaining life of the Royalty Monetization. If we are unable to find a New Arrangement, a contingent gain of up to approximately $64 million may be recognized when it is realized upon expiration of the liability at the end of the Royalty Monetization term. Due to the significant judgments and factors related to the estimates of future payments under the Royalty Monetization, there are significant uncertainties surrounding the amount and timing of future payments and the probability of realization of the estimated contingent gain.

We will record non-cash royalty revenues and non-cash interest (income) expense within our Consolidated Statements of Operations over the term of the Royalty Monetization.

When the expected payments under the Royalty Monetization are lower than the gross proceeds of $65.0 million received, we defer recognition of any probable contingent gain until the Royalty Monetization liability expires.

**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 commercial launch of DSUVIA, our research and development efforts, variations in the level of expenditures related to commercial launch, development efforts and debt service obligations during any given period, and the uncertainty as to the extent and magnitude of the impact from the COVID-19 pandemic. 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. In particular, to the extent our commercial and medical affairs personnel continue to be subject to varying levels of restriction on accessing hospitals and ambulatory surgical centers due to COVID-19, and to the extent government authorities and certain healthcare providers are continuing to limit elective surgeries, we expect our sales volume to be adversely affected.

***Years Ended December 31, 2021 and 2020***

*Revenue*

Product Sales Revenue

Product sales revenue consists of sales of DSUVIA in the U.S. and, prior to May 13, 2021, Zalviso in Europe.

Product sales revenue by product for the years ended December 31, 2021 and 2020, was as follows (in thousands, except percentages):

| | Years Ended December 31, | | $ Change | % Change |
|---|---|---|---|---|
| | 2021 | 2020 | 2021 vs. 2020 | 2021 vs. 2020 |
| DSUVIA | $ 735 | $ 1,409 | $ (674) | (48)% |
| Zalviso | 270 | 1,112 | (842) | (76)% |
| Total product sales revenue | $ 1,005 | $ 2,521 | $ (1,516) | (60)% |

The decrease in product sales revenue for the year ended December 31, 2021, as compared to the year ended December 31, 2020, was primarily the result of a significant purchase from the Department of Defense in the third quarter of 2020 and the termination of the Collaboration and License Agreement and the Manufacture and Supply Agreement, or the Grünenthal Agreements, pursuant to which Grünenthal sold Zalviso in the European Union through May 12, 2021.

Contract and Other Collaboration Revenue

Contract and other collaboration revenue included revenue under the DZUVEO Agreement related to the upfront payment received in the third quarter of 2021, and prior to May 13, 2021, included revenue under the Grünenthal Agreements related to research and development services, non-cash royalty revenue related to the Royalty Monetization, and royalty revenue for sales of Zalviso in Europe.

Contract and other collaboration revenue for the years ended December 31, 2021 and 2020, was as follows (in thousands, except percentages):

| | Years Ended December 31, | | $ Change | % Change |
|---|---|---|---|---|
| | 2021 | 2020 | 2021 vs. 2020 | 2021 vs. 2020 |
| License revenue | $ 1,696 | $ — | $ 1,696 | 100% |
| Non-cash royalty revenue related to Royalty Monetization (See Note 10) | 83 | 242 | (159) | (66)% |
| Royalty revenue | 28 | 81 | (53) | (65)% |
| Other revenue | 6 | 2,572 | (2,566) | (100)% |
| Total contract and other collaboration revenue | $ 1,813 | $ 2,895 | $ (1,082) | (37)% |

On July 14, 2021, we granted Aguettant the license rights to DZUVEO in the European Union. Accordingly, for the year ended December 31, 2021, we recognized $1.7 million of the $2.9 million upfront fee as license revenue under the DZUVEO Agreement. As of December 31, 2021, we had current and non-current portions of deferred revenue under the DZUVEO Agreement of $0.1 million and $1.1 million, respectively. In May 2020, Grünenthal terminated the Grünenthal Agreements, accordingly the rights to market and sell Zalviso in Europe reverted back to us on May 12, 2021. Upon notification of early termination by Grünenthal, we recognized approximately $2.6 million of deferred revenue for the discount on Zalviso manufacturing services which were no longer a performance obligation.

*Cost of goods sold*

Total costs of goods sold for the years ended December 31, 2021 and 2020, were as follows (in thousands, except percentages):

| | Years Ended December 31, | | $ Change | % Change |
|---|---|---|---|---|
| | 2021 | 2020 | 2021 vs. 2020 | 2021 vs. 2020 |
| Direct costs | $ 1,204 | $ 1,900 | $ (696) | (37)% |
| Indirect costs | 2,549 | 4,132 | (1,583) | (38)% |
| Total costs of goods sold | $ 3,753 | $ 6,032 | $ (2,279) | (38)% |

Direct costs from contract manufacturers for DSUVIA and Zalviso totaled $1.2 million and $1.9 million in the years ended December 31, 2021 and 2020, respectively. Direct cost of goods sold for DSUVIA and Zalviso includes the inventory costs of the active pharmaceutical ingredient, or API, third-party contract manufacturing costs, estimated warranty costs, packaging and distribution costs, shipping, handling and storage costs.

We periodically evaluate the carrying value of inventory on hand for potential excess amounts over demand using the same lower of cost or net realizable value approach as that used to value the inventory. During the year ended December 31, 2021, we recorded inventory impairment charges of $0.8 million, primarily as a result of DSUVIA inventory that may expire before being sold. During the year ended December 31, 2020, we recorded inventory impairment charges of $0.7 million, of which $0.3 million related to the termination of the Grünenthal Agreements, and $0.4 million related to DSUVIA, primarily as a result of inventory that may expire before being sold.

The indirect costs to manufacture DSUVIA and Zalviso totaled $2.5 million and $4.1 million in the years ended December 31, 2021 and 2020, respectively. Indirect costs include internal personnel and related costs for purchasing, supply chain, quality assurance, depreciation and related expenses. We expect these indirect costs to represent a smaller percentage of revenue as our product sales increase.

*Research and Development Expenses*

The majority of our operating expenses to date have been for research and development activities related to Zalviso and DSUVIA. 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.

We expect to incur future research and development expenditures to support the FDA regulatory review of our product candidates and anticipated activities required for the development of our nafamostat product candidates, and the preparation and submission of the NDAs for our two in-licensed product candidates from Aguettant. The timing of the resubmission of the Zalviso NDA is in part dependent on the finalization of the FDA's new opioid approval guidelines and process.

We track external development expenses on a program-by-program basis. Our development resources are shared among all 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 for the years ended December 31, 2021 and 2020 (in thousands, except percentages):

| | Years Ended December 31, | | $ Change | % Change |
|---|---|---|---|---|
| | 2021 | 2020 | 2021 vs. 2020 | 2021 vs. 2020 |
| DSUVIA | $ 1,401 | $ 812 | $ 589 | 73% |
| Zalviso | 49 | 95 | (46) | (48)% |
| Other product candidates | 50 | — | 50 | 100% |
| Overhead | 2,595 | 3,110 | (515) | (17)% |
| Total research and development expenses | $ 4,095 | $ 4,017 | $ 78 | 2% |

Research and development expenses during the year ended December 31, 2021, as compared to the year ended December 31, 2020, increased by $0.1 million primarily due to increased Catalent manufacturing-related DSUVIA development expenses, partially offset by decreases in personnel-related overhead expenses and Zalviso-related spending.

*Selling, General and Administrative Expenses*

Selling, general and administrative expenses consisted primarily of salaries, benefits and stock-based compensation for personnel engaged in commercialization, administration, finance and business development activities. Other significant expenses included allocated facility costs and professional fees for general legal, audit and consulting services.

Total selling, general and administrative expenses for the years ended December 31, 2021 and 2020, were as follows (in thousands, except percentages):

| | Years Ended December 31, | | $ Change | % Change |
|---|---|---|---|---|
| | 2021 | 2020 | 2021 vs. 2020 | 2021 vs. 2020 |
| Selling, general and administrative expenses | $ 30,935 | $ 36,330 | $ (5,395) | (15)% |

Selling, general and administrative expenses decreased by $5.4 million during the year ended December 31, 2021, as compared to the year ended December 31, 2020. The decrease is primarily due to a $3.4 million reduction in personnel-related costs, a decrease in business development expenses of $0.8 million, a $0.8 million reduction in DSUVIA commercialization-related expenses, such as travel, and a $0.7 million decrease in legal fees, partially offset by an increase in other net selling, general and administrative expenses of $0.3 million.

In March 2020, we eliminated 30 positions, mainly within the commercial organization. For additional information regarding the Restructuring Costs see Note 1 “Organization and Summary of Significant Accounting Policies” in the notes to the Consolidated Financial Statements.

*Other Income (Expense)*

Total other income (expense) for the years ended December 31, 2021 and 2020, was as follows (in thousands, except percentages):

| | Years Ended December 31, | | $ Change | % Change |
|---|---|---|---|---|
| | 2021 | 2020 | 2021 vs. 2020 | 2021 vs. 2020 |
| Interest expense | $ (2,291) | $ (3,305) | $ 1,014 | (31)% |
| Interest income and other income (expense), net | 124 | 583 | (459) | (79)% |
| Non-cash interest income (expense) on liability related to sale of future royalties | 3,038 | 3,310 | (272) | (8)% |
| Total other income (expense) | $ 871 | $ 588 | $ 283 | 48% |

Interest expense consisted primarily of interest accrued or paid on our debt obligation agreements and amortization of debt discounts. Interest expense decreased for the year ended December 31, 2021, as compared to the year ended December 31, 2020, primarily as a result of a lower average outstanding loan balance. As of December 31, 2021, the outstanding balance due under the Loan Agreement with Oxford was $13.3 million. Refer to Note 8 “Long-Term Debt” in the notes to the Consolidated Financial Statements for additional information.

Interest income and other income (expense), net, for the years ended December 31, 2021 and 2020 primarily consisted of interest earned on our investments and the change in the fair value of our contingent put option. The decrease in interest income and other income (expense), net, in the year ended December 31, 2021, compared to the year ended December 31, 2020, was primarily due to lower yields on our investments and the change in the fair value of our contingent put option.

The non-cash interest income on the liability related to the sale of future royalties is attributable to the Royalty Monetization that we completed in September 2015. As described in Note 10 “Liability Related to Sale of Future Royalties”, the Royalty Monetization has been recorded as debt under the applicable accounting guidance. We 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.

The effective interest income rate for the years ended December 31, 2021 and 2020, was approximately 3.5% and 3.6%, respectively. We anticipate that we will record approximately $3 million in non-cash interest income related to the Royalty Monetization for the year ended December 31, 2022.

**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 2022 and may incur significant losses and negative cash flows from operations in the future. We have funded our operations primarily through issuance of equity securities, borrowings, payments from Grünenthal, monetization of certain future royalties and commercial sales milestones from the European sales of Zalviso by Grünenthal, funding of approximately $22.6 million from the DoD, and more recently with revenues from sales of DSUVIA since the commercial launch in the first quarter of 2019 and the upfront payment under the DZUVEO Agreement with Aguettant.

As of December 31, 2021, we had cash, cash equivalents and investments totaling $51.6 million, compared to $42.9 million as of December 31, 2020. The increase was primarily due to net proceeds received from the issuance of common stock and warrants in connection with equity offerings in the year ended December 31, 2021, partially offset by cash required to fund our continuing operations, including debt service, as we continued our commercialization activities for DSUVIA, including installation of our fully automated packaging line for DSUVIA, and business development activities. We anticipate that our existing capital resources will permit us to meet our capital and operational requirements for at least the next twelve months; however, our expectations may change depending on a number of factors including the extent and magnitude of the impact from the COVID-19 pandemic, in particular the negative impact on sales volumes as our sales force is limited in its access to potential customers, our expenditures related to the development of our product candidates and the United States commercial launch of DSUVIA, and the timing of business development activities. 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 November 17, 2021, we completed a registered direct offering in which we issued and sold 17,500,000 shares of our common stock at a price of $0.80 per share and warrants exercisable for an aggregate of 17,500,000 shares of our common stock at a price of $1.00 per share. The total net proceeds from this offering were approximately $13.9 million. As of December 31, 2021, the 17,500,000 warrants remain outstanding and will be exercisable following the six-month anniversary of the closing date of this offering and expire on November 15, 2026.

On January 22, 2021, we completed an underwritten public offering in which we issued and sold 14,500,000 shares of our common stock to the underwriter at a price of $1.7625 per share. On January 27, 2021, the underwriters exercised their option in full and purchased an additional 2,175,000 shares at a price of $1.7625 per share. The total net proceeds from this offering of an aggregate 16,675,000 shares were approximately $28.9 million.

On December 11, 2020, we completed a registered direct offering in which we issued and sold 8,333,333 shares of our common stock at a price of $1.20 per share. The total net proceeds from this offering were approximately $9.9 million.

On July 23, 2020, we completed a registered direct offering in which we issued and sold 9,433,962 shares of our common stock at a price of $1.06 per share. The total net proceeds from this offering were approximately $10.0 million.

We entered into a Controlled Equity Offering℠ Sales Agreement, or, as amended, the ATM Agreement, with Cantor Fitzgerald & Co., or Cantor, as agent, pursuant to which we may offer and sell, from time to time through Cantor, shares of our common stock. During the year ended December 31, 2021, we had issued and sold an aggregate of approximately 3.0 million shares of common stock pursuant to the ATM Agreement, for which we had received net proceeds of approximately $7.5 million, after deducting fees and expenses. During the year ended December 31, 2020, we issued and sold an aggregate of approximately 0.9 million shares of common stock pursuant to the ATM Agreement, for which we received net proceeds of approximately $1.4 million. As of December 31, 2021, we had the ability to sell approximately $36.1 million of our common stock under the ATM Agreement.

On May 30, 2019, we entered into the Loan Agreement with Oxford. Under the Loan Agreement, we borrowed an aggregate principal amount of $25.0 million under a term loan. After deducting all loan initiation costs and outstanding interest on the prior loan agreement with Hercules, we received $15.9 million in net proceeds. As of December 31, 2021, the outstanding balance under the Loan Agreement was $13.3 million. For more information, see Note 8 “Long-Term Debt” in the accompanying notes to the Consolidated Financial Statements.

On May 18, 2020, we received a notice from Grünenthal that it was exercising its right to terminate the Grünenthal Agreements. Certain terms of the Grünenthal Agreements were extended to May 2021 to enable Grünenthal to sell down its Zalviso inventory. Certain terms of the Grünenthal Agreements were further extended for a period of thirty days after the last Zalviso product distributed by Grünenthal prior to May 13, 2021 expires to enable the parties to manage applicable pharmacovigilance and other requirements. There is a continuing obligation on our part, through the term of the Royalty Monetization, to use commercially reasonable efforts to negotiate a New Arrangement. The Royalty Monetization will be repaid to SWK (assignee of PDL) over the life of the agreement through a portion of the European royalties and milestones received under the Grünenthal Agreements and any New Arrangement, if executed. For more information, see Note 10 “Liability Related to the Sale of Future Royalties” in the accompanying notes to the Consolidated Financial Statements.

Our cash and investment balances are held in a variety of interest-bearing instruments, including obligations of commercial paper, corporate debt securities, U.S. government sponsored enterprise debt securities and money market funds. Cash in excess of immediate requirements is invested with a view toward capital preservation and liquidity. We do not expect COVID-19 to have a material impact on our high quality, short-dated investments.

***Cash Flows***

| | Years Ended December 31, | |
|---|---|---|
| | **2021** | **2020** |
| Net cash used in operating activities | $ (30,002) | $ (38,505) |
| Net cash (used in)/provided by investing activities | (26,123) | 34,139 |
| Net cash provided by financing activities | 41,514 | 16,956 |

*Cash Flows from Operating Activities*

The primary use of cash for our operating activities during these periods was to fund commercial activities for our approved product, DSUVIA. Our cash used in 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 income (expense) related to the sale of future royalties and interest expense related to our debt financings.

Cash used in operating activities of $30.0 million during the year ended December 31, 2021, reflected a net loss of $35.1 million, partially offset by aggregate non-cash charges of $4.9 million and included an approximate $0.2 million net change in our operating assets and liabilities. Non-cash charges included $4.6 million for stock-based compensation expense, $3.0 million in non-cash interest income on the liability related to the Royalty Monetization, and $2.0 million in depreciation and amortization expense. The net change in our operating assets and liabilities included a $1.2 million increase in deferred revenue and a $0.9 million increase in prepaid expenses and other assets.

Cash used in operating activities of $38.5 million during the year ended December 31, 2020, reflected a net loss of $40.4 million, partially offset by aggregate non-cash charges of $4.2 million and included an approximate $2.3 million net change in our operating assets and liabilities. Non-cash charges included $4.4 million for stock-based compensation expense, $3.3 million in non-cash interest income on the liability related to the Royalty Monetization, $1.9 million in depreciation expense and $1.1 million in non-cash interest expense related to debt financing. The net change in our operating assets and liabilities included a $1.0 million increase in accounts payable and a $3.2 million decrease in deferred revenue.

*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, 2021, cash used in investing activities of $26.1 million was primarily the net result of $70.5 million for purchases of investments, $1.8 million for purchases of property and equipment, and $0.8 million in asset acquisition costs related to our acquisition of Lowell, partially offset by $47.0 million in proceeds from the sale and maturity of investments.

During the year ended December 31, 2020, cash provided by investing activities of $34.1 million was the net result of $80.6 million in proceeds from maturity of investments, offset by $44.6 million for purchases of investments and purchases of property and equipment of $1.9 million.

*Cash Flows from Financing Activities*

Cash flows from financing activities primarily reflect proceeds from the sale of our securities and payments made on debt financings.

During the year ended December 31, 2021, cash provided by financing activities of $41.5 million was primarily due to $50.3 million in net proceeds received in connection with equity financings, including the issuance of warrants and shares sold under our ATM Agreement, partially offset by $8.8 million used for payment of long-term debt.

During the year ended December 31, 2020, cash provided by financing activities was primarily due to $21.3 million in net proceeds received in connection with equity financings, and $0.4 million in net proceeds received through our equity plans, partially offset by $4.7 million used for payment of long-term debt.

***Capital Commitments and Capital Resources***

Our current operating plan includes expenditures related to the development of our product candidates and the continued launch of DSUVIA in the United States. This plan includes an assumption that COVID-19 related restrictions will not increase considerably, and includes anticipated activities required to resubmit the Zalviso NDA and anticipated activities required for the development of our nafamostat product candidates, and the preparation and submission of the NDAs for our two in-licensed product candidates from Aguettant. These assumptions may change as a result of many factors. We will continue to evaluate the work necessary to successfully launch DSUVIA and gain approval of our product candidates in the United States and intend to update our cash forecasts accordingly. Our forecast that our existing capital resources will permit us to meet our capital and operational requirements through at least the next twelve months is a forward-looking statement that involves risks and uncertainties, and actual results could vary materially.

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

- the impact and timing of COVID-19 on our operations, our sales representatives' access to hospitals or other healthcare facilities, and our level of sales;
- expenditures related to the launch of DSUVIA and potential commercialization of our product candidates, if approved;
- future manufacturing, selling and marketing costs related to DSUVIA and our product candidates, if approved, including our contractual obligations to Aguettant under the DZUVEO Agreement;
- costs associated with business development activities and licensing transactions;
- the outcome, timing and cost of the regulatory submissions for our product candidates, including our two in-licensed product candidates from Aguettant, and any approvals for our product candidates;
- the outcome, timing and cost of the development of our nafamostat product candidates;
- the initiation, progress, timing and completion of any post-approval clinical trials for DSUVIA, or our product candidates, if approved;
- 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, including the DZUVEO Agreement;
- delays that may be caused by changing regulatory requirements;
- 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 DSUVIA and our product candidates, if approved;

- the extent to which we acquire or invest in businesses, products and product candidates or technologies; and
- the expenses associated with litigation.

In the long-term, 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. 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 sustain our operations and continue our development programs.

Please see “Part II., Item 1A. Risk Factors—Risks Related to Our Financial Condition and Need for Additional Capital.”

We have material cash requirements and other contractual obligations related to our Loan Agreement with Oxford (as described in Note 8 “Long-Term Debt”), contract manufacturing services and office rent (as described in Note 9 “Leases” in the accompanying notes to the Consolidated Financial Statements) and the Royalty Monetization that we completed in September 2015 (as described in Note 10 “Liability Related to Sale of Future Royalties”).

**Item 7A. Quantitative and Qualitative Disclosures about Market Risk**

We are a smaller reporting company as defined by Rule 12b-2 of the Securities Exchange Act of 1934, as amended, or the Exchange Act, and are not required to provide the information specified under this item.

**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**

On July 15, 2021, WithumSmith+Brown, PC, an independent registered public accounting firm (Withum), acquired certain assets of OUM & Co. LLP (OUM), the independent registered public accounting firm for AcelRx Pharmaceuticals, Inc. (the Company) (the Transaction). As a result of this Transaction, on July 15, 2021, OUM resigned as the Company's independent registered public accounting firm. Concurrent with such resignation, the Company, with the approval of its Audit Committee, consented to the engagement of Withum as the Company's new independent registered public accounting firm, effective July 15, 2021.

Prior to the Transaction, the Company did not consult with Withum regarding the application of accounting principles to any specific completed or contemplated transaction or regarding the type of audit opinion that might be rendered by Withum on the Company's financial statements, and Withum did not provide any written or oral advice that was an important factor considered by the Company in reaching a decision as to any accounting, auditing or financial reporting issue.

OUM's Report of Independent Registered Public Accounting Firm (the Audit Report) on the Company's financial statements for the fiscal years ended December 31, 2020 and 2019 did not contain any adverse opinion or disclaimer of opinion and was not qualified or modified as to uncertainty, audit scope or accounting principles.

During the years ended December 31, 2020 and 2019, and during the interim period from the end of the most recently completed fiscal year through July 15, 2021, the date of resignation, there were no “disagreements” (as such term is defined in Item 304(a)(1)(iv) of Regulation S-K and the related instructions to Item 304) with OUM on any matter of accounting principles or practices, financial statement disclosure or auditing scope or procedures, which disagreements, if not resolved to the satisfaction of OUM would have caused it to make reference to such disagreement in its reports. During the fiscal years ended December 31, 2020 and 2019, and the subsequent interim period through July 15, 2021, there have been no “reportable events” (as such term is defined in Item 304 (a)(1)(v) of Regulation S-K).

**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, 2021.

**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, 2021 and has concluded that such internal control over financial reporting was effective.

This Annual Report does not include an attestation report of our registered public accounting firm regarding internal control over financial reporting. Management's report was not subject to attestation by our registered public accounting firm pursuant to the rules of the Securities and Exchange Commission applicable to smaller reporting companies that permit us to provide only management's report in this Annual Report.

**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, 2021.

**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 and our internal control over financial reporting are designed to provide reasonable, not absolute, assurance that the objectives of the control system are met. We continue to implement, improve and refine our disclosure controls and procedures and our internal control over financial reporting.

**Item 9B. Other Information**

None.

**Item 9C. Disclosure Regarding Foreign Jurisdictions that Prevent Inspections.**

Not applicable.

**PART III**

**Item 10. Directors, Executive Officers and Corporate Governance**

Information regarding our directors and executive officers set forth under the headings “Proposal No.1—Election of Directors,” “Information Regarding the Board of Directors and Corporate Governance,” and “Executive Officers of the Registrant” of the 2022 Proxy Statement is incorporated herein by reference.
Information regarding our Audit Committee, including the members of our Audit Committee, set forth under the heading “Information Regarding the Board of Directors and Corporate Governance—Audit Committee” of the 2022 Proxy Statement is incorporated herein by reference.

Information regarding the procedures by which our shareholders may recommend nominees to our Board of Directors set forth under the heading “Information Regarding the Board of Directors and Corporate Governance—Nominating and Corporate Governance Committee” of the 2022 Proxy Statement is incorporated herein by reference.

Information regarding our Code of Business Conduct and Ethics set forth under the heading “Information Regarding the Board of Directors and Corporate Governance—Code of Business Conduct and Ethics” of the 2022 Proxy Statement is incorporated herein by reference.

**Item 11. Executive Compensation**

Information regarding executive compensation and director compensation set forth under the headings “Executive Compensation” and “Director Compensation,” respectively, of the 2022 Proxy Statement is incorporated herein by reference.

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

Information contained in the sections captioned “Security Ownership of Certain Beneficial Owners and Management” and “Equity Compensation Plan Information” of the 2022 Proxy Statement is incorporated herein by reference.

**Item 13. Certain Relationships and Related Transactions and Director Independence**

Information contained in the section captioned “Related Person Transactions and Indemnification” of the 2022 Proxy Statement is incorporated herein by reference.

Information regarding director independence set forth under the heading “Information Regarding the Board of Directors and Corporate Governance” of the 2022 Proxy Statement is incorporated herein by reference.

**Item 14. Principal Accounting Fees and Services**

Information regarding our independent auditor fees and services in the section captioned “Proposal No. 2—Ratification of Selection of Independent Registered Public Accounting Firm” of the 2022 Proxy Statement is incorporated herein by reference.

**PART IV**

**Item 15. Exhibits and 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:

Reference is made to the financial statement schedules included under Item 8 of Part II hereof. All other schedules are omitted because they are not applicable, not required or the information is shown in the financial statements or the notes thereto.

(b) Exhibits

| Exhibit Number | Exhibit Description | Incorporation By Reference | | | |
|---|---|---|---|---|---|
| | | Form | SEC File No. | Exhibit | Filing Date |
| 2.1§ | Agreement and Plan of Merger, dated as of November 14, 2021, by and among the Registrant, Lowell, Merger Sub 1, Merger Sub 2 and the Stockholder Representative. | 10-Q | 001-35068 | 2.1 | 11/15/2021 |
| 3.1 | Amended and Restated Certificate of Incorporation of the Registrant. | 8-K | 001-35068 | 3.1 | 2/18/2011 |
| 3.2 | Certificate of Amendment of Amended and Restated Certificate of Incorporation of the Registrant. | 8-K | 001-35068 | 3.1 | 6/25/2019 |
| 3.3 | Amended and Restated Bylaws of the Registrant. | S-1 | 333-170594 | 3.4 | 1/7/2011 |
| 4.1 | Description of Capital Stock. | 10-K | 001-35068 | 4.1 | 3/15/2021 |
| 4.2 | Reference is made to Exhibits 3.1 through 3.3. | | | | |
| 4.3 | Specimen Common Stock Certificate of the Registrant. | S-1 | 333-170594 | 4.2 | 1/31/2011 |
| 4.4 | Form of Warrant to Purchase Common Stock of the Registrant, dated as of May 30, 2019. | 8-K | 001-35068 | 4.1 | 6/3/2019 |
| 4.5 | Form of Warrant to Purchase Common Stock of the Registrant, dated as of November 15, 2021. | 8-K | 001-35068 | 4.1 | 11/15/2021 |
| 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+ | 2011 Equity Incentive Plan. | S-8 | 333-172409 | 99.3 | 2/24/2011 |
| 10.3+ | 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 |
| 10.4+ | 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 |
| 10.5+ | Amended and Restated 2020 Equity Incentive Plan. | 8-K | 001-350683 | 10.1 | 6/17/2021 |
| 10.6+ | Forms of Stock Option Grant Notice, Stock Option Agreement and Notice of Exercise under the Amended and Restated 2020 Equity Incentive Plan. | S-8 | 333-239213 | 99.2 | 6/16/2020 |
| 10.7+ | Forms of RSU Award Grant Notice and Award Agreement (RSU Award) under the Amended and Restated 2020 Equity Incentive Plan. | S-8 | 333-239213 | 99.3 | 6/16/2020 |
| 10.8+ | Amended and Restated 2011 Employee Stock Purchase Plan. | S-8 | 333-239213 | 99.4 | 6/16/2020 |
| 10.9+ | 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 |
| 10.10+ | Amended and Restated Offer Letter between the Registrant and Pamela Palmer, dated December 29, 2010. | S-1 | 333-170594 | 10.16 | 1/7/2011 |
| 10.11+ | Offer Letter between the Registrant and Vincent J. Angotti, effective as of March 6, 2017. | 10-Q | 001-35068 | 10.4 | 5/8/2017 |
| 10.12+ | Offer Letter between the Registrant and Raffi Asadorian, dated July 18, 2017. | 8-K | 001-35068 | 10.1 | 7/19/2017 |
| 10.13+ | Non-Employee Director Compensation Policy. | | | | |

| Exhibit Number | Exhibit Description | Incorporation By Reference | | | |
|---|---|---|---|---|---|
| | | Form | SEC File No. | Exhibit | Filing Date |
| 10.14+ | Amended and Restated Severance Benefit Plan effective as of February 7, 2017. | 8-K | 001-35068 | 10.2 | 2/9/2017 |
| 10.15§ | Sublease for a Single Sublessee, dated March 26, 2021, by and between the Registrant and Weichert Workforce Mobility Inc., as successor in interest to The MI Group, Inc. | 10-Q | 001-35068 | 10.3 | 5/17/2021 |
| 10.16§# | License and Commercialization Agreement (DZUVEO), dated July 14, 2021, between the Registrant and Laboratoire Aguettant. | 10-Q | 001-35068 | 10.1 | 11/15/2021 |
| 10.17§# | License and Commercialization Agreement (PFS), dated July 14, 2021, between the Registrant and Laboratoire Aguettant. | 10-Q | 001-35068 | 10.2 | 11/15/2021 |
| 10.18 | Contingent Value Rights Agreement, dated as of January 7, 2022, by and among AcelRx Pharmaceuticals, Inc., James Wilkie, solely in his capacity as the representative of the Lowell stockholders and option holders, and Computershare Inc., and its wholly-owned subsidiary, Computershare Trust Company, N.A., a federally chartered trust company, collectively as Rights Agent | 8-K | 001-35068 | 10.1 | 1/12/2022 |
| 10.19§# | Commercial Supply Agreement, effective March 31, 2021 by and between the Registrant and Catalent Pharma Solutions, LLC. | 10-Q | 001-35068 | 10.1 | 8/16/2021 |
| 10.20 | Manufacturing Services Agreement between Registrant and Patheon Pharmaceuticals, Inc., dated as of January 18, 2013. | 10-Q | 001-35068 | 10.1 | 5/8/2013 |
| 10.21 | 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 |
| 10.22 | 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 |
| 10.23# | Amendment #1 to Manufacturing Services Agreement between the Registrant and Patheon Pharmaceuticals, Inc., effective as of January 19, 2016. | 10-Q | 001-35068 | 10.6 | 5/2/2016 |
| 10.24# | Amendment #2 to Manufacturing Services Agreement between the Registrant and Patheon Pharmaceuticals, Inc., effective as of August 4, 2017. | 10-Q | 001-35068 | 10.1 | 11/9/2017 |
| 10.25# | Purchase and Sale Agreement between Registrant and ARPI LLC, dated as of September 18, 2015. | 10-Q | 001-35068 | 10.6 | 11/3/2015 |
| 10.26# | Subsequent Purchase and Sale Agreement between ARPI LLC (a wholly owned subsidiary of the Registrant) and SWK Funding, LLC (assigned of PDL BioPharma, Inc.), dated as of September 18, 2015. | 10-Q | 001-35068 | 10.7 | 11/3/2015 |
| 10.27 | Controlled Equity Offering℠ Sales Agreement between the Registrant and Cantor Fitzgerald & Co., dated as of June 21, 2016. | 8-K | 001-35068 | 10.1 | 6/21/2016 |
| 10.28 | Amendment No. 1 to the Controlled Equity Offering℠ Sales Agreement between the Registrant and Cantor Fitzgerald & Co., dated as of August 29, 2020. | S-3 | 333-239156 | 1.3 | 6/12/2020 |

| Exhibit Number | Exhibit Description | Incorporation By Reference | | | |
|---|---|---|---|---|---|
| | | Form | SEC File No. | Exhibit | Filing Date |
| 10.29 | Loan and Security Agreement between the Registrant and Oxford Finance, LLC, dated as of May 30, 2019. | 8-K | 001-35068 | 10.1 | 6/3/2019 |
| 10.30 | First Amendment to Loan and Security Agreement between the Registrant and Oxford Finance, LLC, dated as of May 5, 2021. | 10-Q | 001-35068 | 10.4 | 11/15/2021 |
| 10.31 | Second Amendment to Loan and Security Agreement between the Registrant and Oxford Finance, LLC, dated as of November 14, 2021. | | | | |
| 10.32# | Agreement between the Registrant and SpecGX, LLC, dated June 16, 2017. | 10-Q | 001-35068 | 10.1 | 11/7/2019 |
| 10.33 | Amendment to Agreement between the Registrant and SpecGX, LLC, dated September 23, 2019. | 10-Q | 001-35068 | 10.2 | 11/7/2019 |
| 23.1 | Consent of Withum Smith & Brown, LLP, Independent Registered Public Accounting Firm. | | | | |
| 23.2 | Consent of OUM & Co. 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- the instance document does not appear in the Interactive Data File because its XBRL tags are embedded within the Inline XBRL document. | | | | |
| 101.SCH | Inline XBRL Taxonomy Schema Document | | | | |
| 101.CAL | Inline XBRL Taxonomy Calculation Linkbase Document | | | | |
| 101.DEF | Inline XBRL Taxonomy Definition Linkbase Document | | | | |
| 101.LAB | Inline XBRL Taxonomy Label Linkbase Document | | | | |

| Exhibit Number | Exhibit Description | Incorporation By Reference | | | |
|---|---|---|---|---|---|
| | | Form | SEC File No. | Exhibit | Filing Date |
| 101.PRE | Inline XBRL Taxonomy Presentation Linkbase Document | | | | |
| 104 | Cover Page Interactive Data File (formatted as inline XBRL with applicable taxonomy extension information contained in Exhibits 101.INS, 101.SCH, 101.CAL, 101.DEF, 101.LAB, and 101.PRE). | | | | |

§ Schedules omitted pursuant to Item 601(a)(5) of Regulation S-K. The Registrant agrees to furnish supplementally a copy of any omitted schedule upon request by the SEC.

+ Indicates management contract or compensatory plan.

# Material in the exhibit marked with am "[*]" has been omitted because it is confidential, not material, and would be competitively harmful if publicly disclosed.

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.

**Item 16. Form 10-K Summary**

None.

**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 10, 2022

**AcelRx Pharmaceuticals, Inc.**
(Registrant)

/s/ Vincent J. Angotti

**Vincent J. Angotti**
**Chief Executive Officer and Director**
**(Principal Executive Officer)**

/s/ Raffi Asadorian

**Raffi Asadorian**
**Chief Financial Officer**
**(Principal Financial and Accounting Officer)**

**POWER OF ATTORNEY**

KNOW ALL PERSONS BY THESE PRESENTS, that each person whose signature appears below constitutes and appoints Vincent J. Angotti and Raffi Asadorian, 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/ Vincent J. Angotti<br>**Vincent J. Angotti** | Chief Executive Officer and Director<br>*(Principal Executive Officer)* | March 10, 2022 |
| /s/ Raffi Asadorian<br>**Raffi Asadorian** | Chief Financial Officer<br>*(Principal Financial and Accounting Officer)* | March 10, 2022 |
| /s/ Adrian Adams<br>**Adrian Adams** | Chairman | March 10, 2022 |
| /s/ Richard Afable, M.D.<br>**Richard Afable, M.D.** | Director | March 10, 2022 |
| /s/ Marina Bozilenko<br>**Marina Bozilenko** | Director | March 10, 2022 |
| /s/ Jill Broadfoot<br>**Jill Broadfoot** | Director | March 10, 2022 |
| /s/ Mark G. Edwards<br>**Mark G. Edwards** | Director | March 10, 2022 |
| /s/ Stephen J. Hoffman, Ph.D., M.D.<br>**Stephen J. Hoffman, Ph.D., M.D.** | Director | March 10, 2022 |
| /s/ Pamela P. Palmer, M.D., Ph.D.<br>**Pamela P. Palmer, M.D., Ph.D.** | Director | March 10, 2022 |
| /s/ Howard B. Rosen<br>**Howard B. Rosen** | Director | March 10, 2022 |
| /s/ Mark Wan<br>**Mark Wan** | Director | March 10, 2022 |

**ACELRX PHARMACEUTICALS, INC.**

**INDEX TO CONSOLIDATED FINANCIAL STATEMENTS**

**Report of Independent Registered Public Accounting Firm**

To the Stockholders and the Board of Directors of
AcelRx Pharmaceuticals, Inc.
Hayward, California

**Opinion on the Financial Statements**

We have audited the accompanying consolidated balance sheet of AcelRx Pharmaceuticals, Inc. (the "Company") as of December 31, 2021, the related consolidated statements of operations, stockholders' deficit, and cash flows for the year ended December 31, 2021, and the related notes and schedule II (collectively referred to as the "consolidated financial statements"). In our opinion, the consolidated financial statements present fairly, in all material respects, the financial position of the Company as of December 31, 2021, and the results of its operations and its cash flows for the year ended December 31, 2021, in conformity with accounting principles generally accepted in the United States of America.

The consolidated financial statements of the Company as of and for the year ended December 31, 2020 were audited by OUM & Co. LLP, who joined WithumSmith+Brown, PC on July 15, 2021, and rendered their opinion on such statements on March 15, 2021.

**Basis for Opinion**

These consolidated financial statements are the responsibility of the Company's management. Our responsibility is to express an opinion on the Company's consolidated financial statements based on our audit. We are a public accounting firm registered with the Public Company Accounting Oversight Board (United States) ("PCAOB") and are required to be independent with respect to the Company in accordance with the U.S. federal securities laws and the applicable rules and regulations of the Securities and Exchange Commission and the PCAOB.

We conducted our audit in accordance with the standards of the PCAOB. Those standards require that we plan and perform the audit to obtain reasonable assurance about whether the consolidated financial statements are free of material misstatement, whether due to error or fraud. The Company is not required to have, nor were we engaged to perform, an audit of its internal control over financial reporting. As part of our audit we are required to obtain an understanding of internal control over financial reporting but not for the purpose of expressing an opinion on the effectiveness of the Company's internal control over financial reporting. Accordingly, we express no such opinion.

Our audit included performing procedures to assess the risks of material misstatement of the consolidated financial statements, whether due to error or fraud, and performing procedures that respond to those risks. Such procedures included examining, on a test basis, evidence regarding the amounts and disclosures in the consolidated financial statements. Our audit also included evaluating the accounting principles used and significant estimates made by management, as well as evaluating the overall presentation of the consolidated financial statements. We believe that our audit provides a reasonable basis for our opinion.

**Critical Audit Matters**

The critical audit matters communicated below are matters arising from the current period audit of the consolidated financial statements that were communicated or required to be communicated to the audit committee and that: (1) relate to accounts or disclosures that are material to the consolidated statements and (2) involved our especially challenging, subjective, or complex judgments. The communication of a critical audit matter does not alter in any way our opinion on the consolidated financial statements, taken as a whole, and we are not, by communicating the critical audit matters below, providing a separate opinion on the critical audit matters or on the accounts or disclosures to which they relate.

*Product Revenue Allowances for Chargebacks, Government Rebates and Product Returns*

*Description of the Matter*

As described in Note 1 to the consolidated financial statements, revenue from product sales is recognized net of estimates for variable consideration consisting of chargebacks, government rebates, returns, distribution fees, GPO fees and product returns. This variable consideration is recorded in the same period that the related revenue is recognized and creates variability for the consideration that the Company expects to receive. Liabilities related to government rebates and rebate programs of managed healthcare organizations involve the use of significant assumptions and judgments that include consideration of legal interpretations of applicable laws and regulations, historical claims experience, the payer channel mix, current contract prices, unbilled claims, claims submission time lags, and inventory levels in the distribution channel. Estimates for product returns consider existing return policies with customers, historical sales and return rates, inventory levels in the distribution channel, and product shelf lives.

Management's estimated allowance for chargebacks, government rebates, and product returns requires a high degree of judgment and is subject to change based on various quantitative and qualitative factors. Accordingly, extensive audit effort and a high degree of auditor judgment were needed to evaluate management's estimates and assumptions used in the determination of chargebacks, government rebates, and product returns.

*How We Addressed the Matter in Our Audit*

We obtained an understanding of and evaluated the design of controls relating to the Company's processes for estimating chargebacks, government rebates, and product returns.

We evaluated the significant accounting policies relating to chargebacks, government rebates, and product returns, as well as management's application of the policies, for appropriateness and reasonableness.

To test management's estimates of chargebacks, rebates and returns, we obtained management's calculations for the respective estimates and performed one or more of the following procedures: clerically tested the calculation, agreed relevant inputs to the terms of relevant contracts, performed retrospective reviews, performed a sensitivity analysis on the inputs and assumptions used in the estimates and assessed subsequent events, evaluated the methodologies and assumptions used and the underlying data used by the Company, evaluated the assumptions used by management against historical trends, evaluated the change in estimated accruals from the prior periods, and assessed the historical accuracy of the Company's estimates against actual results.

*Contract and Other Collaboration Revenue*

*Description of the Matter*

The Company recognized contract and other collaboration revenue of $1.8 million for the year ended December 31, 2021. As described in Note 1 to the consolidated financial statements, these arrangements may include payments for upfront signing or license fees, cost reimbursements for development and manufacturing services, milestone payments, revenue from product sales, and royalties on licensee's future product sales. As discussed in Notes 6 and 7 to the consolidated financial statements, the Company entered into a License and Commercialization Agreement with Laboratoire Aguettant to commercialize Dzuveo in the European Union and certain non-European Union countries. Under the agreement, the Company is entitled to receive up to €47.0 million in a combination of upfront and sales-based milestone payments, of which the Company has received an upfront cash payment of $2.9 million. The license and collaboration agreement contains multiple performance obligations that may require the Company to deliver goods and/or services throughout the term of the agreement.

Auditing the Company's accounting for revenue from collaboration arrangements was complex and required significant judgment, primarily in identifying the performance obligations, determining the standalone selling prices underlying each performance obligation, determining the allocation of arrangement consideration and determining the variable consideration, including variable consideration that is subject to a constraint. The determination of standalone selling prices for certain of the Company's arrangements involves significant judgement as a performance obligation may not have readily observable inputs.

*How the Critical Audit Matter Was Addressed in the Audit*

We obtained an understanding and evaluated the design of controls over the Company's processes for revenue recognition, including identification of performance obligations, determination of standalone selling price underlying each performance obligation, and estimation of variable consideration.

To test the accounting for revenue from the collaboration agreement we tested and evaluated, among other things, the performance obligations identified, the manner in which the performance obligation is satisfied, the estimates and assumptions used to determine transaction price, and the allocation of transaction price to performance obligations. Our audit procedures also included, among other things, reading the agreements and related schedules, reviewing management's analysis for completeness and accuracy by agreeing data to underlying agreements, understanding the methodologies utilized in accordance with the relevant accounting guidance and assessing the reasonableness of management's estimates and judgments through a review of the agreements, inspecting communications from the collaborative partner, and performing a sensitivity analysis.

/s/ WithumSmith+Brown, PC

We have served as the Company's auditor since 2015.

San Francisco, California
March 10, 2022

PCAOB ID Number 100

## REPORT OF INDEPENDENT REGISTERED PUBLIC ACCOUNTING FIRM

Stockholders and Board of Directors
AcelRx Pharmaceuticals, Inc.
Hayward, California

**Opinion on the Consolidated Financial Statements**

We have audited the accompanying consolidated balance sheet of AcelRx Pharmaceuticals, Inc. (the "Company") as of December 31, 2020, the related consolidated statements of operations, stockholders' deficit, and cash flows for the year ended December 31, 2020, and the related notes and schedule (collectively referred to as the "consolidated financial statements"). In our opinion, the consolidated financial statements present fairly, in all material respects, the financial position of the Company at December 31, 2020, and the results of its operations and its cash flows for the year ended December 31, 2020**,** in conformity with accounting principles generally accepted in the United States of America.

**Basis for Opinion**

These consolidated financial statements are the responsibility of the Company's management. Our responsibility is to express an opinion on the Company's consolidated financial statements based on our audit. We are a public accounting firm registered with the Public Company Accounting Oversight Board (United States) ("PCAOB") and are required to be independent with respect to the Company in accordance with the U.S. federal securities laws and the applicable rules and regulations of the Securities and Exchange Commission and the PCAOB.

We conducted our audit in accordance with the standards of the PCAOB. Those standards require that we plan and perform the audit to obtain reasonable assurance about whether the consolidated financial statements are free of material misstatement, whether due to error or fraud. The Company is not required to have, nor were we engaged to perform, an audit of its internal control over financial reporting. As part of our audit we are required to obtain an understanding of internal control over financial reporting but not for the purpose of expressing an opinion on the effectiveness of the Company's internal control over financial reporting. Accordingly, we express no such opinion.

Our audit included performing procedures to assess the risks of material misstatement of the consolidated financial statements, whether due to error or fraud, and performing procedures that respond to those risks. Such procedures included examining, on a test basis, evidence regarding the amounts and disclosures in the consolidated financial statements. Our audit also included evaluating the accounting principles used and significant estimates made by management, as well as evaluating the overall presentation of the consolidated financial statements. We believe that our audit provides a reasonable basis for our opinion.

/s/ OUM & CO. LLP

We have served as the Company's auditor since 2015.

San Francisco, California
March 15, 2021

PCAOB ID Number 252

**AcelRx Pharmaceuticals, Inc.**

**Consolidated Balance Sheets**
**(in thousands, except share data)**

| | December 31, 2021 | December 31, 2020 |
|---|---|---|
| **Assets** | | |
| Current Assets: | | |
| Cash and cash equivalents | $ 12,663 | $ 27,274 |
| Short-term investments | 38,967 | 15,612 |
| Accounts receivable, net | 160 | 635 |
| Inventories, net | 1,111 | 1,626 |
| Prepaid expenses and other current assets | 2,588 | 1,683 |
| Total current assets | 55,489 | 46,830 |
| Operating lease right-of-use assets | 4,302 | 3,150 |
| Property and equipment, net | 15,928 | 15,659 |
| Other assets | 2,174 | 656 |
| Total Assets | $ 77,893 | $ 66,295 |
| | | |
| **Liabilities and Stockholders' Deficit** | | |
| Current Liabilities: | | |
| Accounts payable | $ 2,121 | $ 2,737 |
| Accrued and other liabilities | 6,524 | 5,045 |
| Long-term debt, current portion | 8,796 | 8,735 |
| Operating lease liabilities, current portion | 1,068 | 1,118 |
| Total current liabilities | 18,509 | 17,635 |
| Long-term debt, net of current portion | 5,007 | 13,140 |
| Deferred revenue, net of current portion | 1,151 | — |
| Operating lease liabilities, net of current portion | 3,750 | 2,606 |
| Liability related to the sale of future royalties | 85,288 | 88,365 |
| Other long-term liabilities | 81 | 299 |
| Total liabilities | 113,786 | 122,045 |
| | | |
| Commitments and Contingencies | | |
| Stockholders' Deficit: | | |
| Common stock, $0.001 par value—200,000,000 shares authorized as of December 31, 2021 and 2020; 136,819,647 and 98,812,008 shares issued and outstanding as of December 31, 2021 and 2020, respectively | 137 | 98 |
| Additional paid-in capital | 437,554 | 382,637 |
| Accumulated deficit | (473,584) | (438,485) |
| Total stockholders' deficit | (35,893) | (55,750) |
| Total Liabilities and Stockholders' Deficit | $ 77,893 | $ 66,295 |

See notes to consolidated financial statements.

**AcelRx Pharmaceuticals, Inc.**

**Consolidated Statements of Operations**
**(in thousands, except share and per share data)**

| | Year Ended December 31, | |
|---|---|---|
| | **2021** | **2020** |
| Revenue: | | |
| Product sales | $ 1,005 | $ 2,521 |
| Contract and other collaboration | 1,813 | 2,895 |
| Total revenue | 2,818 | 5,416 |
| | | |
| Operating costs and expenses: | | |
| Cost of goods sold | 3,753 | 6,032 |
| Research and development | 4,095 | 4,017 |
| Selling, general and administrative | 30,935 | 36,330 |
| Total operating costs and expenses | 38,783 | 46,379 |
| | | |
| Loss from operations | (35,965) | (40,963) |
| Other income: | | |
| Interest expense | (2,291) | (3,305) |
| Interest income and other income, net | 124 | 583 |
| Non-cash interest income on liability related to sale of future royalties | 3,038 | 3,310 |
| Total other income | 871 | 588 |
| Net loss before income taxes | (35,094) | (40,375) |
| Provision for income taxes | 5 | 4 |
| Net loss | (35,099) | (40,379) |
| Comprehensive loss | $ (35,099) | $ (40,379) |
| Net loss per share of common stock, basic and diluted | $ (0.29) | $ (0.47) |
| Shares used in computing net loss per share of common stock, basic and diluted –see Note 15 | 119,860,266 | 85,257,008 |

See notes to consolidated financial statements.

**AcelRx Pharmaceuticals, Inc.**

**Consolidated Statements of Stockholders' Deficit**
**(in thousands, except share data)**

| | Common Stock | | Additional Paid-in Capital | Accumulated Deficit | Total Stockholders' Deficit |
|---|---|---|---|---|---|
| | Shares | Amount | | | |
| Balance as of December 31, 2019 | 79,573,101 | $ 79 | $ 356,609 | $ (398,106) | $ (41,418) |
| Stock-based compensation | — | — | 4,424 | — | 4,424 |
| Restricted stock units vested | 254,684 | — | — | — | — |
| Tax payments related to shares withheld for restricted stock units vested | — | — | (86) | — | (86) |
| Net proceeds from issuance of common stock in connection with equity financings | 18,644,095 | 19 | 21,318 | — | 21,337 |
| Issuance of common stock upon ESPP purchase | 340,128 | — | 372 | — | 372 |
| Net loss | — | — | — | (40,379) | (40,379) |
| Balance as of December 31, 2020 | 98,812,008 | 98 | 382,637 | (438,485) | (55,750) |
| Stock-based compensation | — | — | 4,609 | — | 4,609 |
| Restricted stock units vested | 488,715 | — | — | — | — |
| Tax payments related to shares withheld for restricted stock units vested | — | — | (249) | — | (249) |
| Net proceeds from issuance of common stock in connection with equity financings | 37,201,562 | 38 | 44,678 | — | 44,716 |
| Net proceeds from issuance of warrants in connection with equity financings | — | — | 5,562 | — | 5,562 |
| Issuance of common stock upon exercise of stock options | 19,403 | 1 | 16 | — | 17 |
| Issuance of common stock upon ESPP purchase | 297,959 | — | 301 | — | 301 |
| Net loss | — | — | — | (35,099) | (35,099) |
| Balance as of December 31, 2021 | 136,819,647 | $ 137 | $ 437,554 | $ (473,584) | $ (35,893) |

See notes to consolidated financial statements.

**AcelRx Pharmaceuticals, Inc.**

**Consolidated Statements of Cash Flows**
**(in thousands)**

| | Year Ended December 31, | |
|---|---|---|
| | **2021** | **2020** |
| CASH FLOWS FROM OPERATING ACTIVITIES: | | |
| Net loss | $ (35,099) | $ (40,379) |
| Adjustments to reconcile net loss to net cash used in operating activities: | | |
| Non-cash royalty revenue related to royalty monetization | (83) | (242) |
| Non-cash interest income on liability related to royalty monetization | (3,038) | (3,310) |
| Depreciation and amortization | 1,973 | 1,853 |
| Non-cash interest expense related to debt financing | 761 | 1,069 |
| Stock-based compensation | 4,609 | 4,424 |
| Inventory impairment charge | 810 | 712 |
| Other | (138) | (344) |
| Changes in operating assets and liabilities: | | |
| Accounts receivable | 475 | (203) |
| Inventories | (295) | 957 |
| Prepaid expenses and other assets | (908) | 661 |
| Accounts payable | 111 | 1,016 |
| Accrued liabilities | 79 | (638) |
| Operating lease liabilities | (447) | (886) |
| Deferred revenue | 1,188 | (3,195) |
| Net cash used in operating activities | (30,002) | (38,505) |
| CASH FLOWS FROM INVESTING ACTIVITIES: | | |
| Purchase of property and equipment | (1,827) | (1,855) |
| Purchase of investments | (70,459) | (44,611) |
| Asset acquisition costs | (821) | — |
| Proceeds from sale of investments | 2,996 | — |
| Proceeds from maturities of investments | 43,988 | 80,605 |
| Net cash (used in) provided by investing activities | (26,123) | 34,139 |
| CASH FLOWS FROM FINANCING ACTIVITIES: | | |
| Payment of long-term debt | (8,833) | (4,667) |
| Net proceeds from issuance of common stock in connection with equity financings | 44,716 | 21,337 |
| Net proceeds from issuance of warrants in connection with equity financings | 5,562 | — |
| Net proceeds from issuance of common stock through equity plans | 318 | 372 |
| Tax payments related to shares withheld for restricted stock units vested | (249) | (86) |
| Net cash provided by financing activities | 41,514 | 16,956 |
| NET (DECREASE) INCREASE IN CASH, CASH EQUIVALENTS | (14,611) | 12,590 |
| CASH, CASH EQUIVALENTS —Beginning of year | 27,274 | 14,684 |
| CASH, CASH EQUIVALENTS —End of year | $ 12,663 | $ 27,274 |
| SUPPLEMENTAL DISCLOSURES OF CASH FLOW INFORMATION: | | |
| Cash paid for interest | $ 1,595 | $ 2,269 |
| Income taxes paid (refunded) | $ 5 | $ (347) |
| NONCASH INVESTING AND FINANCING ACTIVITIES: | | |
| Purchases of property and equipment in accounts payable and accrued expenses | $ 1,095 | $ — |
| Asset acquisition costs in accounts payable and accrued expenses | $ 1,087 | $ — |
| Establishment of right-of-use asset and lease liability | $ 4,669 | $ — |
| Write-off of right-of-use asset and lease liability | $ (3,128) | $ — |
| Gain on termination of sublease | $ 522 | $ — |
| Leasehold improvements paid with note payable | $ — | $ 326 |

See 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. The Company subsequently changed its name to AcelRx Pharmaceuticals, Inc. The Company's operations are based in Hayward, California.

AcelRx is a specialty pharmaceutical company focused on the development and commercialization of innovative therapies for use in medically supervised settings. DSUVIA® (known as DZUVEO® in Europe) and Zalviso® are both focused on the treatment of acute pain, and each utilize sufentanil, delivered via a non-invasive route of sublingual administration, exclusively for use in medically supervised settings. On November 2, 2018, the U.S. Food and Drug Administration, or FDA, approved DSUVIA for use in adults in a certified medically supervised healthcare setting, such as hospitals, surgical centers, and emergency departments, for the management of acute pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate. The commercial launch of DSUVIA in the United States occurred in the first quarter of 2019. In June 2018, the European Commission, or EC, granted marketing approval of DZUVEO for the management of acute moderate to severe pain in adults in medically monitored settings. AcelRx is further developing a distribution capability and commercial organization to continue to market and sell DSUVIA in the United States. In geographies where AcelRx decides not to commercialize products by itself, the Company may seek to out-license commercialization rights. The Company currently intends to commercialize and promote DSUVIA/DZUVEO outside the United States with one or more strategic partners, and, in July 2021, entered into a License and Commercialization Agreement with Laboratoire Aguettant, or Aguettant, for Aguettant to commercialize DZUVEO in the European Union, Norway, Iceland, Liechtenstein, Andorra, Vatican City, Monaco, Switzerland and the United Kingdom (see Note 6. "Out-License Agreements—DZUVEO" below). The timing of the resubmission of the Zalviso new drug application, or NDA, is in part dependent upon the finalization of the FDA's new opioid approval guidelines and process. AcelRx intends to seek regulatory approval for Zalviso in the United States and, if successful, potentially promote Zalviso either by itself or with strategic partners. Zalviso is approved in Europe and was commercialized by Grünenthal GmbH, or Grünenthal, through May 12, 2021 (see *Termination of Grünenthal Agreements* below). In July 2021, the Company also entered into a separate License and Commercialization Agreement with Aguettant pursuant to which the Company obtained the exclusive right to develop and, subject to FDA approval, commercialize in the United States (i) an ephedrine pre-filled syringe containing 10 ml of a solution of 3 mg/ml ephedrine hydrochloride for injection, and (ii) a phenylephrine pre-filled syringe containing 10 ml of a solution of 50 mcg/ml phenylephrine hydrochloride for injection (see Note 5. "In-License Agreement" below). On January 7, 2022, the Company closed the definitive merger agreement dated as of November 14, 2021, or the Merger Agreement, to acquire Lowell Therapeutics, Inc., or Lowell, a privately held company (see Note 19. "Subsequent Events" below).

The Company has incurred recurring operating losses and negative cash flows from operating activities since inception. As of December 31, 2021 and December 31, 2020, the Company had cash, cash equivalents and short-term investments of $51.6 million and $42.9 million, respectively. Based on the Company's current operating plans and projections, the Company expects that its existing cash, cash equivalents and short-term investments will be sufficient to fund operations for at least one year from the date this Annual Report on Form 10-K is filed with the United States Securities and Exchange Commission, or SEC. Although Zalviso was approved for sale in Europe on September 18, 2015, the Company sold the majority of the royalty rights and certain commercial sales milestones it is entitled to receive under the Amended License Agreement (defined below) with Grünenthal to PDL BioPharma, Inc., or PDL, in a transaction referred to as the Royalty Monetization. On August 31, 2020, PDL announced it sold its royalty interest for Zalviso to SWK Funding, LLC, or SWK. In consideration of the termination of the Amended License Agreement, under the Royalty Monetization, the Company must use commercially reasonable efforts to negotiate a replacement license agreement with a third party.

*Termination of Grünenthal Agreements*

On December 16, 2013, AcelRx and Grünenthal entered into a Collaboration and License Agreement, or the License Agreement, which was amended effective July 17, 2015 and September 20, 2016, or the Amended License Agreement, which granted Grünenthal rights to commercialize the Zalviso PCA system, or the Product, in the 28 European Union, or EU, member states, at the time of the agreement, plus Switzerland, Liechtenstein, Iceland, Norway and Australia (collectively, the Zalviso Territory) for human use in pain treatment within, or dispensed by, hospitals, hospices, nursing homes and other medically supervised settings, (collectively, the Field). In September 2015, the EC granted marketing approval for the marketing authorization application, or MAA, previously submitted to the EMA, for Zalviso for the management of acute moderate-to-severe post-operative pain in adult patients. On December 16, 2013, AcelRx and Grünenthal entered into a Manufacture and Supply Agreement, or the MSA, and together with the License Agreement, the Agreements. Under the MSA, the Company exclusively manufactured and supplied the Product to Grünenthal for the Field in the Zalviso Territory. On July 22, 2015, the Company and Grünenthal amended the MSA, or the Amended MSA, effective as of July 17, 2015. The Amended MSA and the Amended License Agreement are referred to as the Grünenthal Agreements.

On May 18, 2020, the Company received a notice from Grünenthal that it had exercised its right to terminate the Grünenthal Agreements, effective November 13, 2020. The terms of the Grünenthal Agreements were extended to May 12, 2021 to enable Grünenthal to sell down its Zalviso inventory, a right it had under the Grünenthal Agreements. The rights to market and sell Zalviso in the Zalviso Territory reverted back to the Company on May 12, 2021.

***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. In particular, the amounts reported in the Consolidated Balance Sheets as deferred revenue, current portion and liability related to the sale of future royalties, current portion have been reclassified to accrued and other liabilities at December 31, 2020, and the amount reported as an inventory impairment charge in the Consolidated Statements of Cash Flows was recorded as other in the year ended December 31, 2020.

***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 Royalty Monetization 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. All intercompany accounts and transactions have been eliminated in consolidation. Refer to Note 10 “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 believes its most significant accounting estimates relate to revenue recognition, inventory valuation and the liability related to the sale of future royalties. 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 Short-Term Investments***

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.

All marketable securities are classified as available-for-sale and consist of commercial paper, U.S. government sponsored enterprise debt securities and corporate 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:

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 and products for the treatment of pain. The Company's product sales revenue consists of sales of DSUVIA in the United States and, through May 2021, sales of Zalviso in Europe by Grünenthal. The Company's contract and collaboration revenue consists of non-cash royalty revenue, royalty revenue, and other revenue under the Grünenthal Agreements and license revenue under the DZUVEO Agreement.

***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 U.S. government sponsored agencies, commercial paper 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 Sheets.

The Company relies on a single third-party supplier for the supply of sufentanil, the active pharmaceutical ingredient in DSUVIA and Zalviso, and various sole-source third-party contract manufacturer organizations to manufacture the DSUVIA SDA.

DSUVIA sales are concentrated with the DoD and with a limited number of wholesalers in the United States. Zalviso was sold in Europe by Grünenthal through May 2021. In July 2021, Aguettant was granted an exclusive license to commercialize DZUVEO in Europe. DZUVEO sales in Europe by Aguettant have not commenced as of December 31, 2021.

Revenue and accounts receivable have been concentrated with these customers.

Revenues from customers that accounted for 10% or more of our total revenues during the years ended December 31, 2021 and 2020 are as follows:

| | Year Ended December 31, | |
|---|---|---|
| **Percent of Total Revenue** | **2021** | **2020** |
| Aguettant | 61.9% | 0% |
| Grünenthal | 11.7% | 74.0% |
| DoD | 0.3% | 16.9% |
| Wholesaler A | 15.9% | 3.9% |

***Accounts Receivable, net***

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.

The Company believes that the entire accounts receivable balance as of December 31, 2021 is collectible and there was no bad debt allowance provided as of December 31, 2020.

Accounts receivable, net from customers that accounted for 10% or more of our total accounts receivable balance as of December 31, 2021 and 2020 are as follows:

| | As of December 31, | |
|---|---|---|
| **Percent of Accounts Receivable, Net** | **2021** | **2020** |
| Customer A | 73% | 12% |
| Customer B | 0% | 79% |

***Inventories, net***

Inventories are valued at the lower of cost or net realizable value. 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 net realizable value approach as that used to value the inventory.

***Property and Equipment, net***

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 interest income and other income, net in the accompanying Consolidated Statements of Operations.

***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, if the Company is not successful in its commercialization of DSUVIA, and if approved, Zalviso, purchased equipment and manufacturing-related facility improvements the Company has made at its contract manufacturers could become impaired. 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.

***Contingent put option***

The contingent put option associated with the Company’s Loan Agreement with Oxford 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 Operations. For further discussion, see Note 8 “Long-Term Debt”.

***Leases***

The Company follows the provisions of ASU No. 2016-02, *Leases (Topic 842)*. At the inception of an arrangement, the Company determines whether the arrangement is, or contains, a lease based on the unique facts and circumstances present. Operating lease liabilities and their corresponding right-of-use assets are recorded based on the present value of lease payments over the expected lease term. The interest rate implicit in lease contracts is typically not readily determinable. As such, the Company utilizes its incremental borrowing rate, which is the rate incurred to borrow on a collateralized basis over a similar term an amount equal to the lease payments in a similar economic environment. Certain adjustments to the right-of-use asset may be required for items such as initial direct costs paid or incentives received.

Lease expense is recognized over the expected term on a straight-line basis. Operating leases are recognized on the Consolidated Balance Sheets as operating lease right-of-use assets, operating lease liabilities current and operating lease liabilities non-current.

***Revenue from Contracts with Customers***

The Company follows the provisions of Accounting Standards Codification, or ASC, Topic 606, *Revenue from Contracts with Customers*. This guidance provides a unified model to determine how revenue is recognized. The Company recognizes revenue upon transfer of control of promised products or services to customers in an amount that reflects the consideration the Company expects to receive in exchange for those products or services. The Company sells its products primarily through wholesale and specialty distributors.

In determining the appropriate amount of revenue to be recognized as it fulfills its obligations under its agreements, the Company performs the following steps: (i) identification of the promised goods or services in the contract; (ii) determination of whether the promised goods or services are performance obligations, including whether they are distinct in the context of the contract; (iii) measurement of the transaction price, including the constraint on variable consideration; (iv) allocation of the transaction price to the performance obligations based on estimated selling prices; and (v) recognition of revenue when (or as) the Company satisfies each performance obligation.

Product sales revenue

The Company sells its product primarily through distributors. Revenues from product sales are recognized when distributors obtain control of the Company's product, which occurs at a point in time, upon delivery to such distributors. These distributors subsequently resell the product to certified medically supervised healthcare settings. In addition to distribution agreements with these customers, the Company enters into arrangements with group purchasing organizations, or GPOs, and other certified medically supervised healthcare settings that provide for privately negotiated discounts with respect to the purchase of its products. For revenue recognition under bill-and-hold arrangements, wherein the customer agrees to buy product from the Company but requests delivery at a later date, the Company deems that control passes to the customer when the product is ready for delivery. The Company recognizes revenue under these types of arrangements when a signed agreement is in place, the transaction is billable, the customer has significant risk and rewards for the product and the ability to direct the asset, the product has been set aside specifically for the customer, and the product cannot be redirected to another customer. Revenue from product sales is recorded at the transaction price, net of estimates for variable consideration consisting of chargebacks, government rebates, returns, distribution fees, GPO fees and product returns. Variable consideration is recorded at the time product sales are recognized resulting in a reduction in product revenue. The amount of variable consideration that is included in the transaction price may be constrained and is included in the net sales price only to the extent that it is probable that a significant reversal in the amount of the cumulative revenue recognized will not occur in a future period. Variable consideration is estimated using the most-likely amount method, which is the single-most likely outcome under a contract and is typically at the stated contractual rate. Where appropriate, these estimates take into consideration a range of possible outcomes that are probability-weighted in accordance with the expected value method under ASC Topic 606 for relevant factors. These factors include current contractual and statutory requirements, specific known market events and trends, industry data, and/or forecasted customer buying and payment patterns. Actual amounts of consideration ultimately received may differ from the Company's estimates. If actual results vary materially from the Company's estimates, the Company will adjust these estimates, which will affect revenue from product sales and earnings in the period such estimates are adjusted. These estimates include:

Chargebacks – The Company's customers subsequently resell its product to qualified healthcare providers. In addition to distribution agreements with customers, the Company enters into arrangements with qualified healthcare providers that provide discounts with respect to the purchase of its product. Chargebacks represent the estimated obligations resulting from contractual commitments to sell product to qualified healthcare providers at prices lower than the list prices charged to customers who directly purchase the product from the Company. Customers charge the Company for the difference between what they pay for the product and the ultimate selling price to the qualified healthcare providers. These reserves are established in the same period that the related revenue is recognized, resulting in a reduction of product revenue-related accrued liabilities on the Consolidated Balance Sheets. Chargeback amounts are determined at the time of resale to the qualified healthcare providers by customers, and the Company issues credits for such amounts generally within a few weeks of the customer's notification to the Company of the resale. Reserves for chargebacks consists of credits that the Company expects to issue for units that remain in the distribution channel inventories at each reporting period end that the Company expects will be sold to the qualified healthcare providers, and chargebacks for units that the Company's customers have sold to the qualified healthcare providers, but for which credits have not been issued.

Government Rebates – The Company is subject to discount obligations under state Medicaid programs. The Company estimates its Medicaid rebates, and reserves are recorded in the same period the related product revenue is recognized, resulting in a reduction of product revenue and the establishment of a current liability that is included in accrued liabilities on the Consolidated Balance Sheet.

Returns – The Company allows its distributors to return product for credit 6 months prior to, and up to 12 months after, the product expiration date. As such, there may be a significant period of time between the time the product is shipped and the time the credit is issued on returned product.

Distribution Fees – Distribution fees include fees paid to certain customers for sales order management, data and distribution services. Distribution fees are recorded as a reduction of revenue in the period the related product revenue is recognized.

GPO Fees – The Company pays administrative fees to GPOs for services and access to data. These fees are based on contracted terms and are paid after the quarter in which the product was purchased by the GPOs' members.

Trade Discounts and Allowances - The Company provides its customers with discounts which include early payment incentives that are explicitly stated in its contracts and are recorded as a reduction of revenue in the period the related product revenue is recognized.

The Company believes its estimated allowances for chargebacks, government rebates and product returns require a high degree of judgment and are subject to change based on its limited experience and certain quantitative and qualitative factors. The Company believes its estimated allowances for distribution fees, GPO fees and trade discounts and allowances do not require a high degree of judgment because the amounts are settled within a relatively short period of time. The Company will continue to assess its estimates of variable consideration as it accumulates additional historical data and will adjust these estimates accordingly. Changes in product revenue allowance estimates could materially affect the Company's results of operations and financial position.

Contract and other collaboration revenue

The Company generates revenue from collaboration agreements. These agreements typically include payments for upfront signing or license fees, cost reimbursements for development and manufacturing services, milestone payments, product sales, and royalties on licensee's future product sales. Product sales related revenue under these collaboration agreements is classified as product sales revenue, while other revenue generated from collaboration agreements is classified as contract and other collaboration revenue.

*Performance Obligations*

A performance obligation is a promise in a contract to transfer a distinct good or service to the customer and is the unit of account in ASC Topic 606. The Company's performance obligations include delivering product to its distributors, commercialization license rights, development services, services associated with the regulatory approval process, joint steering committee services, demonstration devices, manufacturing services, material rights for discounts on manufacturing services, and product supply.

The Company has optional additional items in contracts, which are considered marketing offers and are accounted for as separate contracts when the customer elects such options. Arrangements that include a promise for future commercial product supply and optional research and development services at the customer's or the Company's discretion are generally considered as options. The Company assesses if these options provide a material right to the licensee and if so, such material rights are accounted for as separate performance obligations. If the Company is entitled to additional payments when the customer exercises these options, any additional payments are recorded in revenue when the customer obtains control of the goods or services.

*Transaction Price*

The Company has both fixed and variable consideration. Variable consideration for product revenue is described as Net product sales in the Consolidated Statements of Operations. For collaboration agreements, non-refundable upfront fees and product supply selling prices are considered fixed, while milestone payments are identified as variable consideration when determining the transaction price. Funding of research and development activities is considered variable until such costs are reimbursed at which point, they are considered fixed. The Company allocates the total transaction price to each performance obligation based on the relative estimated standalone selling prices of the promised goods or services for each performance obligation.

At the inception of each arrangement that includes milestone payments, the Company evaluates whether the milestones are considered probable of being achieved and estimates the amount to be included in the transaction price using the most likely amount method. If it is probable that a significant revenue reversal would not occur, the value of the associated milestone (such as a regulatory submission by the Company) is included in the transaction price. Milestone payments that are not within the control of the Company, such as approvals from regulators, are not considered probable of being achieved until those approvals are received.

For arrangements that include sales-based royalties, including milestone payments based on the level of sales, and the license is deemed to be the predominant item to which the royalties relate, the Company recognizes revenue at the later of (a) when the related sales occur, or (b) when the performance obligation to which some or all of the royalty has been allocated has been satisfied (or partially satisfied).

*Allocation of Consideration*

As part of the accounting for collaboration arrangements, the Company must develop assumptions that require judgment to determine the stand-alone selling price of each performance obligation identified in the contract. Estimated selling prices for license rights and material rights for discounts on manufacturing services are calculated using an income approach model and can include the following key assumptions: the development timeline, sales forecasts, costs of product sales, commercialization expenses, discount rate, the time which the manufacturing services are expected to be performed, and probabilities of technical and regulatory success. For all other performance obligations, the Company uses a cost-plus margin approach.

*Timing of Recognition*

Significant management judgment is required to determine the level of effort required under collaboration arrangements and the period over which the Company expects to complete its performance obligations under the arrangement. The Company estimates the performance period or measure of progress at the inception of the arrangement and re-evaluates it each reporting period. This re-evaluation may shorten or lengthen the period over which revenue is recognized. Changes to these estimates are recorded on a cumulative catch-up basis. If the Company cannot reasonably estimate when its performance obligations either are completed or become inconsequential, then revenue recognition is deferred until the Company can reasonably make such estimates. Revenue is then recognized over the remaining estimated period of performance using the cumulative catch-up method. Revenue is recognized for products at a point in time when control of the product is transferred to the customer in an amount that reflects the consideration the Company expects to be entitled to in exchange for those product sales, which is typically once the product physically arrives at the customer, and for licenses of functional intellectual property at the point in time the customer can use and benefit from the license. For performance obligations that are services, revenue is recognized over time proportionate to the costs that the Company has incurred to perform the services using the cost-to-cost input method.

***Cost of Goods Sold***

Cost of goods sold for product revenue includes third party manufacturing costs, shipping and handling costs, and indirect overhead costs associated with production and distribution which are allocated to the appropriate cost pool and recognized when revenue is recognized. Indirect overhead costs in excess of normal capacity are recorded as period costs in the period incurred.

Under the Grünenthal Agreements, the Company sold Zalviso to Grünenthal at predetermined, contractual transfer prices that were less than the direct costs of manufacturing and recognized indirect costs as period costs where they were in excess of normal capacity and not recoverable on a lower of cost or net realizable value basis. Cost of goods sold for Zalviso shipped to Grünenthal included 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 stock-based payment awards made to employees and directors, including employee stock options and restricted stock units related to the 2020 Equity Incentive Plan, or 2020 EIP, the 2011 Equity Incentive Plan, or 2011 EIP, and employee share purchases related to the Amended and Restated 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 Company applies the graded-vesting attribution method to awards with market conditions that include graded-vesting features. Additionally, the Company uses the Monte Carlo Simulation model to evaluate the derived service period and fair value of awards with market conditions, including assumptions of historical volatility and risk-free interest rate commensurate with the vesting term.

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. The expected term, which represents the period of time that options granted are expected to be outstanding, is derived by analyzing the historical experience of similar awards, giving consideration to the contractual terms of the stock-based awards, vesting schedules and expectations of future employee behavior. Expected volatilities are estimated using the historical stock price performance over the expected term of the option, which are adjusted as necessary for any other factors which may reasonably affect the volatility of AcelRx's stock in the future. The risk-free interest rate is based on the U.S. Treasury yield in effect at the time of the grant for the expected term of the award. The Company recognizes forfeitures when they occur and does not anticipate paying dividends in the near future.

***Warrants Issued in Connection with Financings***

The Company generally accounts for warrants issued in connection with debt and equity financings as a component of equity, unless the warrants include a conditional obligation to issue a variable number of shares or there is a deemed possibility that the Company may need to settle the warrants in cash. For warrants issued with a conditional obligation to issue a variable number of shares or the deemed possibility of a cash settlement, the Company records the fair value of the warrants as a liability at each balance sheet date and records changes in fair value in other (income) expense in the Consolidated Statements of Operations.

***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 Company notifies the employee, unless the employee must provide future service, in which case the benefits are expensed ratably over the future service period.

On March 16, 2020, in connection with entering into the Co-Promotion Agreement, the Company initiated a reduction in headcount, designed to eliminate the overlap with the Tetraphase commercial team in order to more efficiently commercialize DSUVIA alongside the Tetraphase commercial team and reduce operating expenses. The Company eliminated 30 positions, primarily within the commercial organization. For the year ended December 31, 2020, the Company incurred and paid $0.5 million in employee termination benefits related to this restructuring. The headcount reduction was completed in the first quarter of 2020. There were no such restructuring costs for the year ended December 31, 2021.

***Non-Cash Interest Income (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 Grünenthal to PDL for gross proceeds of $65.0 million. Grünenthal terminated the Grünenthal Agreements effective November 13, 2020. The terms of the Grünenthal Agreements were extended to May 2021 to enable Grünenthal to sell down its Zalviso inventory. The rights to market and sell Zalviso in the Territory reverted back to the Company in May 2021.

Under the Royalty Monetization, the Company has a continuing obligation to use commercially reasonable efforts to negotiate a replacement license agreement, or New Arrangement. Under the relevant accounting guidance, because of the Company's significant continuing involvement, the Royalty Monetization is accounted for as a liability that is being amortized using the effective 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 ARPI LLC and payments made to PDL, up to a capped amount of $195.0 million, over the life of the arrangement. The aggregate future estimated royalty and milestone payments (subject to the capped amount), less the $61.2 million of net proceeds the Company received, are amortized 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, or interest income, as these estimates are updated.

There are a number of factors that could materially affect the amount and timing of royalty and milestone payments from Zalviso in Europe, most of which are not within the Company's control. Such factors include, but are not limited to, the success of any future sales and promotion of Zalviso under any New Arrangement, if achieved; changing standards of care; the introduction of competing products; manufacturing or other delays; intellectual property matters; adverse events that result in governmental health authority imposed restrictions on the use of Zalviso; significant changes in foreign exchange rates as the royalties remitted to ARPI LLC are made in U.S. dollars; and other events or circumstances that could result in reduced royalty payments from European sales of Zalviso, all of which may result in a reduction of non-cash royalty revenues and the non-cash interest expense over the life of the Royalty Monetization. Conversely, if sales of Zalviso in Europe are greater than expected, the non-cash royalty revenues and the non-cash interest expense recorded by the Company would be greater over the term of the Royalty Monetization. The Company periodically assesses 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 the Company's 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 effective interest rate. Because estimated sales forecasts and payments may vary over the life of the Royalty Monetization, the Company may be required to recognize interest income as the imputed interest rate is adjusted prospectively to reflect the revised effective interest rate over the term of the Royalty Monetization.

The Company records non-cash royalty revenues and non-cash interest income (expense), net, within its Consolidated Statements of Operations over the term of the Royalty Monetization.

When the expected payments under the Royalty Monetization are lower than the gross proceeds of $65.0 million received, the Company defers recognition of any probable contingent gain until the Royalty Monetization liability expires.

***Comprehensive Loss***

Comprehensive loss is comprised of net loss and other comprehensive income (loss) and is disclosed in the Consolidated Statements of Operations. 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, restricted stock units, 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 15 "Net Loss per Share of Common Stock".

***Recently Adopted Accounting Standards***

In December 2019, the Financial Accounting Standards Board, or FASB, issued Accounting Standards Update, or ASU, 2019-12, "*Simplifying the Accounting for Income Taxes*". ASU 2019-12 eliminates certain exceptions related to the approach for intra-period tax allocation, the methodology for calculating income taxes in an interim period and the recognition of deferred tax liabilities for outside basis differences. It also clarifies and simplifies other aspects of the accounting for income taxes. ASU 2019-12 is effective for fiscal years beginning after December 15, 2020, and interim periods within those fiscal years. The Company adopted ASU 2019-12 on January 1, 2021, which did not have a material impact on the Company's Consolidated Financial Statements.

In August 2020, the FASB issued ASU 2020-06, "*Debt - Debt with Conversion and Other Options (Subtopic 470-20) and Derivatives and Hedging - Contracts in Entity's Own Equity (Subtopic 815-40): Accounting for Convertible Instruments and Contracts in an Entity's Own Equity*". The standard simplifies accounting for convertible instruments by removing major separation models required under current GAAP. Consequently, more convertible debt instruments will be reported as a single liability instrument with no separate accounting for embedded conversion features. ASU 2020-06 removes certain settlement conditions that are required for equity contracts to qualify for the derivative scope exception, which will permit more equity contracts to qualify for it. The standard also simplifies the diluted net income per share calculation in certain areas. ASU 2020-06 is effective for fiscal years beginning after December 15, 2023, and interim periods within those fiscal years for smaller reporting companies, with early adoption permitted. The Company early adopted ASU 2020-06 on January 1, 2021, which did not have a material impact on the Company's Consolidated Financial Statements on the date of adoption.

***Recently Issued Accounting Pronouncements***

In June 2016, the FASB issued ASU 2016-13, "*Financial Instruments – Credit Losses: Measurement of Credit Losses on Financial Instruments*," or ASU 2016-13. ASU 2016-13 replaces the incurred loss impairment model in current GAAP with a model that reflects expected credit losses and requires consideration of a broader range of reasonable and supportable information to determine credit loss estimates. ASU 2016-13 is effective for the Company beginning January 1, 2023, with early adoption allowed beginning January 1, 2020. In May 2019, the FASB issued ASU 2019-05, "*Financial Instruments – Credit Losses*," or ASU 2019-05, to allow entities to irrevocably elect the fair value option for certain financial assets previously measured at amortized cost upon adoption of the new credit losses standard. The new effective dates and transition align with those of ASU 2016-13. Management is currently assessing the date of adoption and the impact ASU 2016-13 and ASU 2019-05 will have on the Company, but it does not anticipate adoption of these new standards to have a material impact on the Company's financial position, results of operations or cash flows.

In March 2020, the FASB issued ASU 2020-04, "*Reference Rate Reform (Topic 848): Facilitation of the Effects of Reference Rate Reform on Financial Reporting*," which provides elective amendments for entities that have contracts, hedging relationships and other transactions that reference LIBOR or another reference rate expected to be discontinued because of reference rate reform. These amendments are effective immediately and may be applied prospectively to contract modifications made and hedging relationships entered into or evaluated on or before December 31, 2022. In January 2021, the FASB issued ASU 2021-01, "*Reference Rate Reform (Topic 848),*" to expand and clarify the scope of Topic 848 to include derivative instruments on discounting transactions. The amendments in this ASU are effective in the same timeframe as ASU 2020-04. The Company is currently evaluating the impact this guidance will have on its Consolidated Financial Statements.

**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 (loss). 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, 2021 | | | |
|---|---|---|---|---|
| | Amortized Cost | Gross Unrealized Gains | Gross Unrealized Losses | Fair Value |
| Cash and cash equivalents: | | | | |
| Cash | $ 1,443 | $ — | $ — | $ 1,443 |
| Money market funds | 2,822 | — | — | 2,822 |
| Commercial paper | 8,398 | — | — | 8,398 |
| Total cash and cash equivalents | 12,663 | — | — | 12,663 |
| | | | | |
| Short-term investments: | | | | |
| Commercial paper | 29,504 | — | — | 29,504 |
| Corporate debt securities | 9,463 | — | — | 9,463 |
| Total short-term investments | 38,967 | — | — | 38,967 |
| Total cash, cash equivalents and short-term investments | $ 51,630 | $ — | $ — | $ 51,630 |

| | As of December 31, 2020 | | | |
|---|---|---|---|---|
| | Amortized Cost | Gross Unrealized Gains | Gross Unrealized Losses | Fair Value |
| Cash and cash equivalents: | | | | |
| Cash | $ 5,181 | $ — | $ — | $ 5,181 |
| Money market funds | 3,996 | — | — | 3,996 |
| Commercial paper | 18,097 | — | — | 18,097 |
| Total cash and cash equivalents | 27,274 | — | — | 27,274 |
| | | | | |
| Short-term investments: | | | | |
| U.S. government agency securities | 5,818 | — | — | 5,818 |
| Commercial paper | 9,794 | — | — | 9,794 |
| Total short-term investments | 15,612 | — | — | 15,612 |
| Total cash, cash equivalents and short-term investments | $ 42,886 | $ — | $ — | $ 42,886 |

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, 2021 and 2020. There were no other-than-temporary impairments for these securities as of December 31, 2021 or 2020. 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 (loss) to earnings during the years ended December 31, 2021 and 2020.

As of December 31, 2021 and 2020, 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 II assets and Level III liabilities. Money market funds are highly liquid investments and are actively traded. The pricing information on these investment instruments are readily available and can be independently validated as of the measurement date. This approach results in the classification of these securities as Level 1 of the fair value hierarchy. 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, U.S. government agency securities and commercial paper. As of December 31, 2021, and December 31, 2020, the Company held, in addition to Level II assets, a contingent put option liability associated with the Loan Agreement with Oxford. See Note 8 "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, which is included under other long-term liabilities on the Consolidated Balance Sheets. Changes to the estimated fair value of this liability is recorded in interest income and other income (expense), net in the Consolidated Statements of Operations. 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 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, 2021 | | | |
|---|---|---|---|---|
| | Fair Value | Level I | Level II | Level III |
| **Assets** | | | | |
| Money market funds | $ 2,822 | $ 2,822 | $ — | $ — |
| Commercial paper | 37,902 | — | 37,902 | — |
| Corporate debt securities | 9,463 | — | 9,463 | — |
| Total assets measured at fair value | $ 50,187 | $ 2,822 | $ 47,365 | $ — |
| | | | | |
| **Liabilities** | | | | |
| Contingent put option liability | $ 81 | $ — | $ — | $ 81 |
| Total liabilities measured at fair value | $ 81 | $ — | $ — | $ 81 |

| | As of December 31, 2020 | | | |
|---|---|---|---|---|
| | Fair Value | Level I | Level II | Level III |
| **Assets** | | | | |
| Money market funds | $ 3,996 | $ 3,996 | $ — | $ — |
| U.S. government agency securities | 5,818 | — | 5,818 | — |
| Commercial paper | 27,891 | — | 27,891 | — |
| Total assets measured at fair value | $ 37,705 | $ 3,996 | $ 33,709 | $ — |
| | | | | |
| **Liabilities** | | | | |
| Contingent put option liability | $ 246 | $ — | $ — | $ 246 |
| Total liabilities measured at fair value | $ 246 | $ — | $ — | $ 246 |

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, 2021 and 2020 (in thousands):

| | Year Ended December 31, 2021 |
|---|---|
| Fair value—beginning of period | $ 246 |
| Change in fair value of contingent put option associated with the Loan Agreement | (165) |
| Fair value—end of period | $ 81 |

| | Year Ended December 31, 2020 |
|---|---|
| Fair value—beginning of period | $ 437 |
| Change in fair value of contingent put option associated with the Loan Agreement | (191) |
| Fair value—end of period | $ 246 |

**3. Inventories, net**

Inventories consist of finished goods, raw materials and work in process and are stated at the lower of cost or net realizable value and consist of the following (in thousands):

| | As of December 31, | |
|---|---|---|
| | 2021 | 2020 |
| Raw materials | $ 722 | $ 257 |
| Work-in-process | 159 | 30 |
| Finished goods | 230 | 1,339 |
| Inventories | $ 1,111 | $ 1,626 |

During the year ended December 31, 2021, the Company recorded inventory impairment charges of approximately $0.8 million, primarily as a result of DSUVIA inventory that may expire before being sold. During the year ended December 31, 2020, the Company recorded inventory impairment charges of approximately $0.7 million, of which $0.3 million related to the termination of the Amended Agreements, while $0.4 million related to DSUVIA inventory, primarily inventory that may expire before being sold.

**4. Property and Equipment, net**

Property and equipment, net consist of the following (in thousands):

| | As of December 31, | |
|---|---|---|
| | 2021 | 2020 |
| Laboratory equipment | $ 4,406 | $ 4,406 |
| Leasehold improvements | 5,838 | 4,616 |
| Computer equipment and software | 1,589 | 1,724 |
| Construction in process | 13,805 | 14,101 |
| Tooling | 826 | 1,109 |
| Furniture and fixtures | 250 | 292 |
| | 26,714 | 26,248 |
| Less accumulated depreciation and amortization | (10,786) | (10,589) |
| Property and equipment, net | $ 15,928 | $ 15,659 |

Depreciation and amortization expense was $1.1 million for each of the years ended December 31, 2021 and 2020, respectively.

**5. In-License Agreement**

On July 14, 2021, the Company entered into a License and Commercialization Agreement, or the PFS Agreement, with Aguettant pursuant to which the Company obtained the exclusive right to develop and, subject to FDA approval, commercialize in the United States (i) an ephedrine pre-filled syringe containing 10 ml of a solution of 3 mg/ml ephedrine hydrochloride for injection, and (ii) a phenylephrine pre-filled syringe containing 10 ml of a solution of 50 mcg/ml phenylephrine hydrochloride for injection. Aguettant will supply the Company with the products for use in commercialization, if they are approved in the U.S.

The PFS Agreement has an initial term of ten (10) marketing years, with the first marketing year ending on December 31 of the calendar year after the first launch of a product (or December 31 of the same calendar year if the first launch of a product occurs between January 1 and April 30 of a calendar year). The term will automatically renew for successive five marketing year periods unless a party notifies the other party of its intention not to renew at least six (6) months prior to the expiration of the then-current term.

Aguettant is entitled to receive up to $24.0 million in sales-based milestone payments. The Company will purchase each product from Aguettant at an agreed price, or the PFS Purchase Price, subject to adjustment. The Company will also make revenue share payments that, combined with the PFS Purchase Price, will range from 40% to 45% of net sales in the United States.

The Company and Aguettant will agree on minimum sales obligations twelve (12) months prior to the launch of each product.

The Company has the right to grant sublicenses to its affiliates or, with the prior approval of Aguettant, third parties, subject to certain limitations.

As of December 31, 2021, there have been no payments by the Company to Aguettant under the PFS Agreement.

**6. Out-license Agreements**

***DZUVEO***

On July 14, 2021, the Company entered into a License and Commercialization Agreement, or the DZUVEO Agreement, with Aguettant, pursuant to which Aguettant obtained the exclusive right to develop and commercialize DZUVEO in the European Union, Norway, Iceland, Liechtenstein, Andorra, Vatican City, Monaco, Switzerland and the United Kingdom, or the DZUVEO Territory, for the management of acute moderate to severe pain in adults in medically monitored settings. The Company will supply Aguettant with product.

The DZUVEO Agreement has an initial term of ten (10) marketing years, with the first marketing year ending on December 31 of the calendar year after the launch of DZUVEO (or December 31, 2022, if the launch occurs between January 1, 2022 and April 30, 2022). The term will automatically renew for successive five marketing year periods unless a party notifies the other party of its intention not to renew at least six (6) months prior to the expiration of the then-current term. The DZUVEO Agreement may be terminated for cause by either party based on uncured material breach by the other party, insolvency of the other party, or force majeure event. Upon early termination, all ongoing activities under the agreement and all rights and commercialization licenses and sublicenses with respect to DZUVEO will terminate. Additionally, if terminated early by either party, any accrued liability at the time of such termination will not be released.

The Company is entitled to receive up to €47.0 million in a combination of up-front and sales-based milestone payments, of which the Company received €2.5 million, or approximately $2.9 million, in the third quarter of 2021, for which it recognized revenue of $1.7 million in the third quarter of 2021. Aguettant will purchase product from the Company at an agreed price, or the DZUVEO Purchase Price, subject to adjustment. Aguettant will also make revenue share payments that, combined with the DZUVEO Purchase Price, range from 35% to 45% of net sales in the DZUVEO Territory.

Beginning in the third marketing year, the parties will establish binding annual minimums for purchase orders to be submitted by Aguettant. Aguettant has the right to grant sublicenses to its affiliates or, with the prior approval of the Company, third parties, subject to certain limitations.

The DZUVEO Agreement also provides Aguettant with a right of first negotiation for eighteen (18) months before the Company can enter into a collaboration regarding Zalviso in Europe.

***Zalviso***

On May 18, 2020, the Company received a notice from Grünenthal that it had exercised its right to terminate the Grünenthal Agreements, effective November 13, 2020. The terms of the Grünenthal Agreements were extended to May 12, 2021 to enable Grünenthal to sell down its Zalviso inventory, a right it had under the Grünenthal Agreements. The rights to market and sell Zalviso in the Zalviso Territory reverted back to the Company on May 12, 2021.

Amended License Agreement

Under the Amended License Agreement with Grünenthal, the Company was 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). A portion of the tiered royalty payments earned were paid to PDL in connection with the Royalty Monetization. For additional information on the Royalty Monetization with PDL, see Note 10 “Liability Related to Sale of Future Royalties”. On August 31, 2020, PDL announced it sold its royalty interest for Zalviso to SWK Funding, LLC.

Amended MSA

Under the terms of the Amended MSA with Grünenthal, the Company manufactured and supplied the Product for use in the Field for the Territory exclusively for Grünenthal. The Product was supplied at prices approximating the Company’s manufacturing cost, subject to certain caps, as defined in the MSA Amendment.

The Grünenthal Agreements entitled the Company to receive additional payments upon the achievement of certain development milestones which related to post approval product enhancements, expanded market opportunities and manufacturing efficiencies for Zalviso and required future research, development and regulatory activities. These payments were excluded from the transaction price as they were considered payments for optional additional services elected by Grünenthal.

The Grünenthal Agreements also included milestone payments related to specified net sales targets, totaling $166.0 million. These payments were considered sales-based license royalties under ASC Topic 606 and would have been recognized apart from the other contract consideration when the related sales occurred. These net sales targets were not achieved prior to the termination of the Grünenthal Agreements.

**7. Revenue from Contracts with Customers**

The following table summarizes revenue from contracts with customers for the years ended December 31, 2021 and 2020 into categories that depict how the nature, amount, timing and uncertainty of revenue and cash flows are affected by economic factors (in thousands):

| | December 31, | |
|---|---|---|
| | **2021** | **2020** |
| Product sales: | | |
| DSUVIA | $ 735 | $ 1,409 |
| Zalviso | 270 | 1,112 |
| Total product sales | 1,005 | 2,521 |
| Contract and other collaboration: | | |
| License revenue | 1,696 | — |
| Non-cash royalty revenue related to Royalty Monetization (See Note 10) | 83 | 242 |
| Royalty revenue | 28 | 81 |
| Other revenue | 6 | 2,572 |
| Total revenues from contract and other collaboration | 1,813 | 2,895 |
| Total revenue | $ 2,818 | $ 5,416 |

For additional detail on the Company's accounting policy regarding revenue recognition, refer to Note 1 "Organization and Summary of Significant Accounting Policies - Revenue from Contracts with Customers."

***Product Sales***

The Company's commercial launch of DSUVIA in the United States occurred in the first quarter of 2019. Zalviso was sold in Europe by Grünenthal through May 12, 2021. DZUVEO sales in Europe by the Company's collaboration partner, Aguettant, have not commenced as of December 31, 2021.

***Contract and Other Collaboration***

Contract and other collaboration revenue includes revenue under the Grünenthal Agreements related to research and development services, non-cash royalty revenue related to the Royalty Monetization and royalty revenue for sales of Zalviso in Europe and license revenue recognized under the DZUVEO Agreement.

The Company concluded that Aguettant is a customer and therefore revenue recognition for the DZUVEO Agreement in Europe should be accounted for in accordance with FASB Accounting Standards Codification, or ASC, Topic 606, "*Revenue from Contracts with Customers*", because the Company granted to Aguettant licenses and will provide the supply of product, as defined below, all of which are outputs of the Company's ongoing activities, in exchange for consideration.

The Company identified the following promises under the DZUVEO Agreement at inception, namely: (a) granting of the licenses, (b) manufacturing services inclusive of quality control testing and stability testing which are options in the initial arrangement, and (c) a material right associated with the discounted price for future optional orders of DZUVEO commercial product supply.

The licenses are considered to be functional intellectual property. The Company determined that the licenses are capable of being distinct because Aguettant can benefit from the license on its own by commercializing the underlying product using its own resources. The Company manufacturing services are not highly specialized in nature and can be performed by third party contract manufacturing organizations. There are no binding commitments for manufacturing purchase orders at inception of the arrangement. Therefore, the manufacturing services are considered to be an option and not a performance obligation in the initial arrangement. However, the Company has determined that the discounted price per unit on future optional product orders constitutes a material right and is a performance obligation. The right to purchase at a discount is capable of being used by the customer on a standalone basis, because this relates to future product purchases and occur after the licenses' performance obligations are transferred.

The Company evaluated if there is an interdependence between the performance obligations and determined that the licenses are a combined solution and the predominant performance obligation. The material right is separately identifiable in the context of the contract and is not modified by, and does not modify, the license performance obligation and is not highly interdependent or interrelated with the material right performance obligations in the contract.

The transaction price at the inception of the DZUVEO Agreement consisted of the upfront fee of €2.5 million, or approximately $2.9 million. The variable consideration related to product supply and reimbursables has been constrained as of December 31, 2021 as there has been no forecast provided by Aguettant. The Company will re-evaluate the transaction price each reporting period and as uncertain events are resolved or other changes in circumstances occur.

The Company determined that the $52.2 million sales-based milestone payments and revenue share payments were probable of significant revenue reversal, as their achievement was highly dependent on factors outside the Company's control. As a result, these payments were fully constrained and were not included in the transaction price. Any variable consideration related to sales-based milestones (including royalties) will be recognized when the related sales occur, as they were determined to relate predominantly to the licenses granted to Aguettant and the optional manufacturing services provided by the Company.

The transaction price is allocated to the performance obligations based on relative standalone selling price which were determined for the licenses using the adjusted market approach, and for the manufacturing services and the material right associated with discounted DZUVEO product supply using the cost-plus reasonable margin approach. Variable consideration is allocated to the specific performance obligations to which it relates.

For revenue recognition purposes, the Company determined that the duration of the contract began on the effective date in July 2021 and ends after an initial term of 10 marketing years, unless it automatically renews for a successive five marketing years. The Company also analyzed the impact if Aguettant terminated the agreement prior to the end of the term and determined, considering both quantitative and qualitative factors, that there were substantive non-monetary penalties to Aguettant for doing so.

Revenue for the granting of the licenses was recognized on the effective date of the DZUVEO Agreement at the point in time that the licenses are effective. The manufacturing services inclusive of quality control testing and stability testing will be recognized at a point in time when, or as, the Company transfers the associated promised goods and services to Aguettant. The material right for the discounted price per unit on future optional orders will be recognized over time with the measure of progress being straight-line over the period in which the Company stands ready to provide the discounted price per unit on the manufacturing services.

For the year ended December 31, 2021, the Company recorded $1.7 million in contract and other collaboration revenue as a result of satisfying its licenses performance obligation by transferring the license rights to Aguettant.

***Contract Liabilities***

A contract liability of $1.2 million was recorded on the Consolidated Balance Sheets as deferred revenue as of December 31, 2021, $0.1 million of which represented the current portion, for the portion of the upfront fee received under the DZUVEO Agreement allocated to the material right for discounted price on future optional product supply which has not yet been satisfied. The material right contract liability will be recognized over the period the discount on future product supply is made available. There was no contract asset as of December 31, 2021 associated with the DZUVEO Agreement.

As of December 31, 2021, deferred contract acquisition costs were negligible and deferred contract acquisition costs amortized during the year ended December 31, 2021 were $0.3 million.

The following table presents changes in the Company's contract liability for the years ended December 31, 2021 and 2020 (in thousands):

| | | |
|---|---|---|
| Balance at January 1, 2020 | $ | 3,244 |
| Deductions for performance obligations satisfied: | | |
| In current period | | ( 623) |
| In prior periods[1] | | (2,572) |
| Balance at December 31, 2020 | $ | 49 |
| Additions[2] | | 1,237 |
| Deductions for performance obligations satisfied: | | |
| In current period | | (49) |
| Balance at December 31, 2021 | $ | 1,237 |

(1) In May 2020, upon notification of early termination by Grünenthal, the Company recognized approximately $2.6 million of deferred revenue under the Grünenthal Agreements.

(2) Deferred revenue under the DZUVEO Agreement with Aguettant.

**8. Long-Term Debt**

***Loan Agreement with Oxford***

On May 30, 2019, the Company entered into the Loan Agreement with Oxford as the Lender. Under the Loan Agreement, the Lender made a term loan to the Company in an aggregate principal amount of $25.0 million, or the Loan, which was funded on May 30, 2019. The Company used approximately $8.9 million of the proceeds from the Loan to repay its outstanding obligations under its prior debt agreement. After deducting all loan initiation costs and outstanding interest on the prior debt agreement, the Company received $15.9 million in net proceeds.

The interest rate is calculated at a rate equal to the sum of (a) the greater of (i) the 30-day U.S. LIBOR rate reported in The Wall Street Journal on the last business day of the month that immediately precedes the month in which the interest will accrue and (ii) 2.50%, plus (b) 6.75%. On July 27, 2017, the Financial Conduct Authority, or FCA, in the U.K. announced that it would phase out LIBOR as a benchmark by the end of 2021. It is unclear whether new methods of calculating LIBOR will be established such that it continues to exist after 2021 or if LIBOR will be replaced with an alternative reference rate; however, the Company does not believe such changes would have a material adverse effect on its financing costs. Payments on the Loan were interest-only until July 1, 2020 followed by equal principal payments and monthly accrued interest payments through the scheduled maturity date of June 1, 2023. The Company's obligations under the Loan Agreement are secured by a security interest in all the assets of the Company, other than the Company's intellectual property which is subject to a negative pledge.

The Company may prepay the Loan at any time. If the Loan is paid prior to the maturity date, the Company will pay the Lender a prepayment charge, based on a percentage of the then outstanding principal balance, equal to 1%. Upon voluntary or mandatory prepayment, in addition to the prepayment charge, the Company is required to pay the EOT Fee, Lender's expenses and all outstanding principal and accrued interest through the prepayment date.

The Loan Agreement includes customary representations and covenants that, subject to exceptions, will restrict the Company's ability to do the following things: declare dividends or redeem or repurchase equity interests; incur additional liens; make loans and investments; incur additional indebtedness; engage in mergers, acquisitions, and asset sales; transact with affiliates; undergo a change in control; add or change business locations; and engage in businesses that are not related to its existing business. The Loan Agreement requires that the Company always maintain unrestricted cash of not less than $5.0 million in accounts subject to control agreements in favor of Lender, tested monthly as of the last day of the month.

The Loan Agreement 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 the Lender's security interest or in the value of the collateral, a material adverse change in business, operations or the prospect of repayment, events relating to bankruptcy or insolvency. The Loan also contains a cross default provision, under which if a third party (under any agreement) has the right to accelerate indebtedness greater than $250,000, the Loan would also be considered in default. In addition, the Loan defines events which negatively impact government approvals, judgments in excess of $500,000 and the delisting of the Company's shares of common stock on the Nasdaq Global Market, or Nasdaq, as events of default. Upon the occurrence of an event of default, a default interest rate of an additional 5% may be applied to the outstanding loan balances, and the Lender may declare all outstanding obligations immediately due and payable and take such other actions as set forth in the Loan Agreement. Acceleration would result in the payment of any applicable prepayment charges and application of the default interest rate to the outstanding balance until payment is made in full. The Company bifurcated a compound derivative liability related to a contingent interest feature and acceleration upon default provision (contingent put option) provided to the Lender. The bifurcated embedded derivative must be valued and separately accounted for in the Company's Consolidated Financial Statements. The contingent put option liability is classified as a component of other long-term liabilities. As of December 31, 2021, the estimated fair value of the contingent put option liability was $0.1 million 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. See Note 2 "Investments and Fair Value Measurement" for further description.

In connection with the Loan Agreement, on May 30, 2019, the Company issued warrants to the Lender and its affiliates, which are exercisable for an aggregate of 176,679 shares of the Company's common stock with a per share exercise price of $2.83, or the Warrants. The Warrants have been classified within stockholders' (deficit) equity and accounted for as a discount to the loan by allocating the gross proceeds on a relative fair value basis. For further discussion, see Note 11 "Warrants".

The outstanding balance due under the Loan Agreement was $13.3 million and $21.0 million at December 31, 2021 and 2020, respectively. Interest expense related to the Loan Agreement was $2.2 million, of which $0.7 million represented amortization of the debt discount, and $3.2 million, $0.9 million of which represented amortization of the debt discount, for the years ended December 31, 2021 and 2020, respectively, and the effective interest rate was 13.15% in both periods.

***Non-Interest Bearing Payments for the Construction of Leasehold Improvements***

In August 2019, the Company entered into a Site Readiness Agreement, or SRA, with a potential Contract Manufacturing Organization, or CMO, in contemplation of entering into a commercial supply agreement for its product DSUVIA® at a future date. Under the SRA, the Company is building out a suite within the CMO's production facility. If additional equipment and facility modifications are required to meet the Company's product needs, the Company may be required to contribute to the cost of such additional equipment and facility modifications. The Company has determined that it is the owner of the leasehold improvements related to the build-out which will be paid for in four annual installments of $0.5 million through July 2022. As of December 31, 2021 and 2020, the accrued balance under the SRA is $0.5 million and $0.8 million, respectively, and $1.7 million of these leasehold improvements have been capitalized. The effective interest rate related to the payments at December 31, 2021 and 2020 was 14.35%. The leasehold improvements are recorded as property and equipment, net, in the Consolidated Balance Sheets.

***Future Payments on Long-Term Debt***

The following table summarizes the outstanding future payments associated with the Company's long-term debt as of December 31, 2021 (in thousands):

| | |
|---|---|
| 2022 | $ 9,647 |
| 2023 | 5,530 |
| Total payments | 15,177 |
| Less amount representing interest | (927) |
| Notes payable, gross | 14,250 |
| Less: Unamortized portion of EOT Fee | (200) |
| Less: Unamortized discount on notes payable | (247) |
| Long-term debt | 13,803 |
| Less current portion | (8,796) |
| Long-term debt, net of current portion | $ 5,007 |

**9. Leases**

***Office Lease***

The Company leased office and laboratory space for its former corporate headquarters, located at 301 – 351 Galveston Drive, Redwood City, California, and entered into an agreement to sublease approximately 12,106 square feet of this office and laboratory space.

On March 26, 2021, the Company entered into a Lease Termination Agreement with its landlord and a Sublease Termination Agreement with its sublessee, to terminate the lease and sublease agreements at its former corporate headquarters. The termination of both the lease and sublease was effective on April 30, 2021. As of the date of the Lease Termination Agreement, the Company remeasured its lease liability and recorded a gain of $0.5 million upon derecognition of the lease liability and right of use asset for the master lease, which was included in operating expenses for the year ended December 31, 2021. In connection with the Sublease Termination, the remaining deferred costs of $0.3 million were fully amortized through April 30, 2021, the effective date of the Sublease Termination, and included in operating expenses for the year ended December 31, 2021.

On March 26, 2021, the Company entered into a Sublease Agreement to sublet space for its new corporate headquarters, located at 25821 Industrial Boulevard, Hayward, California. The Sublease Agreement commencement date was April 1, 2021. The Sublease Agreement is for a period of two years and three months with monthly rental payments of $17,000, including one month of abated rent. On the lease commencement date, the Company recognized an operating lease right-of-use asset in the amount of $0.4 million.

***Contract Manufacturing Leases***

On December 12, 2012, the Company entered into an agreement for commercial supply manufacturing services related to the Company's Zalviso drug product with a contract manufacturing organization. The initial term of the agreement was through December 31, 2017, which term automatically renews in two-year increments unless earlier terminated by either party by giving eighteen months' notice. Commencing in 2013, the Company is required to make overhead fee payments each year of $0.2 million, prorated based on aggregate revenues. The Company has determined that this fee is an in-substance fixed lease payment as it represents the minimum annual payment under the contract. The Company concluded that this agreement contains an embedded lease as the clean rooms have been built specifically for production of the Company's product and their use is effectively controlled by the Company as it has priority over the space during the term of the agreement. The Company accounts for the agreement as an operating lease and has evaluated the non-cancelable term to be through the binding commitment date of June 30, 2023.

On April 21, 2021, the Company entered into a Commercial Supply Agreement, or the CSA, with Catalent Pharma Solutions, LLC, or Catalent, effective March 31, 2021, under which Catalent provides certain services to the Company in connection with the processing and packaging of a packaged single dose applicator containing the sublingual tablet 30 mcg sufentanil dosage form contained in the pharmaceutical product, DSUVIA (sufentanil), intended for commercialization.

The term of the CSA is for a period of five years from the first date upon which the FDA approves Catalent as a manufacturer of DSUVIA in the United States, or the Commencement Date. The term shall automatically be extended for successive two-year periods, unless and until one party gives the other party at least 24 months' prior written notice of its desire to terminate as of the end of the then-current term.

The Company will pay Catalent an annual fee of $1.0 million beginning January 1, 2022. Pursuant to the CSA, the Company will purchase each 10-pack carton of DSUVIA from Catalent at an agreed price through December 31, 2022, and pay other fees set forth in the CSA. All pricing and fees, with the exception of raw materials, may be adjusted on an annual basis, effective on January 1 of each calendar year, beginning with January 1, 2023, subject to certain limitations. Price increases for raw materials will be passed through to the Company.

The Company has determined that the fixed fees in the CSA are in-substance lease payments. The Company concluded that this agreement contains an embedded lease as the clean rooms have been built specifically for production of the Company's product and their use is effectively controlled by the Company as it has sole use over the space during the term of the agreement. The Company accounts for the agreement as an operating lease and has evaluated the non-cancelable lease term to be through the binding commitment date of May 15, 2027.

The components of lease expense are presented in the following table (in thousands):

| | Year ended December 31, 2021 | Year ended December 31, 2020 |
|---|---|---|
| Operating lease costs | $ 1,467 | $ 1,360 |
| Gain on derecognition of operating lease | (522) | — |
| Sublease income | (199) | (598) |
| Loss on termination of sublease | 331 | — |
| Net lease costs | $ 1,077 | $ 762 |

The weighted average remaining lease term and discount rate related to the operating leases are presented in the following table:

| | December 31, 2021 | December 31, 2020 |
|---|---|---|
| Weighted-average remaining lease term – operating leases (in years) | 4.97 | 3.1 |
| Weighted-average remaining discount rate – operating leases (in years) | 12.8% | 11.7% |

Maturities of lease liabilities as of December 31, 2021 are presented in the following table (in thousands):

| | |
|---|---|
| Year: | |
| 2022 | $ 1,608 |
| 2023 | 1,244 |
| 2024 | 1,040 |
| 2025 | 1,040 |
| 2026 | 1,040 |
| Thereafter | 415 |
| Total future minimum lease payments | 6,387 |
| Less imputed interest | (1,569) |
| Total | $ 4,818 |
| Reported as: | |
| Operating lease liabilities | $ 4,818 |
| Operating lease liabilities, current portion | (1,068) |
| Operating lease liabilities, net of current portion | $ 3,750 |

**10. Liability Related to Sale of Future Royalties**

On September 18, 2015, the Company entered into the Royalty Monetization with PDL for which it received gross proceeds of $65.0 million. Under the Royalty Monetization, PDL was to 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), up to a capped amount of $195.0 million over the life of the arrangement.

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 effective 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 ARPI LLC and paid to PDL, up to a capped amount of $195.0 million, over the life of the arrangement. The aggregate future estimated royalty and milestone payments (subject to the capped amount), 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 relating to the Royalty Monetization accordingly.

The Company periodically assesses 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 the Company's 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 effective interest rate. During the three months ended June 30, 2020, Grünenthal notified the Company that it was terminating the Amended License Agreement, effective November 13, 2020. The terms of the Grünenthal Agreements were extended to May 12, 2021 to enable Grünenthal to sell down its Zalviso inventory. The rights to market and sell Zalviso in the Zalviso Territory reverted back to the Company on May 12, 2021. There is a continuing obligation on the Company's part, through the term of the Royalty Monetization with SWK (assignee of PDL), to use commercially reasonable efforts to negotiate a replacement license agreement, or New Arrangement. If the Company is unable to find a New Arrangement, a contingent gain of up to approximately $64 million may be recognized when it is realized upon expiration of the liability at the end of the Royalty Monetization term. Due to the significant judgments and factors related to the estimates of future payments under the Royalty Monetization, there are significant uncertainties surrounding the amount and timing of future payments and the probability of realization of the estimated contingent gain.

The effective interest rate over the life of the liability will be 0% as the Company records interest income over the remaining term of the arrangement as an offset to the interest expense that was recognized in prior periods. The effective interest income rate for the years ended December 31, 2021 and 2020 was approximately 3.5% and 3.6%, respectively.

The following table shows the activity within the liability account during the year ended December 31, 2021 (in thousands):

| | Year ended December 31, 2021 | Period from inception to December 31, 2021 |
|---|---|---|
| Liability related to sale of future royalties — beginning balance | $ 88,471 | $ — |
| Proceeds from sale of future royalties | — | 61,184 |
| Non-cash royalty revenue | (145) | (1,083) |
| Non-cash interest (income) expense recognized | (3,038) | 25,187 |
| Liability related to sale of future royalties as of December 31, 2021 | $ 85,288 | $ 85,288 |

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 (income) expense within its Consolidated Statements of Operations over the term of the Royalty Monetization. The liability related to the sale of future royalties, current portion, is recorded as accrued liabilities in the Company's Consolidated Balance Sheets.

**11. Warrants**

***November 2021 Financing Warrants***

On November 15, 2021, the Company entered into a securities purchase agreement with certain investors pursuant to which the Company, in a registered direct offering, sold (i) an aggregate of 17,500,000 shares of the Company's common stock, and (ii) warrants to purchase up to an aggregate of 17,500,000 shares of common stock, for an aggregate purchase price of $14.0 million (see Note 13 "Stockholders' Equity"). The November 2021 Financing Warrants have an exercise price of $1.00 per share and become exercisable, if the holder's post-exercise beneficial ownership is less than or equal to 9.99%, 6 months after their issuance date and have a five-year term ( November 15, 2026). All common stock issuable under the issued warrants, were added to the Company's effective registration statement on November 15, 2021.

The November 2021 Financing warrants were valued at approximately $8.6 million using the Black-Scholes option pricing model as follows: exercise price of $1.00 per share, stock price of $0.7461 per share, expected life of five years, volatility of 91.77%, and a risk-free rate of 1.26%. The common stock and warrants were issued in a unit structure; therefore, in accordance with ASC Topic 815, the aggregate gross proceeds of $14.0 million were allocated to the two securities using the relative fair value method, resulting in the common stock and warrants being allocated values of $8.4 million and $5.6 million, respectively, and recorded to stockholders' equity.

***Loan Agreement Warrants***

In connection with the Loan Agreement, on May 30, 2019, the Company issued warrants to the Lender and its affiliates, which are exercisable for an aggregate of 176,679 shares of the Company's common stock with a per share exercise price of $2.83, or the Loan Agreement Warrants. The Loan Agreement Warrants may be exercised on a cashless basis. The Loan Agreement Warrants are exercisable for a term beginning on the date of issuance and ending on the earlier to occur of ten years from the date of issuance or the consummation of certain acquisitions of the Company as set forth in the Loan Agreement Warrants. The number of shares for which the Loan Agreement Warrants are exercisable and the associated exercise price are subject to certain proportional adjustments as set forth in the Loan Agreement Warrants.

The Company estimated the fair value of these Loan Agreement Warrants as of the issuance date to be $0.4 million, which was used in estimating the fair value of the debt instrument and was recorded as equity. The fair value of the Loan Agreement Warrants was calculated using the Black-Scholes option-valuation model, and was based on the strike price of $2.83, the stock price at issuance of $2.66, the ten-year contractual term of the warrants, a risk-free interest rate of 2.22%, expected volatility of 80.22% and 0% expected dividend yield.

As of December 31, 2021, Loan Agreement Warrants to purchase 176,679 shares of common stock issued to the Lender and its affiliates had not been exercised and were still outstanding. These warrants expire in May 2029.

**12. Commitments and Contingencies**

***Litigation***

On June 8, 2021, a securities class action complaint was filed in the U.S. District Court for the Northern District of California against the Company and two of its officers. The plaintiff is a purported stockholder of the Company. The complaint alleges that defendants violated Sections 10(b) and 20(a) of the Exchange Act and SEC Rule 10b-5 by making false and misleading statements and omissions of material fact about the Company's disclosure controls and procedures with respect to its marketing of DSUVIA. The complaint seeks unspecified damages, interest, attorneys' fees, and other costs. On December 16, 2021, the Court appointed co-lead plaintiffs. Plaintiffs' amended complaint was filed on March 7, 2022. The amended complaint names the Company and three of its officers and continues to allege that defendants violated Sections 10(b) and 20(a) of the Exchange Act and SEC Rule 10b-5 by making false and misleading statements and omissions of material fact about the Company's disclosure controls and procedures with respect to its marketing of DSUVIA. The complaint also alleges a violation of Section 20A of the Exchange Act against the individual defendants for alleged insider trading. Defendants' motion to dismiss the amended complaint is due May 6, 2022.

On July 6, 2021, a purported shareholder derivative complaint was filed in the U.S. District Court for the Northern District of California. The complaint names ten of the Company's officers and directors and asserts state and federal claims based on the same alleged misstatements as the shareholder class action complaint. On September 30, 2021, October 26, 2021, and November 17, 2021, three additional purported shareholder derivative complaints were filed in the U.S. District Court for the Northern District of California. The complaints name nine of the Company's officers and directors and also assert state and federal claims based on the same alleged misstatements as the shareholder class action complaint. All four complaints seek unspecified damages, attorneys' fees, and other costs. On December 6, 2021, the Court entered an order consolidating all four actions and staying the consolidated action pending the outcome of any motion to dismiss the securities class action. Please see "Part II., Item 1A. Risk Factors—Risks of a General Nature—Litigation may substantially increase our costs and harm our business."

The Company believes that these lawsuits are without merit and intends to vigorously defend against them. Given the uncertainty of litigation, the preliminary stage of the cases, and the legal standards that must be met for, among other things, class certification and success on the merits, the Company cannot estimate the reasonably possible loss or range of loss that may result from these actions.

**13. Stockholders' Equity**

***Common Stock***

*2021 Underwritten Public Offering*

On January 22, 2021, the Company completed an underwritten public offering in which the Company issued and sold 14,500,000 shares of its common stock to the underwriter at a price of $1.7625 per share. On January 27, 2021, the underwriters exercised their option in full and purchased an additional 2,175,000 shares at a price of $1.7625 per share. The total net proceeds from this offering of an aggregate 16,675,000 shares were approximately $28.9 million.

*2021 Registered Direct Offering*

On November 17, 2021, the Company completed a registered direct offering in which the Company issued and sold 17,500,000 shares of its common stock at a price of $0.80 per share and warrants exercisable for an aggregate of 17,500,000 shares of its common stock at a price of $1.00 per share. The total net proceeds from this offering were approximately $13.9 million. The November 2021 issued shares were valued at approximately $13.1 million based on the closing stock price of $0.7491 per share on November 15, 2021. The common stock and warrants were issued in a unit structure; therefore, in accordance with ASC Topic 815, the aggregate gross proceeds of $14.0 million were allocated to the two securities using the relative fair value method, resulting in the common stock and warrants being allocated values of $8.4 million and $5.6 million, respectively.

*2020 Registered Direct Offerings*

On July 23, 2020, the Company completed a registered direct offering in which it issued and sold 9,433,962 shares of its common stock at a price of $1.06 per share. The total net proceeds from this offering were approximately $10.0 million, after deducting estimated expenses payable by the Company of $49,000. No underwriter or placement agent participated in the offering.

On December 11, 2020, the Company completed a registered direct offering in which it issued and sold 8,333,333 shares of its common stock at a price of $1.20 per share. The total net proceeds from this offering were approximately $9.9 million, after deducting estimated expenses payable by the Company of $51,000. No underwriter or placement agent participated in the offering.

*ATM Agreement*

On June 21, 2016, the Company entered into a Controlled Equity Offering℠ Sales Agreement, or the ATM Agreement, with Cantor Fitzgerald & Co., or Cantor, as agent, pursuant to which the Company may offer and sell, from time to time through Cantor, shares of the Company's common stock, or the Common Stock having an aggregate offering price of up to $40.0 million, or the Shares. On May 9, 2019, the Company increased the aggregate offering price of shares of the Company's common stock which may be offered and sold under the ATM Agreement by $40.0 million, for a total of $80.0 million, or the Shares. The offering of Shares pursuant to the ATM Agreement will terminate upon the earlier of (a) the sale of all of the Shares subject to the ATM Agreement or (b) the termination of the ATM Agreement by Cantor or the Company, as permitted therein. The Company will pay Cantor a commission rate in the low single digits on the aggregate gross proceeds from each sale of Shares and have agreed to provide Cantor with customary indemnification and contribution rights.

During the year ended December 31, 2021, the Company issued and sold approximately 3.0 million shares of common stock pursuant to the ATM Agreement, and received net proceeds of approximately $7.5 million, after deducting fees and expenses. During the year ended December 31, 2020, the Company issued and sold 876,800 shares of common stock pursuant to the ATM Agreement, for which the Company received net proceeds of approximately $1.4 million.

As of December 31, 2021, the Company had the ability to offer and sell shares of the Company's common stock having an aggregate offering price of up to $36.1 million under the ATM Agreement.

***Stock Plans***

*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 EIP. The initial aggregate number of shares of the Company's common stock that were issuable pursuant to stock awards under the 2011 EIP was approximately 1.9 million shares. The number of shares of common stock reserved for issuance under the 2011 EIP automatically increased on January 1 of 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.

As of June 16, 2020, no more awards may be granted under the 2011 Equity Incentive Plan, or the 2011 EIP, although all outstanding stock options and other stock awards previously granted under the 2011 EIP will continue to remain subject to the terms of the 2011 EIP.

*Amended 2020 Plan*

On June 16, 2020, at the 2020 Annual Meeting of Stockholders of the Company, the Company's stockholders, upon the recommendation of the Company's Board of Directors, approved the Company's 2020 Equity Incentive Plan, or the 2020 EIP.

The initial aggregate number of shares of the Company's common stock issuable pursuant to stock awards under the 2020 EIP was 5,500,000 shares. In addition, the share reserve will be increased by the number of returning shares, if any, as such shares become available from time to time under the 2011 EIP, for an additional number of shares not to exceed 14,892,170 shares. The term of any option granted under the 2020 EIP is determined on the date of grant but shall not be longer than 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 stock-based programs.

On June 17, 2021, at the 2021 Annual Meeting of Stockholders of the Company, upon the recommendation of the Company's Board of Directors, the Company's stockholders approved an amendment and restatement of the Company's 2020 Equity Incentive Plan, or 2020 Plan, or as amended and restated, the Amended 2020 Plan, to increase the number of authorized shares reserved for issuance thereunder by 4,300,000 shares, subject to adjustment for certain changes in the Company's capitalization. The aggregate number of shares of the Company's common stock that may be issued under the Amended 2020 Plan will not exceed the sum of: (i) 4,300,000 shares approved in connection with the adoption of the Amended 2020 Plan, (ii) 5,500,000 shares approved in connection with the original adoption of the 2020 Plan, and (iii) certain shares subject to outstanding awards granted under the 2011 Equity Incentive Plan that may become available for issuance under the 2020 Plan and Amended 2020 Plan, as such shares become available from time to time.

*Amended and Restated 2011 Employee Stock Purchase Plan*

Additionally, on June 16, 2020, the Company's stockholders, upon the recommendation of the Company's Board of Directors, approved the Amended and Restated 2011 Employee Stock Purchase Plan, or the Amended ESPP, which increased the aggregate number of shares of the Company's common stock reserved for issuance under the 2011 Employee Stock Purchase Plan, or ESPP, to 4,900,000 shares, subject to adjustment for certain changes in the Company's capitalization, and removed the "evergreen" provision from the ESPP.

In the year ended December 31, 2021, there were 297,959 shares issued under the Amended ESPP. The weighted average fair value of shares issued under the Amended ESPP in 2021 and 2020 was $1.01 and $1.09 per share, respectively. As of December 31, 2021, there were 4,456,364 shares available for future grant under the Amended ESPP.

**14. Stock-Based Compensation**

The Company recorded total stock-based compensation expense for stock options, stock awards and the Amended ESPP as follows (in thousands):

| | December 31, 2021 | December 31, 2020 |
|---|---|---|
| Cost of goods sold | $ 92 | $ 123 |
| Research and development | 813 | 764 |
| Selling, general and administrative | 3,704 | 3,537 |
| Total | $ 4,609 | $ 4,424 |

The following table summarizes restricted stock unit activity under the Company's Equity Incentive Plans:

| | Number of Restricted Stock Units | Weighted Average Grant Date Fair Value |
|---|---|---|
| Restricted stock units outstanding, January 1, 2020 | 988,645 | $ 2.53 |
| Granted | 908,300 | 1.30 |
| Vested | (304,810) | 2.53 |
| Forfeited | (194,152) | 2.16 |
| Restricted stock units outstanding, December 31, 2020 | 1,397,983 | $ 1.79 |
| Granted | 1,149,632 | 1.68 |
| Vested | (587,214) | 1.89 |
| Forfeited | (186,025) | 1.58 |
| Restricted stock units outstanding, December 31, 2021 | 1,774,376 | $ 1.71 |

The following table summarizes stock option activity under the Company's Equity Incentive Plans:

| | Number of Stock Options Outstanding | Weighted-Average Exercise Price | Weighted-Average Remaining Contractual Life (Years) | Aggregate Intrinsic Value (in thousands) |
|---|---|---|---|---|
| December 31, 2020 | 12,813,022 | $ 3.20 | | |
| Granted | 2,667,612 | 1.82 | | |
| Forfeited | (375,432) | 1.79 | | |
| Expired | (801,749) | 3.03 | | |
| Exercised | (19,403) | 0.84 | | |
| December 31, 2021 | 14,284,050 | $ 2.99 | 5.8 | $ — |
| Vested and exercisable options—December 31, 2021 | 10,496,744 | $ 3.42 | 4.8 | $ — |
| Vested and expected to vest—December 31, 2021 | 14,284,050 | $ 2.99 | 5.8 | $ — |

As of December 31, 2021, there were 7,858,933 shares available for future grant under the 2020 EIP.

Additional information regarding the Company's stock options outstanding and vested and exercisable as of December 31, 2021 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 |
| $0.72 - $1.12 | 695,482 | 8.1 | $ 0.85 | 280,047 | $ 0.84 |
| $1.26 - $1.89 | 3,402,418 | 8.9 | $ 1.80 | 496,679 | $ 1.67 |
| $2.00 - $3.00 | 5,310,550 | 6.1 | $ 2.44 | 4,856,618 | $ 2.43 |
| $3.10 - $4.65 | 3,066,819 | 3.8 | $ 3.37 | 3,054,619 | $ 3.38 |
| $4.73 - $7.10 | 1,295,781 | 1.8 | $ 5.71 | 1,295,781 | $ 5.71 |
| $8.18 - $12.27 | 513,000 | 2.1 | $ 10.28 | 513,000 | $ 10.28 |
| | 14,284,050 | 5.8 | $ 2.99 | 10,496,744 | $ 3.42 |

The weighted average grant-date fair value of options granted during the years ended December 31, 2021 and 2020 was $1.24 and $0.92 per share, respectively. As of December 31, 2021, total stock-based compensation expense related to unvested options to be recognized in future periods was $3.8 million which is expected to be recognized over a weighted-average period of 2.1 years. The grant date fair value of shares vested during the years ended December 31, 2021 and 2020 was $2.4 million and $3.6 million, respectively. The total intrinsic value of options exercised during the years ended December 31, 2021 and 2020 was $5.7 thousand and $0.0 million, respectively.

On March 3, 2021, the Company granted 1.27 million performance-based stock options to certain of its executive officers, which are included in the stock option tables and associated disclosures above. The awards were granted under the 2020 EIP with an exercise price of $1.88 per share, the closing sales price as reported on the Nasdaq on the date of grant. The performance-based stock options are eligible to vest subject to the satisfaction of the service-based vesting requirements and attainment of share price target goals, a market-based condition. No performance-based stock options vested during the year ended December 31, 2021, and there were no performance-based stock options granted for the year ended December 31, 2020.

The Company uses the Monte Carlo Simulation model to evaluate the derived service period and fair value of awards with market conditions, including assumptions of historical volatility and risk-free interest rate commensurate with the vesting term.

The Company used the following assumptions to calculate the fair value of each performance-based stock option:

| | Year Ended December 31, | |
|---|---|---|
| | 2021 | 2020 |
| Derived service period (in years) | 2.3 – 2.6 | — |
| Risk-free interest rate | 1.5% | — |
| Expected volatility | 90% | — |
| Expected dividend rate | 0% | — |

The Company used the following assumptions to calculate the fair value of each time-based stock option:

| | Year Ended December 31, | |
|---|---|---|
| | 2021 | 2020 |
| Expected term (in years) | 6.0 - 6.2 | 6.2 |
| Risk-free interest rate | 0.9% - 1.3% | 0.4% - 1.5% |
| Expected volatility | 90% | 83% |
| Expected dividend rate | 0% | 0% |

**15. 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, restricted stock units 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.

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, | |
|---|---|---|
| | 2021 | 2020 |
| ESPP, RSUs and stock options to purchase common stock | 16,328,426 | 14,541,005 |
| Common stock warrants | 17,676,679 | 176,679 |

**16. Accrued Liabilities**

Accrued liabilities consist of the following (in thousands):

| | December 31, | |
|---|---|---|
| | 2021 | 2020 |
| Accrued compensation and employee benefits | $ 2,974 | $ 3,323 |
| Accrued professional services | 1,523 | 179 |
| Accrued product returns and sales allowances | 775 | 656 |
| Deferred revenue | 86 | 49 |
| Other accrued liabilities | 1,166 | 838 |
| Total accrued liabilities | $ 6,524 | $ 5,045 |

**17. 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 $0.4 million and $0.5 million for the years ended December 31, 2021 and 2020, respectively.

**18. Income Taxes**

The Company recorded a provision for income taxes of $5.0 thousand and $4.0 thousand during the years ended December 31, 2021 and 2020, respectively.

Net deferred tax assets as of December 31, 2021 and 2020 consist of the following (in thousands):

| | December 31, 2021 | December 31, 2020 |
|---|---|---|
| Deferred tax assets: | | |
| Accruals and other | $ 3,989 | $ 4,136 |
| Research credits | 7,275 | 7,275 |
| Net operating loss carryforward | 75,452 | 65,274 |
| Section 59(e) R&D expenditures | 5,070 | 7,473 |
| Deferred revenue | 19,666 | 20,848 |
| Total deferred tax assets | 111,452 | 105,006 |
| Valuation allowance | (111,452) | (105,006) |
| Net deferred tax assets | $ — | $ — |

Reconciliations of the statutory federal income tax to the Company's effective tax during the years ended December 31, 2021 and 2020 are as follows (in thousands):

| | Year Ended December 31, | |
|---|---|---|
| | 2021 | 2020 |
| Tax at statutory federal rate | $ (7,370) | $ (8,486) |
| State tax—net of federal benefit | 231 | (3,587) |
| Stock options | 718 | 636 |
| Other | (20) | — |
| Change in valuation allowance | 6,446 | 11,441 |
| Provision for income taxes | $ 5 | $ 4 |

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 $6.4 million and $11.4 million during the years ended December 31, 2021 and 2020, respectively.

As of December 31, 2021, the Company had federal net operating loss carryforwards of $308.5 million, of which $114.9 million federal net operating losses generated before January 1, 2018 will begin to expire in 2029. Federal net operating losses of $193.6 million generated from 2018 to 2021 will carryforward indefinitely but are subject to the 80% taxable income limitation. As of December 31, 2021, the Company had state net operating loss carryforwards of $154.7 million, which begin to expire in 2028.

As of December 31, 2021, the Company had federal research credit carryovers of $6.5 million, which begin to expire in 2026. As of December 31, 2021, the Company had state research credit carryovers of $4.0 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 thousand 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, 2021 and 2020 is as follows (in thousands):

| | Year Ended December 31, | |
|---|---|---|
| | 2021 | 2020 |
| Unrecognized benefit—beginning of period | $ 2,635 | $ 2,635 |
| Gross increases—prior period tax positions | — | — |
| Gross increases—current period tax positions | — | — |
| Unrecognized benefit—end of period | $ 2,635 | $ 2,635 |

The entire amount of the unrecognized tax benefits would not impact the Company's effective tax rate if recognized.

There were no accrued interest or penalties related to unrecognized tax benefits in the years ended December 31, 2021 and 2020. The Company files income tax returns in the United States, California, and other states. The tax years 2005 through 2014, and 2016 through 2021, remain open in all 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.

In March 2020, the Coronavirus Aid, Relief and Economic Security, or CARES, Act was signed into law. The CARES Act included several tax changes as part of its economic package. These changes principally related to expanded net operating loss carryback periods, increases to interest deductibility limitations, and accelerated alternative minimum tax refunds. The Company has evaluated these items and determined that the items do not have a material effect on the Company's financial statements as of December 31, 2021. Additionally, the CARES Act enacted the Employee Retention Credit, or ERC, to incentivize companies to retain employees, which was subsequently modified by extension of the CARES Act. Under the provisions of the CARES Act and its subsequent extension, the Company was eligible for ERCs, subject to certain criteria. Accordingly, the Company has recorded a reduction in payroll taxes related to ERCs claimed for $1.4 million in the year ended December 31, 2021. These credits are recorded in the Consolidated Statements of Operations as an offset to the related payroll expenses in the respective operating costs and expenses line item. Such claimed ERCs not settled prior to year-end in the amount of $1.4 million are expected to be settled shortly thereafter and are disclosed within prepaid expenses and other current assets on the Company's Consolidated Balance Sheets at December 31, 2021.

**19. Subsequent Events**

On January 7, 2022, the Company closed the Merger Agreement with Lowell in a transaction for consideration of approximately $32.5 million plus net cash acquired and certain other adjustments. Pursuant to the terms of the Merger Agreement, all options to purchase capital stock and all shares of Lowell capital stock issued and outstanding immediately before the effective time of the merger were cancelled in exchange for the right to receive (i) 9,009,538 shares of AcelRx common stock, and cash in the amount of $3,519,129, (ii) 1,396,526 shares of AcelRx common stock to be held back to satisfy any potential indemnification and other obligations of Lowell and its securityholders, and (iii) up to $26.0 million of contingent consideration payable in cash or stock at AcelRx's option, upon the achievement of regulatory and sales-based milestones.

The 1,396,526 of held back shares of AcelRx common stock issued in connection with the closing was calculated based on a fixed value of $0.57284 per share, which is the arithmetic average of the daily volume weighted average price per share of AcelRx common stock during the five consecutive full trading days ending on and including the last full trading day immediately prior to the date of the closing. The shares issued pursuant to the Merger Agreement were issued in private placements pursuant to the exemption from registration under Section 4(a)(2) of the Securities Act of 1933, as amended, or the Securities Act, including Rule 506 of Regulation D promulgated under the Securities Act, or Regulation D, without general solicitation as a transaction not involving any public offering.

The Merger Agreement will be accounted for in the first quarter of 2022 as an acquisition of assets that does not meet the definition of a business. The asset acquisition does not constitute a business as substantially all of the fair value of the gross assets acquired was concentrated in Lowell’s intellectual property, including NIYAD™ and LTX-608. The acquired assets and liabilities will be recorded at their relative fair values and the contingent consideration will be recorded when it becomes probable of achievement or the consideration becomes payable. Accordingly, the Company has classified $1.9 million of expenses related to the Merger Agreement as Other assets in the Consolidated Balance Sheet at December 31, 2021.

**SCHEDULE II: VALUATION AND QUALIFYING ACCOUNTS**
**(in thousands)**

| Description | Balance at Beginning of Period | Additions Charged as a Reduction to Revenue | Deductions* | Balance at End of Period |
|---|---|---|---|---|
| Sales & return allowances, discounts, chargebacks and rebates: | | | | |
| Year ended December 31, 2021 | $ 668 | $ 1,012 | $ (900) | $ 780 |
| Year ended December 31, 2020 | $ 161 | $ 645 | $ (138) | $ 668 |

* Deductions to sales discounts and allowances relate to discounts or allowances actually taken or paid.

***Non-Employee Director Compensation Policy***

Compensation for our non-employee directors consists of cash, restricted stock unit awards ("RSUs") and stock options. The Compensation Committee periodically reviews the compensation paid to non-employee directors for their service on the Board and its committees and recommends any changes considered appropriate to the full Board for its approval. Each member of our Board who is not our employee receives an annual retainer of $40,000. In addition, our non-employee directors receive the following cash compensation for Board services, as applicable:

- the Board Chair receives an additional annual retainer of $30,000;
- the Audit Committee Chair receives an additional annual retainer of $20,000;
- the Finance and Strategic Transactions Committee ("FAST Committee") Chair receives an additional annual retainer of $20,000;
- the Compensation Committee Chair receives an additional annual retainer of $15,000;
- the Nominating and Corporate Governance Committee Chair receives an additional annual retainer of $10,000;
- an Audit Committee member receives an additional annual retainer of $10,000;
- a FAST Committee member receives an additional annual retainer of $10,000;
- a Compensation Committee member receives an additional annual retainer of $7,500; and
- a Nominating and Corporate Governance Committee member receives an additional retainer of $5,000.

Beginning in February 2022, upon election or appointment to our Board, a new non-employee director will be granted an initial stock option to purchase 46,500 shares of our common stock, which will vest as to 1/3rd of the shares subject to the option on the one-year anniversary of the date of grant and as to the remaining shares subject to the option on an equal monthly basis over the following two-year period, and 23,250 RSUs, which will vest as to 1/3rd of the RSUs on each anniversary of the date of grant over a three-year period. Each non-employee director who is then serving as a director or who is elected to our Board on the date of an annual meeting will be granted a stock option to purchase 31,000 shares of our common stock, which will vest in full on the one-year anniversary of the date of grant, and 15,500 RSUs, which will vest in full on the one-year anniversary of the date of grant.

All Board and committee retainers accrue and are payable on a quarterly basis at the end of each calendar quarter of service. We continue to reimburse our non-employee directors for travel, lodging and other reasonable expenses incurred in connection with their attendance at Board or committee meetings.

**Exhibit 10.31**

**SECOND AMENDMENT TO**
**LOAN AND SECURITY AGREEMENT**

THIS SECOND AMENDMENT to Loan and Security Agreement (this "**Amendment**") is entered into as of January 10, 2022, by and between **OXFORD FINANCE LLC**, a Delaware limited liability company with an office located at 115 South Union Street, Suite 300, Alexandria, Virginia 22314 ("**Oxford**"), as collateral agent (in such capacity, "**Collateral Agent**"), the Lenders listed on Schedule 1.1 of the Loan Agreement (as defined below) or otherwise party thereto from time to time (each a "**Lender**" and collectively, the "**Lenders**") including Oxford in its capacity as a Lender, **ACELRX PHARMACEUTICALS, INC.**, a Delaware corporation with offices located at 25821 Industrial Blvd., Suite 400, Hayward, California 94545 ("**Existing Borrower**"), and **LOWELL THERAPEUTICS, LLC**, a Delaware limited liability company with offices located at 25821 Industrial Blvd., Suite 400, Hayward, California 94545 ("**New Borrower**" and together with Existing Borrower, individually and collectively, jointly and severally, "**Borrower**").

**RECITALS**

**A.** Collateral Agent, Lenders and Borrower have entered into that certain Loan and Security Agreement dated as of May 30, 2019, as amended by that certain First Amendment to Loan and Security Agreement dated as of May 5, 2021 (as amended or modified from time to time, collectively, the "**Loan Agreement**").

**B.** Lenders have extended credit to Borrower for the purposes permitted in the Loan Agreement.

**C.** Existing Borrower has acquired New Borrower, and New Borrower has become a wholly owned subsidiary of Existing Borrower, pursuant to the terms of that certain Agreement and Plan of Merger dated as of November 14, 2021 by and among Existing Borrower, Lowell Therapeutics, Inc., AcelRx Intermediate Sub, Inc., AcelRx Consolidation Sub, LLC and James Wilkie, as stockholder representative.

**D.** Existing Borrower has requested that Collateral Agent and Lenders (i) add New Borrower as a Borrower under the Loan Agreement and (ii) make certain other revisions to the Loan Agreement as more fully set forth herein.

**E.** Collateral Agent and Lenders have agreed to modify and amend certain provisions of the Loan Agreement, but only to the extent, in accordance with the terms, subject to the conditions and in reliance upon the representations and warranties set forth below.

**AGREEMENT**

**NOW, THEREFORE,** IN CONSIDERATION OF THE FOREGOING RECITALS AND OTHER GOOD AND VALUABLE CONSIDERATION, THE RECEIPT AND ADEQUACY OF WHICH IS HEREBY ACKNOWLEDGED, AND INTENDING TO BE LEGALLY BOUND, THE PARTIES HERETO AGREE AS FOLLOWS:

**1. Definitions.** Capitalized terms used but not defined in this Amendment shall have the meanings given to them in the Loan Agreement.

**2. Joinder.**

**2.1 New Borrower**. New Borrower hereby is added as a "Borrower" under the Loan Agreement. All references in the Loan Agreement to "Borrower" shall hereafter mean and include the Existing Borrower and New Borrower individually and collectively, jointly and severally; and New Borrower shall hereafter have all rights, duties and obligations of "Borrower" thereunder.

**2.2 Joinder to Loan Agreement**. New Borrower hereby joins the Loan Agreement and each of the Loan Documents (other than the Warrants) and agrees to comply with and be bound by all of the terms, conditions and covenants of the Loan Agreement and Loan Documents (other than the Warrants), as if it were originally named a "Borrower" therein. Without limiting the generality of the preceding sentence, New Borrower agrees that it will be jointly and severally liable, together with Existing Borrower, for the payment and performance of all obligations and liabilities of Borrower under the Loan Agreement, including, without limitation, the Obligations. Each Borrower hereby appoints the other as agent for the other for all purposes hereunder. Each Borrower hereunder shall be obligated to repay all Credit Extensions made pursuant to the Loan Agreement, regardless of which Borrower actually receives said Credit Extension, as if each Borrower hereunder directly received all Credit Extensions.

**2.3** **Subrogation and Similar Rights**. Each Borrower waives (a) any suretyship defenses available to it under the Code or any other applicable law, including, without limitation, the benefit of California Civil Code Section 2815 permitting revocation as to future transactions and the benefit of California Civil Code Sections 1432, 2809, 2810, 2819, 2839, 2845, 2847, 2848, 2849, 2850, and 2899 and 3433, and (b) any right to require Collateral Agent or any Lender to: (i) proceed against any Borrower or any other person; (ii) proceed against or exhaust any security; or (iii) pursue any other remedy. Collateral Agent and or any Lender may exercise or not exercise any right or remedy it has against any Borrower or any security it holds (including the right to foreclose by judicial or non-judicial sale) without affecting any Borrower's liability. Notwithstanding any other provision of this Amendment, the Loan Agreement, the Loan Documents or any other related documents, each Borrower irrevocably waives all rights that it may have at law or in equity (including, without limitation, any law subrogating Borrower to the rights of Collateral Agent and the Lenders under this Amendment and the Loan Agreement) to seek contribution, indemnification or any other form of reimbursement from any other Borrower, or any other Person now or hereafter primarily or secondarily liable for any of the Obligations, for any payment made by Borrower with respect to the Obligations in connection with this Amendment, the Loan Agreement or otherwise and all rights that it might have to benefit from, or to participate in, any security for the Obligations as a result of any payment made by Borrower with respect to the Obligations in connection with this Amendment, the Loan Agreement or otherwise. Any agreement providing for indemnification, reimbursement or any other arrangement prohibited under this Section shall be null and void. If any payment is made to a Borrower in contravention of this Section, such Borrower shall hold such payment in trust for Collateral Agent and the Lenders and such payment shall be promptly delivered to Collateral Agent for application to the Obligations, whether matured or unmatured.

**2.4** **Grant of Security Interest**. New Borrower hereby grants Collateral Agent, for the ratable benefit of the Lenders, to secure the payment and performance in full of all of the Obligations, a continuing security interest in, and pledges to Collateral Agent, for the ratable benefit of the Lenders, the Collateral, wherever located, whether now owned or hereafter acquired or arising, and all proceeds and products thereof. New Borrower represents, warrants, and covenants that the security interest granted herein is and shall at all times continue to be a first priority perfected security interest in the Collateral, subject only to Permitted Liens that are permitted by the terms of the Loan Agreement to have priority to Collateral Agent's Lien. New Borrower hereby authorizes Collateral Agent to file financing statements or take any other action required to perfect Collateral Agent's security interests in the Collateral, without notice to Borrower, with all appropriate jurisdictions to perfect or protect Collateral Agent's interest or rights under the Loan Documents, including a notice that any disposition of the Collateral, except to the extent permitted by the terms of the Loan Agreement, by New Borrower, or any other Person, shall be deemed to violate the rights of Collateral Agent under the Code.

**2.5** **Representations and Warranties**. New Borrower hereby represents and warrants to Collateral Agent and each Lender that all representations and warranties in the Loan Documents made on the part of Existing Borrower are true and correct on the date hereof with respect to Existing Borrower and New Borrower, with the same force and effect as if New Borrower were named as "Borrower" in the Loan Documents in addition to Existing Borrower.

**3.** **Amendment to Loan Agreement.**

**3.1** **General**. Each reference to the phrase "[n]either Borrower" in the Loan Agreement hereby is replaced with "[n]o Borrower."

**4.** **Limitation of Joinder and Amendment.**

**4.1** The joinder and amendment set forth in **Sections 2** and **3** are effective for the purposes set forth herein and shall be limited precisely as written and shall not be deemed to (a) be a consent to any amendment, waiver or modification of any other term or condition of any Loan Document, or (b) otherwise prejudice any right or remedy which Collateral Agent or any Lender may now have or may have in the future under or in connection with any Loan Document.

**4.2** This Amendment shall be construed in connection with and as part of the Loan Documents and all terms, conditions, representations, warranties, covenants and agreements set forth in the Loan Documents, except as herein amended, are hereby ratified and confirmed and shall remain in full force and effect.

**5. Representations and Warranties.** To induce Collateral Agent and Lenders to enter into this Amendment, Borrower hereby represents and warrants to Collateral Agent and Lenders as follows:

**5.1** Immediately after giving effect to this Amendment (a) the representations and warranties contained in the Loan Documents are true, accurate and complete in all material respects as of the date hereof (provided, however, that such materiality qualifier shall not be applicable to any representations and warranties that are already qualified or modified by materiality in the text thereof), except to the extent such representations and warranties relate to an earlier date, in which case they are true and correct in all material respects as of such date, and (b) no Event of Default has occurred and is continuing;

**5.2** Borrower has the power and authority to execute and deliver this Amendment and to perform its obligations under the Loan Agreement, as amended by this Amendment;

**5.3** The organizational documents of Borrower delivered to Collateral Agent and Lenders prior to the date hereof remain true, accurate and complete and have not been amended, supplemented or restated and are and continue to be in full force and effect;

**5.4** The execution and delivery by Borrower of this Amendment and the performance by Borrower of its obligations under the Loan Agreement, as amended by this Amendment, have been duly authorized;

**5.5** The execution and delivery by Borrower of this Amendment and the performance by Borrower of its obligations under the Loan Agreement, as amended by this Amendment, do not and will not contravene (a) any law or regulation binding on or affecting Borrower, (b) any contractual restriction with a Person binding on Borrower, (c) any order, judgment or decree of any court or other governmental or public body or authority, or subdivision thereof, binding on Borrower, or (d) the organizational documents of Borrower;

**5.6** The execution and delivery by Borrower of this Amendment and the performance by Borrower of its obligations under the Loan Agreement, as amended by this Amendment, do not require any order, consent, approval, license, authorization or validation of, or filing, recording or registration with, or exemption by any governmental or public body or authority, or subdivision thereof, binding on Borrower; and

**5.7** This Amendment has been duly executed and delivered by Borrower and is the binding obligation of Borrower, enforceable against Borrower in accordance with its terms, except as such enforceability may be limited by bankruptcy, insolvency, reorganization, liquidation, moratorium or other similar laws of general application and equitable principles relating to or affecting creditors' rights.

**6. Counterparts.** This Amendment may be executed in any number of counterparts and all of such counterparts taken together shall be deemed to constitute one and the same instrument.

**7. Effectiveness.** This Amendment shall be deemed effective upon the due execution and delivery to Collateral Agent and Lenders of the following (unless otherwise waived by the Collateral Agent and Lenders):

(a) this Amendment duly executed by each party hereto;

(b) a Limited Liability Company Borrowing Certificate duly executed by New Borrower;

(c) a Perfection Certificate duly executed by New Borrower;

(d) Amended and Restated Secured Promissory Notes duly executed by each Borrower;

(e) good standing certificates for New Borrower certified by the Secretary of State (or equivalent agency) of the State of Delaware and each jurisdiction in which New Borrower is qualified to conduct business, each as of a date no earlier than thirty (30) days prior to the date of this Amendment;

(f) a duly filed UCC Financing Statement with the Secretary of State of the State of Delaware, identifying New Borrower as a debtor;

(g) the certificates and information required by Sections 2(b)(ix), 2(b)(xii) and 2(b)(xiii) of that certain Consent under Loan and Security Agreement dated as of November 14, 2021 by and among Collateral Agent, Lenders and Existing Borrower, with such modifications as approved by the Collateral Agent and Lenders; and

(h) Borrower's payment of all Lenders' Expenses to the extent invoiced through the date of this Amendment.

**8. Conditions Subsequent.** Borrower agrees to provide each of the following to Collateral Agent and Lenders and Borrower acknowledges and agrees that its failure to deliver any of the following in accordance with the deadline for such item shall be an immediate Event of Default under the Loan Agreement:

(a) no later than (i) thirty (30) days (or such longer period as Collateral Agent shall agree in writing in its discretion), Collateral Agent and Lenders shall have received, in form and substance reasonably satisfactory to Collateral Agent, fully-executed Control Agreements in favor of Collateral Agent for all Collateral Accounts of New Borrower (other than the Collateral Account of New Borrower at Middlesex Savings Bank disclosed on the Perfection Certificate delivered pursuant to Section 7(c) of this Amendment) required by Section 6.6 of the Loan Agreement and (ii) sixty (60) days (or such longer period as Collateral Agent shall agree in writing in its discretion), Collateral Agent and Lenders shall have received, in form and substance reasonably satisfactory to Collateral Agent, (A) evidence that such Collateral Account of New Borrower at Middlesex Savings Bank has been closed or (B) a fully-executed Control Agreement in favor of Collateral Agent for such Collateral Account of New Borrower at Middlesex Savings Bank; and

(b) no later than sixty (60) days (or such longer period as Collateral Agent shall agree in writing in its discretion), Collateral Agent and Lenders shall have received, in form and substance reasonably satisfactory to Collateral Agent, (x) a fully-executed landlord waiver for New Borrower's leased real property at 110 Canal Street, Lowell, Massachusetts 01852 or (y) evidence in form and substance reasonably satisfactory to Collateral Agent that such lease has been terminated.

**[*Balance of Page Intentionally Left Blank*]**

**In Witness Whereof**, the parties hereto have caused this amendment to be duly executed and delivered as of the date first written above.

**COLLATERAL AGENT AND LENDER:**

OXFORD FINANCE LLC

By: /s/ Joshua Friedman
Name: Joshua Friedman
Title: Chief Financial Officer

**BORROWER:**

ACELRX PHARMACEUTICALS, INC.

By: /s/ Raffi Asadorian
Name: Raffi Asadorian
Title: Chief Financial Officer

LOWELL THERAPEUTICS, LLC

By: /s/ Raffi Asadorian
Name: Raffi Asadorian
Title: Chief Financial Officer

**Exhibit 23.1**

**CONSENT OF INDEPENDENT REGISTERED PUBLIC ACCOUNTING FIRM**

We hereby consent to the incorporation by reference in the Registration Statements on Form S-3 (No. 333-239156) and Form S-8 (Nos. 333-258896, 333-239213, 333-230139, 333-223535, 333-216492, 333-202709, 333-194634, 333-187206, 333-237195, 333-209998, 333-180334 and 333-172409) of AcelRx Pharmaceuticals, Inc. of our report dated March 10, 2022, relating to the consolidated financial statements and schedule II, which appears in this Annual Report on Form 10-K.

/s/ WithumSmith+Brown, PC

San Francisco, California
March 10, 2022

**Exhibit 23.2**

**CONSENT OF INDEPENDENT REGISTERED PUBLIC ACCOUNTING FIRM**

We hereby consent to the incorporation by reference in the following Registration Statements:

(i) Registration Statement on Form S-8 (No. 333-258896) pertaining to the Amended and Restated 2020 Equity Incentive Plan,

(ii) Registration Statement on Form S-8 (No. 333-239213) pertaining to the 2020 Equity Incentive Plan and Amended and Restated 2011 Employee Stock Purchase Plan,

(iii) Registration Statements on Form S-8 (Nos. 333-230139, 333-223535, 333-216492, 333-202709, 333-194634 and 333-187206) pertaining to the 2011 Equity Incentive Plan,

(iii) Registration Statements on Form S-8 (Nos. 333-237195, 333-209998 and 333-180334) pertaining to the 2011 Equity Incentive Plan and 2011 Employee Stock Purchase Plan,

(iv) Registration Statement on Form S-8 (No. 333-172409) pertaining to the 2006 Stock Plan, 2011 Equity Incentive Plan and 2011 Employee Stock Purchase Plan, and

(v) Registration Statement on Form S-3 (No. 333-239156)

of our report dated March 15, 2021 with respect to the consolidated financial statements and schedule of AcelRx Pharmaceuticals, Inc. as of and for the year ended December 31, 2020, which appears in this Annual Report on Form 10-K.

/s/ OUM & CO. LLP

San Francisco, California

March 10, 2022

**Exhibit 31.1**

**CERTIFICATIONS**

I, Vincent J. Angotti, certify that:

1. I have reviewed this annual report on Form 10-K of AcelRx Pharmaceuticals, Inc.;

2. Based on my knowledge, this report does not contain any untrue statement of a material fact or omit to state a material fact necessary to make the statements made, in light of the circumstances under which such statements were made, not misleading with respect to the period covered by this report;

3. Based on my knowledge, the financial statements, and other financial information included in this report, fairly present in all material respects the financial condition, results of operations and cash flows of the registrant as of, and for, the periods presented in this report;

4. The registrant's other certifying officer(s) and I are responsible for establishing and maintaining disclosure controls and procedures (as defined in Exchange Act Rules 13a-15(e) and 15d-15(e)) and internal control over financial reporting (as defined in Exchange Act Rules 13a-15(f) and 15d-15(f)) for the registrant and have:

(a) Designed such disclosure controls and procedures, or caused such disclosure controls and procedures to be designed under our supervision, to ensure that material information relating to the registrant, including its consolidated subsidiaries, is made known to us by others within those entities, particularly during the period in which this report is being prepared;

(b) Designed such internal control over financial reporting, or caused such internal control over financial reporting to be designed under our supervision, to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles;

(c) Evaluated the effectiveness of the registrant's disclosure controls and procedures and presented in this report our conclusions about the effectiveness of the disclosure controls and procedures, as of the end of the period covered by this report based on such evaluation; and

(d) Disclosed in this report any change in the registrant's internal control over financial reporting that occurred during the registrant's most recent fiscal quarter (the registrant's fourth fiscal quarter in the case of an annual report) that has materially affected, or is reasonably likely to materially affect, the registrant's internal control over financial reporting; and

5. The registrant's other certifying officer(s) and I have disclosed, based on our most recent evaluation of internal control over financial reporting, to the registrant's auditors and the audit committee of the registrant's Board of Directors (or persons performing the equivalent functions):

(a) All significant deficiencies and material weaknesses in the design or operation of internal control over financial reporting which are reasonably likely to adversely affect the registrant's ability to record, process, summarize and report financial information; and

(b) Any fraud, whether or not material, that involves management or other employees who have a significant role in the registrant's internal control over financial reporting.

Date: March 10, 2022

/s/ Vincent J. Angotti
Vincent J. Angotti
Chief Executive Officer
(Principal Executive Officer)

**Exhibit 31.2**

**CERTIFICATIONS**

I, Raffi Asadorian, certify that:

1. I have reviewed this annual report on Form 10-K of AcelRx Pharmaceuticals, Inc.;

2. Based on my knowledge, this report does not contain any untrue statement of a material fact or omit to state a material fact necessary to make the statements made, in light of the circumstances under which such statements were made, not misleading with respect to the period covered by this report;

3. Based on my knowledge, the financial statements, and other financial information included in this report, fairly present in all material respects the financial condition, results of operations and cash flows of the registrant as of, and for, the periods presented in this report;

4. The registrant's other certifying officer(s) and I are responsible for establishing and maintaining disclosure controls and procedures (as defined in Exchange Act Rules 13a-15(e) and 15d-15(e)) and internal control over financial reporting (as defined in Exchange Act Rules 13a-15(f) and 15d-15(f)) for the registrant and have:

(a) Designed such disclosure controls and procedures, or caused such disclosure controls and procedures to be designed under our supervision, to ensure that material information relating to the registrant, including its consolidated subsidiaries, is made known to us by others within those entities, particularly during the period in which this report is being prepared;

(b) Designed such internal control over financial reporting, or caused such internal control over financial reporting to be designed under our supervision, to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles;

(c) Evaluated the effectiveness of the registrant's disclosure controls and procedures and presented in this report our conclusions about the effectiveness of the disclosure controls and procedures, as of the end of the period covered by this report based on such evaluation; and

(d) Disclosed in this report any change in the registrant's internal control over financial reporting that occurred during the registrant's most recent fiscal quarter (the registrant's fourth fiscal quarter in the case of an annual report) that has materially affected, or is reasonably likely to materially affect, the registrant's internal control over financial reporting; and

5. The registrant's other certifying officer(s) and I have disclosed, based on our most recent evaluation of internal control over financial reporting, to the registrant's auditors and the audit committee of the registrant's Board of Directors (or persons performing the equivalent functions):

(a) All significant deficiencies and material weaknesses in the design or operation of internal control over financial reporting which are reasonably likely to adversely affect the registrant's ability to record, process, summarize and report financial information; and

(b) Any fraud, whether or not material, that involves management or other employees who have a significant role in the registrant's internal control over financial reporting.

Date: March 10, 2022

/s/ Raffi Asadorian
Raffi Asadorian
Chief Financial Officer
(Principal Financial Officer)

**Exhibit 32.1**

**CERTIFICATION**

Pursuant to the requirement set forth in Rule 13a-14(b) of the Securities Exchange Act of 1934, as amended (the "Exchange Act"), and Section 1350 of Chapter 63 of Title 18 of the United States Code (18 U.S.C. §1350), Vincent J. Angotti, Chief Executive Officer of AcelRx Pharmaceuticals, Inc. (the "Company"), and Raffi Asadorian, Chief Financial Officer of the Company, each hereby certifies that, to the best of his or her knowledge:

1. The Company's Annual Report on Form 10-K for the period ended December 31, 2021, to which this Certification is attached as Exhibit 32.1 (the "Annual Report") fully complies with the requirements of Section 13(a) or Section 15(d) of the Exchange Act, and

2. The information contained in the Annual Report fairly presents, in all material respects, the financial condition and results of operations of the Company.

**In Witness Whereof**, the undersigned have set their hands hereto as of the 10th day of March 2022.

| | |
|---|---|
| /s/ Vincent J. Angotti | /s/ Raffi Asadorian |
| Vincent J. Angotti | Raffi Asadorian |
| Chief Executive Officer | Chief Financial Officer |

"This certification accompanies the Form 10-K to which it relates, is not deemed filed with the Securities and Exchange Commission and is not to be incorporated by reference into any filing of AcelRx Pharmaceuticals, Inc. under the Securities Act of 1933, as amended, or the Securities Exchange Act of 1934, as amended (whether made before or after the date of the Form 10-K), irrespective of any general incorporation language contained in such filing."