

DURECT CORP
Form 10-K
March 02, 2012
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UNITED STATES
SECURITIES AND EXCHANGE COMMISSION

Washington, D.C. 20549

Form 10-K

(Mark One)

ANNUAL REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934
For the fiscal year ended December 31, 2011

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: 000-31615

DURECT CORPORATION

(Exact name of registrant as specified in its charter)

Delaware
(State or other jurisdiction of
incorporation or organization)

94-3297098
(I.R.S. Employer
Identification No.)

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10260 Bubb Road

Cupertino, CA 95014

(Address of principal executive offices, including zip code)

Registrant's telephone number, including area code: (408) 777-1417

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

| Title of Each Class | Name of Each Exchange on Which Registered |
|---|---|
| Common Stock \$0.0001 par value per share | The NASDAQ Stock Market LLC |
| Preferred Share Purchase Rights | (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 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 than the registrant was required to file such reports), and (2) has been subject to such filing requirements for the past 90 days. YES NO

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

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

Indicate by check mark whether the registrant is a large accelerated filer, an accelerated filer, or a non-accelerated filer. See definition of large accelerated filer and accelerated filer and smaller reporting company in Rule 12b-2 of the Exchange Act. (Check one):

Large accelerated filer Accelerated filer Non-accelerated filer Smaller reporting company
Indicate by check mark whether the registrant is a shell company (as defined in Rule 12b-2 of the Act). YES NO

The aggregate market value of the voting stock held by non-affiliates of the registrant was approximately \$167,868,268 as of June 30, 2011 based upon the closing sale price on the NASDAQ Global Market reported for such date. Shares of Common Stock held by each officer and director and by each person who may be deemed to be an affiliate have been excluded. This determination of affiliate status is not necessarily a conclusive determination for other purposes.

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There were 87,547,149 shares of the registrant's Common Stock issued and outstanding as of February 29, 2012.

DOCUMENTS INCORPORATED BY REFERENCE

Part III incorporates information by reference from the definitive Proxy Statement for the 2012 annual meeting of stockholders, which is expected to be filed not later than 120 days after the Registrant's fiscal year ended December 31, 2011.

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DURECT CORPORATION
ANNUAL REPORT ON FORM 10-K
FOR THE FISCAL YEAR ENDED DECEMBER 31, 2011
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Overview**

We are a specialty pharmaceutical company focused on the development of pharmaceutical products based on our proprietary drug delivery technology platforms. Our product pipeline currently consists of seven investigational drug candidates in clinical development, with one program the subject of a New Drug Application (NDA) with the U.S. Food and Drug Administration (FDA) for which a Complete Response Letter was received in June 2011, one program in Phase III, two programs in Phase II and three programs in Phase I. The more advanced programs are in the field of pain management and we believe that each of these targets large market opportunities with product features that are differentiated from existing therapeutics. We have other programs underway in fields outside of pain management, including several efforts underway which seek to improve the administration of biotechnology agents such as proteins and peptides.

A central aspect of our business strategy involves advancing multiple product candidates at one time, which is enabled by leveraging our resources with those of corporate collaborators. Thus, certain of our programs are currently licensed to corporate collaborators on terms which typically call for our collaborator to fund all or a substantial portion of future development costs and then pay us milestone payments based on specific development or commercial achievements plus a royalty on product sales. At the same time, we have retained the rights to other programs, which are the basis of future collaborations and over time may provide a pathway for us to develop our own commercial, sales and marketing organization.

Product Research and Development Programs

Our development efforts are focused on the application of our pharmaceutical systems technologies to potential products in a variety of chronic and episodic disease areas including pain, central nervous system (CNS) disorders, cardiovascular disease and other chronic diseases. Our more advanced product research and development efforts in these areas are set forth in the following table:

| Product Candidate | Disease/Indication | Collaborator | Technology Platform | Stage |
|---|---------------------------|---|----------------------------|---|
| Remoxy (Oral controlled release oxycodone) | Chronic Pain | Pfizer/Pain Therapeutics (worldwide) | ORADUR | NDA resubmitted in December 2010 but not approved/ Complete Response Letter received in June 2011 |
| POSIDUR (Controlled release injection of bupivacaine) | Post-Operative Pain | Hospira (U.S. and Canada); DURECT retains rights in rest of world | SABER | Phase III |
| ELADUR (Transdermal bupivacaine) | Pain | DURECT retains worldwide rights | TRANSDUR | Phase II |
| TRANSDUR-Sufentanil (Transdermal sufentanil) | Chronic Pain | DURECT retains worldwide rights | TRANSDUR | Phase II |

NOTE: POSIDUR, SABER, TRANSDUR, ORADUR®, ELADUR®, DURIN®, CHRONOGESIC®, MICRODUR, ALZET® and LACTEL® are trademarks of DURECT Corporation. Other trademarks referred to belong to their respective owners.

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| Product Candidate | Disease/Indication | Collaborator | Technology Platform | Stage |
|-------------------------------------|--|--|----------------------------|-----------------------------|
| ORADUR-based opioid (hydrocodone) | Pain | Pfizer/Pain Therapeutics (worldwide) | ORADUR | Phase I |
| ORADUR-based opioid (hydromorphone) | Pain | Pfizer/Pain Therapeutics (worldwide) | ORADUR | Phase I |
| ORADUR-ADHD | Attention Deficit Hyperactivity Disorder (ADHD) | Orient Pharma (defined Asian and South Pacific countries); DURECT retains development and commercialization rights in North America, Europe, Japan and all other countries | ORADUR | Phase I |
| ORADUR-based opioid (oxymorphone) | Pain | Pfizer/Pain Therapeutics (worldwide) | ORADUR | IND accepted by the FDA |
| Relday (risperidone) | Schizophrenia/biopolar disorder | Zogenix (worldwide) | SABER | Preclinical |
| Various | Biologics Programs/Research Programs in other Therapeutic Categories | DURECT retains worldwide rights, except for certain feasibility projects whereby our collaborator generally has an option on rights | SABER/ DURIN | Preclinical/ Research Stage |

Remoxy (ORADUR-Oxycodone)

Market Opportunity. Chronic pain is usually the result of an ongoing condition or significant problem associated with chronic diseases, including cancer, various neurological and skeletal disorders and other ailments such as severe arthritis or a debilitating back injury. As the condition gets worse, the pain often gets worse. Also, long-lasting pain can affect the nervous system to the point where pain persists even if the condition that originally caused the pain is stabilized or improved. This is one reason patients often need stronger pain medication even if their underlying condition has been treated. Chronic pain affects as many as 50 million Americans annually. OxyContin®, a brand name extended-release oral oxycodone-based painkiller, accounted for over \$3.0 billion in worldwide sales in 2010.

Development Strategy. Remoxy is an oral, long-acting oxycodone gelatin capsule under development with Pain Therapeutics, Inc. (Pain Therapeutics) to which we have licensed exclusive, worldwide, development and commercialization rights under a development and license agreement entered into in December 2002. Subsequently, Pain Therapeutics has sublicensed the worldwide commercialization rights of Remoxy (except for Australia and New Zealand) to King Pharmaceuticals, Inc. (King) and, as of March 2009, we began working directly with King on further development of Remoxy. In February 2011, Pfizer Inc (Pfizer) acquired King and thereby assumed the rights and obligations of King with respect to Remoxy. Remoxy is formulated with our ORADUR technology and incorporates several abuse-deterrent properties with the convenience of twice-a-day dosing. Oxycodone is also the active drug ingredient in OxyContin, a brand name extended-release oral

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painkiller, which achieved annual worldwide sales of greater than \$3.0 billion in 2010. Under the agreement with Pain Therapeutics, subject to and upon the achievement of predetermined development and regulatory milestones, we are entitled to receive milestone payments of up to \$9.3 million in the aggregate for Remoxy and other licensed ORADUR-based opioids. As of December 31, 2011, we had received \$1.7 million in cumulative milestone payments. We also receive reimbursement for our research and development efforts on Remoxy and a manufacturing profit on our supply of key product excipients for use in Remoxy. In addition, if commercialized, we will receive royalties for Remoxy and other licensed products which do not contain an opioid antagonist of between 6.0% to 11.5% of net sales depending on sales volumes.

Clinical Program. In December 2007, Pain Therapeutics and King announced that the pivotal Phase III trial for Remoxy successfully met its primary endpoint ($p < 0.01$) that was prospectively defined by the FDA during the Special Protocol Assessment process. In addition, the study achieved statistically significant results in secondary endpoints such as Quality of Analgesia ($p < 0.01$) and Global Assessment ($p < 0.01$). Pain Therapeutics submitted an NDA for Remoxy to the FDA in June 2008, and in August 2008 the FDA accepted the NDA and granted priority review. In December 2008, Pain Therapeutics received a Complete Response Letter for its NDA for Remoxy in which the FDA determined that the NDA was not approved. According to Pain Therapeutics, the FDA indicated that additional non-clinical data would be required to support the approval of Remoxy, but the FDA has not requested or recommended additional clinical efficacy studies prior to approval. King assumed responsibility for further development of Remoxy from Pain Therapeutics in March 2009. In July 2009, King met with the FDA to discuss the Complete Response Letter. According to King and Pain Therapeutics, the outcome of that meeting provided King with a clearer path forward to resubmit the Remoxy NDA and to address all FDA comments in the Complete Response Letter. King took over the NDA from Pain Therapeutics and resubmitted the NDA in December of 2010. On June 23, 2011, a Complete Response Letter from the FDA was received by Pfizer on the resubmission to the NDA for REMOXY. The FDA's June 2011 Complete Response Letter raised concerns related to, among other matters, the Chemistry, Manufacturing, and Controls section of the NDA for REMOXY. Pfizer has efforts underway to resolve these issues. Sufficient information does not yet exist to accurately assess the time required to resolve the concerns raised in the FDA's Complete Response Letter. On January 31, 2012, Pfizer stated that it intended to conduct two bioavailability studies in the second quarter of 2012 and anticipated meeting with the FDA during the third quarter to discuss next steps.

Additional ORADUR-Opioid Products in Development

Since 2006, we also worked with Pain Therapeutics and King on the development of three additional ORADUR abuse-resistant opioid drug candidates which would address the chronic pain market. Phase I clinical trials have been conducted for two of these ORADUR-based products (hydrocodone and hydromorphone), and an IND has been accepted by the FDA for the third ORADUR-based opioid (oxymorphone).

POSIDUR

Market Opportunity. According to data published by the Center for Disease Control and Prevention, there are approximately 72 million ambulatory and inpatient surgical procedures performed annually in the U.S. Epidemiological studies indicate that up to 100% of surgical patients experience postoperative pain, with 50-75% reporting inadequate pain relief. The current standard of care for post-surgical pain includes oral opiate and non-opiate analgesics and muscle relaxants. While systemic opioids can effectively control post-surgical pain, they commonly cause side effects including drowsiness, constipation, nausea and vomiting and cognitive impairment. Effective pain management can be compromised if patients fail to adhere to recommended dosing regimens because they are suffering from these side effects. Post-surgical pain also can be treated effectively with local anesthetics; however, the usefulness of current conventional medications is limited by their short duration of action.

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Development Strategy. We are developing POSIDUR, a sustained-release formulation of bupivacaine, using our SABER delivery system for the treatment of post-surgical pain. Bupivacaine is a local anesthetic agent currently used in the hospital for anesthesia and analgesia and for which the patent covering the chemical entity has expired. The physician would administer POSIDUR at the time of surgery to the surgical site. This formulation is designed to provide sustained regional analgesia from a single dose. We believe that by delivering effective amounts of a potent analgesic to the location from which the pain originates, improved pain control can be achieved with minimal exposure to the remainder of the body and reduced need for systemic analgesics, thus minimizing side effects. POSIDUR is intended to provide local analgesia for up to 3 days, which we believe coincides with the time period of greatest need for post-surgical pain control in most patients.

POSIDUR is the subject of a collaboration agreement with Hospira, Inc. (Hospira) to develop and commercialize POSIDUR in the U.S. and Canada. POSIDUR was also the subject of a collaboration agreement with Nycomed Danmark ApS (Nycomed) to develop and commercialize POSIDUR in the European Union (E.U.) and certain other countries. In January 2012 Nycomed (now owned by Takeda) gave notice that its rights with respect to POSIDUR were being returned to us. Please see [Third Party Collaborations](#) for additional information.

Clinical Program. Our POSIDUR clinical development program has been devised to establish the safety and efficacy of POSIDUR for the treatment of post-surgical pain for up to 3 days. Toward that end, we have conducted 13 clinical studies in a variety of surgical models including hernia, appendectomy, shoulder surgery and various abdominal procedures. We have dosed over 1,000 humans with either POSIDUR or SABER-placebo, of which over 680 patients received POSIDUR. Leveraging on the well established history of use of bupivacaine, our strategy is to pursue a section 505(b)2 NDA application.

Phase IIb Inguinal Hernia Trial

Design

The POSIDUR Phase IIb clinical trial was designed to evaluate the tolerability, activity, dose response and pharmacokinetics of POSIDUR in patients undergoing open inguinal hernia repair. The trial was conducted in Australia and New Zealand as a multi-center, randomized, double blind, placebo-controlled study in 122 patients. Study patients were randomized into three treatment groups: patients that were treated with POSIDUR 2.5 mL (n=43), POSIDUR 5 mL (n=47) and placebo (n=32). The co-primary efficacy endpoints for the study were Mean Pain Intensity on Movement area under the curve (AUC), a measure of pain over a period of 1-72 hours post-surgery, and the proportion of patients requiring supplemental opioid analgesic medication during the study. Secondary efficacy endpoints included Mean Pain Intensity on Movement AUC over the period 1-48 hours post-surgery, mean total consumption of supplemental opioid analgesic medication, and time to first use of supplemental opioid analgesic medication. The threshold for statistical significance was considered to be at the $p < 0.05$ level.

Results

Pain Control

In relation to the co-primary endpoint of pain reduction as measured by Mean Pain Intensity on Movement AUC 1-72 hours post-surgery, the patient group treated with POSIDUR 5 mL reported thirty-one percent (31%) less pain versus placebo ($p=0.0033$). A secondary endpoint measure reported a thirty-five percent (35%) reduction of pain as measured by Mean Pain Intensity on Movement AUC for the period 1-48 hours post-surgery between the POSIDUR 5 mL treatment group versus placebo ($p=0.0007$).

Consumption of Supplemental Opioid Analgesic Medication

Fifty-three percent (53%) of the study patients in the POSIDUR 5 mL group took supplemental opioid analgesic medications versus seventy-two percent (72%) of the placebo patients ($p=0.0909$). Although this

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positive trend for this co-primary endpoint in favor of the POSIDUR 5 mL group was not statistically significant, both secondary endpoints measuring opioid analgesic medication consumption were met at a statistically significant level. During the periods of 1-24 hours, 24-48 hours and 48-72 hours after surgery, placebo patients consumed approximately 3.5 (p=0.0009), 2.9 (p=0.0190) and 3.6 (p=0.0172) times more supplemental opioid analgesic medications (mean total daily consumption of opioid analgesic medication in morphine equivalents), respectively, than the POSIDUR 5 mL treatment group. In addition, the median time to first use of supplemental opioid analgesic medication after surgery for the placebo patients was 2.7 hours versus >72 hours for the POSIDUR 5 mL treatment group (p=0.0197).

Dose Finding

POSIDUR administered at the dose of 5 mL showed statistically significant activity relative to placebo whereas POSIDUR administered at 2.5 mL showed a positive trend relative to placebo on certain parameters but the results were not statistically significant.

Safety

The patient groups treated with POSIDUR 5 mL and POSIDUR 2.5 mL showed comparable safety profiles as the patient groups treated with placebo, and the drug administration appeared well tolerated. The side effects commonly observed with opioid medication use were less frequent in the POSIDUR 5 mL and 2.5 mL treatment groups compared to placebo.

Other Phase II Clinical Trials

In addition to the Phase IIb clinical trial described above, we have also conducted smaller exploratory Phase II studies in hernia, shoulder arthroscopy and appendectomy surgeries to evaluate different application techniques, clinical design and conduct as well as other investigational factors. These trials have been conducted in multiple cohorts, generally consisting of approximately 6 to 21 patients in each treatment group. In all the exploratory studies, patient groups treated with POSIDUR 5 mL and POSIDUR 2.5 mL showed comparable safety profiles as the patient groups treated with placebo, and the drug administration appeared well tolerated. Some treatment groups from these exploratory studies utilizing POSIDUR have shown positive activity as measured by reduction of pain or consumption of supplemental opioid analgesic medication versus placebo, while other treatment groups have not. We have evaluated these studies to understand the different results observed, and have applied our learnings in the design of our Phase III program.

In December 2009, we announced results from a 60 patient Phase IIb clinical trial of POSIDUR in patients undergoing arthroscopic shoulder surgery. Top line results showed a consistent reduction of pain scores (as measured by mean pain intensity on movement AUC, time normalized under the curve, during the period 0 to 72 hours post-surgery) in parallel with a reduction of opioid use (as measured by the amount of opioids taken in the three days post-surgery) in favor of POSIDUR versus placebo. These reductions were not statistically significant given the size of the study. In addition, there was a comparable safety profile between the two groups in this study and POSIDUR appeared well tolerated.

In June 2010, we announced results from a European Phase IIb hysterectomy clinical trial conducted by Nycomed of POSIDUR. In this study, 115 patients were randomly assigned to one of three treatment groups prior to undergoing open hysterectomy surgery: POSIDUR at a dose of 5 mL, an active comparator (commercially available bupivacaine HCl solution) or SABER-Placebo (SABER vehicle without drug). All patients were given a background pain treatment consisting of a daily dose of two or four grams (depending on the patient's weight) of paracetamol (acetaminophen). In addition, each patient was provided supplemental opioid rescue medication, if needed. With respect to efficacy, the primary endpoints of the study were to demonstrate: (1) non-inferiority of POSIDUR to SABER-Placebo (with all groups taking the background and supplemental pain treatment as

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described above) in terms of pain intensity on movement area under the curve (AUC) during the period 1-72 hours post-surgery, and (2) superiority of POSIDUR against SABER-Placebo in the total use of opioid rescue analgesia 0-72 hours post-surgery. Results from this study show that the first primary efficacy endpoint was met. With respect to the second primary efficacy endpoint, no statistically significant difference was shown in opioid use between the POSIDUR and SABER-Placebo groups. Secondary comparisons were performed towards the active comparator group with similar results. In this study, patients in all treatment groups only took a meaningful amount of opioids during a shorter period of time after surgery than was expected. In this study, there were no indications of systemic safety issues. The plasma concentration profiles were consistent with previous studies, confirming the sustained release profile of the product. Local observations (most commonly coded as post procedural haematomas) at the surgical site were observed with frequency in the POSIDUR and SABER-Placebo groups and not observed in the active comparator group. These events were temporary and resolved without treatment.

In February 2011, we announced results from a European Phase IIb shoulder clinical trial conducted by Nycomed of POSIDUR. In this study, 107 patients were randomly assigned to one of three treatment groups prior to undergoing elective arthroscopic shoulder surgery: POSIDUR at a dose of 5 mL, an active comparator (commercially available bupivacaine HCl solution) or SABER-Placebo (SABER vehicle without drug). All patients were given a background pain treatment consisting of a daily dose of two or four grams (depending on the patient's weight) of paracetamol (acetaminophen). In addition, each patient was provided supplemental opioid rescue medication, if needed. With respect to efficacy, the primary endpoints of the study were to demonstrate: (1) non-inferiority of POSIDUR to SABER-Placebo (with all groups taking the background and supplemental pain treatment as described above) in terms of pain intensity on movement area under the curve (AUC) during the period 1-72 hours post-surgery, and (2) superiority of POSIDUR against SABER-Placebo in the total use of opioid rescue analgesia 0-72 hours post-surgery. Results from this study demonstrate that the POSIDUR group experienced a statistically significant reduction in pain intensity of approximately 19% ($p=0.0219$) versus SABER-Placebo. The results of the pre-specified primary analysis indicated a clear clinically relevant trend in opioid sparing for POSIDUR compared to SABER-placebo and the pre-specified sensitivity analysis showed a statistically significant reduction of approximately 67% ($p=0.013$) in median opioid use in favor of POSIDUR. No statistical differences were found when POSIDUR was compared to the active comparator arm. Overall there was a comparable safety profile between the three groups in this study and POSIDUR appeared well tolerated.

U.S. Phase III Program

In January 2012, we announced top-line results for BESST (Bupivacaine Effectiveness and Safety in SABER Trial), a Phase III clinical trial in the U.S. BESST was an international, multi-center, randomized, double-blind, controlled trial evaluating the safety, efficacy, effectiveness, and pharmacokinetics of POSIDUR in 305 patients undergoing a variety of general abdominal surgical procedures. Eligible patients were randomly assigned to one of three cohorts:

Cohort 1: An active comparator cohort in which patients were randomized to receive either POSIDUR 5.0 mL or commercially available Bupivacaine HCl solution after laparotomy.

Cohort 2: An active comparator cohort in which patients were randomized to receive either POSIDUR 5.0 mL or commercially available Bupivacaine HCl solution after laparoscopic cholecystectomy.

Cohort 3: A double blind, placebo controlled cohort in which patients were randomized to receive either POSIDUR 5.0 mL or SABER-Placebo after laparoscopically-assisted colectomy.

Efficacy evaluation in the BESST trial encompassed a number of parameters. The two co-primary efficacy endpoints for Cohort 3 were mean pain intensity on movement (normalized) Area Under the Curve (AUC) during the period 0-72 hours post-dose and mean total morphine equivalent opioid dose for supplemental analgesia during the period 0-72 hours post-dose. The purpose of Cohorts 1 and 2 was to give us additional experience with the use of POSIDUR in a broader group of surgeries and patients.

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Results

Primary Endpoints Cohort 3 (POSIDUR versus SABER-Placebo, laparoscopically-assisted colectomy)

With respect to the co-primary efficacy endpoint of pain reduction as measured by mean pain intensity on movement (normalized) Area Under the Curve (AUC) during the period 0-72 hours post-dose, the patient group treated with POSIDUR 5.0 mL (660 mg) reported a mean pain reduction in pain scores of approximately 7% ($p=0.1466$). The statistical analysis plan included pain on movement as recorded at scheduled times through an electronic diary plus pain scores reported whenever supplemental opioids were administered with such scores attributed as if they were pain on movement. In the prespecified sensitivity analysis (which includes only scheduled pain assessment on movement scores as collected on the electronic diary), the patient group treated with POSIDUR 5.0 mL reported approximately 10% less pain versus placebo ($p=0.0410$). In relation to the co-primary efficacy endpoint of median total morphine-equivalent opioid dose for supplemental analgesia during the period 0-72 hours post-dose, the patient group treated with POSIDUR reported approximately 16% less opioids consumed versus the placebo group ($p=0.5897$). The prespecified level for statistical significance is $p<0.05$, unless one of the co-primary efficacy endpoints is not met in which case the standard for statistical significance for the remaining endpoint is $p<0.025$.

Cohorts 1 and 2 (POSIDUR versus commercially available Bupivacaine HCl solution after laparotomy and after laparoscopic cholecystectomy, respectively)

Cohorts 1 and 2 were prespecified to be pooled due to their small sample size. For Cohorts 1 and 2 (pooled), the mean reduction in pain on movement was approximately 20% ($p=0.0111$) for the POSIDUR group compared to the patient group treated with bupivacaine HCl. The median total morphine-equivalent opioid dose for supplemental analgesia during the period 0-72 hours post-dose for Cohorts 1 and 2 (pooled), the patient group treated with POSIDUR reported approximately 18% less opioids consumed compared to the bupivacaine HCl group ($p=0.5455$).

Safety

Overall, the POSIDUR patient groups showed a similar systemic safety profile as the patient groups treated with SABER-Placebo and active comparator. There were no signs of systemic safety issues. Local site reactions were observed more frequently in the POSIDUR and SABER-Placebo groups than in the active comparator groups; most of these observations were discolorations, the majority of which resolved without treatment during the trial. No negative safety signal has been seen in the initial cardiac and neurologic safety assessment in BESST; however further analysis is underway.

Next Steps

After a complete analysis of the BESST data and preparation of integrated safety and efficacy summaries combining our previous well controlled studies, we intend to hold a pre-NDA meeting with the FDA which we expect to occur in mid-2012, with a potential NDA submission under section 505(b)2 later this year.

ELADUR

Market Opportunity. Pain can arise from a variety of diseases and conditions, and in many instances, pain originates from a localized point in the body and can benefit from treatments which are administered and act locally as opposed to in a systemic fashion. One such example is post-herpetic neuralgia (PHN or post-shingles pain), a debilitating complication of herpes zoster, which is usually defined as the presence of pain at the site of eruption that lasts more than a month after the onset of a zoster eruption. The prevalence of PHN (including PHN lasting more than one year) is estimated to be approximately 144,000 people in the U.S. In addition to PHN, there are a number of other widely prevalent chronic and acute local pain conditions (e.g., neuropathic pain, sprains, strains, and contusions) that could benefit from a locally acting pain product.

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Development Strategy. Our transdermal bupivacaine patch (ELADUR) under development is intended to provide continuous delivery of bupivacaine for up to three days from a single application, as compared to a wearing time limited to 12 hours with currently available lidocaine patches. We anticipate that ELADUR will have several potential differentiating attributes compared with currently marketed lidocaine patches, including extended duration of action and better wearability. During 2008, we received Orphan Drug Designation for bupivacaine for relief of persistent pain associated with PHN, such that if ELADUR is the first bupivacaine product approved for PHN, ELADUR would be eligible to receive seven years of data exclusivity following its approval by the FDA. There can be no assurance that ELADUR will be the first bupivacaine product approved for PHN, and therefore ELADUR may not be entitled to the seven year data exclusivity period for orphan drugs. Effective October 2008, we licensed the worldwide development and commercialization rights for ELADUR to Alpharma Ireland Limited (Alpharma), which was acquired by King in December 2008. In February 2011, Pfizer acquired King and thereby assumed the rights and obligations of King with respect to ELADUR. In February 2012, Pfizer gave notice that its rights with respect to ELADUR were being returned to us. We intend to initiate discussions with other potential partners regarding licensing development and commercialization rights to this program. Please see *Third Party Collaborations* for additional information.

Clinical Program. In 2007, we reported positive results from a 60 patient Phase IIa clinical trial for ELADUR. In this study of patients suffering from PHN, ELADUR showed improved pain control versus placebo during the 3-day continuous treatment period. In addition, ELADUR appeared well tolerated overall, and patients treated with ELADUR and placebo exhibited similar safety profiles. In 2008, we conducted manufacturing scale-up and processing studies to secure additional supplies for Phase II and Phase III clinical trials, and developed our clinical and regulatory strategy for further development of this program. We reported top line data from a Phase II clinical trial conducted by King for ELADUR in April 2011. In this study of 263 patients suffering from chronic low back pain, the primary efficacy endpoint of demonstrating a positive treatment difference for the mean change in pain intensity scores from baseline to the mean of weeks 11 and 12 between ELADUR as compared to placebo was not met.

TRANSDUR-Sufentanil Patch

Market Opportunity. Chronic pain affects as many as 50 million Americans annually. One major class of drugs utilized to treat chronic pain is comprised of oral opioids, such as OxyContin, a branded extended-release oral oxycodone-based painkiller which accounted for over \$3.0 billion in worldwide sales in 2010. Another major class of drugs utilized to treat chronic pain is transdermally delivered opioids such as Duragesic®, a leading transdermal fentanyl product which accounted for approximately \$750 million in worldwide sales in 2010. It is our belief that a best-in-class sufentanil patch could compete effectively in both the transdermal fentanyl patch market and in the oral opioid market.

Development Strategy. Our transdermal sufentanil patch (TRANSDUR-Sufentanil) under development is based on our proprietary TRANSDUR transdermal technology and is intended to provide continuous delivery of sufentanil for up to seven days from a single application, as compared to the two to three days of relief provided by currently available fentanyl patches. Sufentanil is a highly potent opioid that is currently used in hospitals as an analgesic for which the patent covering the chemical entity has expired. We anticipate that the small size of our sufentanil patch (potentially as small as 1/5th the size of currently marketed transdermal fentanyl patches for a therapeutically equivalent dose) and longer duration of delivery may offer improved convenience and compliance for patients.

In March 2005, we entered into an agreement with Endo Pharmaceuticals, Inc. (Endo) granting Endo exclusive rights to develop, market and commercialize TRANSDUR-Sufentanil in the U.S. and Canada. In February 2009, Endo notified us that it was terminating the license agreement with us, and thereby returning Endo's rights to develop and commercialize TRANSDUR-Sufentanil in the U.S. and Canada to us effective August 26, 2009. We are in discussions with potential collaborators regarding licensing development and commercialization rights to this program to which we hold worldwide rights.

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Clinical Program. In 2008, Endo successfully completed a Phase II clinical trial for TRANSDUR-Sufentanil in which they evaluated the conversion of patients on oral and transdermal opioids to TRANSDUR-Sufentanil. This Phase II trial met its primary and secondary objectives of establishing a successful dose-titration regimen and dose potency relationships, demonstrating safety and tolerability at the therapeutic dose, and achieving effective analgesic pain control. The Phase II data, extensive non-clinical data that had been generated by Endo and a potential regulatory pathway for the Phase III program were reviewed with the FDA at an end-of-Phase II meeting on February 19, 2009. It is our expectation that future development of this product candidate will follow a 505(b)2 pathway as discussed with FDA, which would allow us to reference third-party data, potentially reducing time and expense.

ORADUR-ADHD Program

Market Opportunity. Attention Deficit Hyperactivity Disorder (ADHD) is a neurobehavioral condition that is estimated to affect approximately 8% of U.S. children ages 4-17, according to the U.S. Centers for Disease Control and Prevention (the CDC). The principal characteristics of ADHD are inattention, hyperactivity, and impulsivity. The condition presents itself in childhood and can be life long as 65% of children with ADHD continue to present symptoms as adults. Over 50% of children with ADHD are currently treated with stimulants such as amphetamine or methylphenidate and sales of ADHD treatments were approximately \$5.8 billion in 2010. The National Survey on Drug Use & Health estimates that 1.4 million Americans over the age of 12 abuse stimulants for euphoric highs and increased performance or wakefulness.

Development Strategy. We are developing a drug candidate (ORADUR-ADHD) based on DURECT's ORADUR Technology for the treatment of ADHD. This drug candidate is intended to provide once-a-day dosing with added tamper resistant characteristics to address common methods of abuse and misuse of these types of drugs. In August 2009, we entered into a development and license agreement with Orient Pharma Co., Ltd., a diversified multinational pharmaceutical, healthcare and consumer products company with headquarters in Taiwan, under which we granted to Orient Pharma development and commercialization rights in certain defined Asian and South Pacific countries to ORADUR-ADHD. DURECT retains rights to North America, Europe, Japan and all other countries not specifically licensed to Orient Pharma. Under our agreement with Orient Pharma, the parties will collaborate to perform a clinical development program through a Phase II study intended to produce a data package suitable for further development of the drug candidate by us as well as Orient Pharma in their respective territories. We will be responsible for formulation and study design of the Phase I and Phase II clinical program which Orient Pharma has agreed to fund and execute. Orient Pharma would be responsible for all remaining development and commercialization activities for ORADUR-ADHD in the licensed territory. If commercialized, we will be entitled to receive a royalty on sales of ORADUR-ADHD by Orient Pharma. Orient Pharma has committed to supply a portion of DURECT's commercial requirements in all territories other than the U.S. for ORADUR-ADHD. In 2010 and 2011, we conducted several Phase I clinical trials in this program with multiple formulations. Based on information from these trials, we are continuing to evaluate the lead formulations and are planning next steps in our ORADUR-ADHD program.

Relday

Market Opportunity. Risperidone is one of the most widely prescribed medications used to treat the symptoms of schizophrenia and bipolar I disorder in adults and teenagers 13 years of age and older. Relday is being developed to address unmet clinical needs in this large patient population. The existing long-acting injectable risperidone product, which achieved global net sales of \$1.5 billion in 2010, requires twice monthly, 2 mL intramuscular injections with a 21 gauge or larger needle. We and Zogenix expect that, if approved, Relday will be the first once-monthly, subcutaneous antipsychotic product available in a needle-free delivery system to enter the long-acting injectable antipsychotic market. We and Zogenix also expect that, if approved, Relday will provide a new long-acting treatment option for patients that currently use daily oral antipsychotic products. The combined market for oral and injectable antipsychotic products is estimated at more than \$16 billion in 2010. We and Zogenix believe the SABER controlled-release technology combined with Zogenix's DosePro technology

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will allow Relday to be delivered subcutaneously without a needle on a once-monthly basis with a simplified dosing regimen, improved pharmacokinetic profile and significant reduction in injection volume.

Development Strategy. Under the development and license agreement entered into in July 2011 after working together since October 2007 under a feasibility agreement, Zogenix will be responsible for the clinical development and commercialization of a proprietary, long-acting injectable formulation of risperidone using our SABER controlled-release formulation technology in combination with Zogenix's DosePro needle-free, subcutaneous drug delivery system. We will share non-clinical development responsibilities. Zogenix expects to initiate clinical studies for the new product candidate, Relday, in patients with schizophrenia in 2012 following filing of an Investigational New Drug (IND) application.

Biologics Programs

The proteins and genes identified by the biotechnology industry are large, complex, intricate molecules, and many are unsuitable as drugs. If these molecules are given orally, they are often digested before they can have an effect; if given by injection, they may be destroyed by the body's natural processes before they can reach their intended sites of action. The body's natural elimination processes require frequent, high dose injections that may result in unwanted side effects. As a result, the development of biotechnology molecules for the treatment of human diseases has been limited, and advanced drug delivery systems such as we possess are required to realize the full potential of many of these protein and peptide drugs. We have active programs underway to apply our drug delivery systems to various biotechnology drugs and drug candidates, and have entered into a number of feasibility studies with biotechnology and pharmaceutical companies to test their products in our systems.

Research Programs in other Therapeutic Categories

We have underway a number of research programs covering medical diseases and conditions other than pain. Such programs include various diseases and disorders including schizophrenia and cancer. In conducting our research programs and determining which particular efforts to prioritize for formal development, we employ a rigorous opportunity assessment process that takes into account the unmet medical need, commercial opportunity, technical feasibility, clinical viability, intellectual property considerations, and the development path including costs to achieve various critical milestones.

Industry Background

Chronic Diseases and Conditions

Although the pharmaceutical, biotechnology and medical device industries have played key roles in increasing life expectancy and improving health, many chronic, debilitating diseases continue to be inadequately addressed with current drugs or medical devices. Cardiovascular disease, cancer, neurodegenerative diseases, diabetes, arthritis, epilepsy and other chronic diseases claim the lives of millions of Americans each year. These illnesses are prolonged, are rarely cured completely, and pose a significant societal burden in mortality, morbidity and cost. The CDC estimates that the major chronic diseases are responsible for approximately 1.7 million deaths annually, or 70% of all deaths in the U.S. Chronic diseases cause major limitations in daily living for more than 25 million Americans. These diseases account for more than 70% of the cost of health care each year in the U.S. Demographic trends suggest that, as the U.S. population ages, the cost of treating chronic diseases will increase.

Current Approaches to Treatment

Drugs are available to treat many chronic diseases, but harmful side effects can limit prolonged treatment. In addition, patients with chronic diseases commonly take multiple medications, often several times a day, for the remainder of their lives. If patients fail to take drugs as prescribed, they often do not receive the intended benefits or may experience side effects, which are harmful or decrease quality of life. These problems become more

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common as the number of drugs being taken increases, the regimen of dosing becomes more complicated, or the patient ages or becomes cognitively impaired. It is estimated that only half of prescribed medicines are taken correctly.

The Pharmaceutical Industry. The pharmaceutical industry has traditionally focused on the chemical structure of small molecules to create drugs that can treat diseases and medical conditions. The ability to use these molecules as drugs is based on their potency, safety and efficacy. Therapeutic outcome and ultimately the suitability of a molecule as a drug depends to a large extent on how it gets into the body, distributes throughout the body, reacts with its intended site of action and is eliminated from the body. However, small molecules can act in diverse tissues throughout the body resulting in unwanted side effects.

Most drugs require a minimum level in blood and tissues to have significant therapeutic effects. Above a maximum level, however, the drug becomes toxic or has some unwanted side effects. These two levels define the therapeutic range of the drug. With conventional oral dosing and injections, typically a large quantity of drug is administered to the patient at one time, which results in high blood levels of drug immediately after dosing. Because of these high levels, the patient can be over-medicated during the period immediately following dosing, resulting in wasted drug and possible side effects. Due to distribution processes and drug clearance, the blood level of drug falls as time elapses from the last dose. For some duration, the patient is within the desired therapeutic range of blood levels. Eventually, the blood level of drug falls sufficiently such that the patient becomes under-medicated and experiences little or no drug effect until the next dose is administered.

The Biotechnology Industry. Over the past twenty-five years, the biotechnology revolution and the expanding field of genomics have led to the discovery of huge numbers of proteins and genes. Tremendous resources have been committed in the hope of developing drug therapies that would better mimic the body's own processes and allow for greater therapeutic specificity than is possible with small molecule drugs. Unfortunately, this huge effort has led to only a limited number of therapeutic products. The proteins and genes identified by the biotechnology industry are large, complex, intricate molecules, and many are unsuitable as drugs. If these molecules are given orally, they are often digested before they can have an effect; if given by injection, they may be destroyed by the body's natural processes before they can reach their intended sites of action. The body's natural elimination processes require frequent, high dose injections that may result in unwanted side effects. As a result, the development of biotechnology molecules for the treatment of human diseases has been limited.

The Drug Delivery Industry. In the last forty years, a multibillion dollar drug delivery industry has developed on the basis that medicine can be improved by delivering drugs to patients in a precise, controlled fashion. Several commercially successful oral controlled release products, transdermal controlled release patches, and injectable controlled release formulations have been developed. These products demonstrate that the delivery system can be as important to the ultimate therapeutic value of a pharmaceutical product as the active molecule or compound itself. However, drug delivery products on the market today can still be improved, for example, by providing reduced abuse potential, targeted delivery to minimize systemic effects and longer delivery durations where useful. Furthermore, traditional drug delivery products are generally not capable of administering biotechnology agents such as proteins and peptides.

The DURECT Solution: Pharmaceutical Systems

We are developing and commercializing pharmaceutical systems that will deliver the right drug to the right place, in the right amount and at the right time to treat chronic and episodic diseases and conditions. Our pharmaceutical systems enable optimized therapy for a given disease or patient population by controlling the rate and duration of drug administration. In addition, if advantageous for the therapy, our pharmaceutical systems can target the delivery of the drug to its intended site of action.

The Right Drug: By precisely controlling the dosage or targeting delivery to a specific site, we can expand the therapeutic use of compounds that would otherwise be too potent to be administered systemically, do not remain in the body long enough to be effective, or have significant side effects

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when administered systemically. This flexibility allows us to work with a variety of drug candidates including small molecules, proteins, peptides or genes.

The Right Place: In addition to enabling systemic delivery, if advantageous for the therapy, with precise placement of our proprietary catheters or biodegradable drug delivery formulations, we can design our pharmaceutical systems to deliver drugs directly to the intended site of action. This can ensure that the drug reaches the target tissue in effective concentrations, eliminate many side effects caused by delivery of the drug to unintended sites in the body, and reduce the total amount of drug administered to the body.

The Right Amount: Our pharmaceutical systems can automatically deliver drug dosages continuously within the desired therapeutic range for the duration of the treatment period, from days to up to months, without the fluctuations in drug levels typically associated with conventional pills or injections. This can reduce side effects, eliminate gaps in drug therapy, conveniently ensure accurate dosing and patient compliance, and may reduce the total amount of drug administered to the body.

The Right Time: Our pharmaceutical systems technologies are designed to minimize the need for intervention by the patient or care-giver and to enhance dosing compliance. In addition to reducing the cost of care, continuous drug therapy frees the patient from repeated treatment or hospitalization, improving convenience and quality of life. Our systems are well-suited to deliver drug for the right period of time for the intended indication, whether for hours or days for acute indications or months or years for treating chronic, debilitating diseases such as chronic pain, cancer, heart disease, and neurodegenerative diseases. We believe that it is more effective to treat chronic diseases with continuous, long-term therapy than with alternatives such as multiple conventional injections or oral dosage forms that create short-term effects.

DURECT Pharmaceutical Systems Technology

Our pharmaceutical systems combine engineering with proprietary small molecule pharmaceutical and biotechnology drug formulations to yield proprietary delivery technologies and products. Through this combination, we are able to control the rate and duration of drug administration, as well as, when desired, target the delivery of the drug to its intended site of action, allowing our pharmaceutical systems to meet the special challenges associated with treating medical conditions over an extended period of time. Our pharmaceutical systems can enable new drug therapies or optimize existing therapies based on a broad range of compounds, including small molecule pharmaceuticals as well as biologics such as proteins, peptides and genes.

Our pharmaceutical systems are suitable for providing long-term drug therapy because they store highly concentrated, stabilized drugs in a small volume and can protect the drug from degradation by the body. This, in combination with our ability to continuously deliver precise and accurate doses of a drug, allows us to extend the therapeutic value of a wide variety of drugs, including those which would otherwise be ineffective, too unstable, too potent or cause adverse side effects. In some cases, delivering the drug directly to the intended site of action can improve efficacy while minimizing unwanted side effects elsewhere in the body, which often limit the long-term use of many drugs. Our pharmaceutical systems can thus provide better therapy for chronic diseases or conditions, or for certain acute conditions where longer drug dosing is required or advantageous, by replacing multiple injection therapy or oral dosing, improving drug efficacy, reducing side effects and ensuring dosing compliance. Our pharmaceutical systems can improve patients' quality of life by eliminating more repetitive treatments, reducing dependence on caregivers and allowing patients to lead more independent lives.

We currently have five major technology platforms:

The SABER Delivery System

The SABER system is a patented controlled-release technology that can be formulated for systemic or local administration of active agents via the parenteral or oral route. We are researching and developing a variety of

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controlled-release products based on the SABER technology. These include injectable controlled release products for systemic and local delivery and oral products. We believe that our SABER system can provide the basis for the development of a state-of-the-art biodegradable, controlled-release injectable. The SABER system uses a high-viscosity base component, such as sucrose acetate isobutyrate (SAIB), to provide controlled release of a drug. When the high viscosity SAIB is formulated with drug, biocompatible excipients and other additives, the resulting formulation is liquid enough to inject easily with standard syringes and needles. After injection of a SABER formulation, the excipients diffuse away, leaving a viscous depot. Depending on how it is formulated, the SABER system can successfully deliver therapeutic levels of a wide spectrum of drugs from one day to three months from a single injection. Based on research and development work to date, our SABER technology has shown the following advantages:

Peptide/Protein Delivery The chemical nature of the SABER system tends to repel water and body enzymes from its interior and thereby stabilizes proteins and peptides. For this reason, we believe that the SABER system is well suited as a platform for biotechnology therapeutics based on proteins and peptides.

Less Burst Typically, controlled release injections are associated with an initial higher release of drug immediately after injection (also called "burst"). Animal and human studies have shown that injectables based on the SABER technology can be associated with less post-injection burst than is typically associated with other commercially available injectable controlled release technologies.

High Drug Concentration Drug concentration in a SABER formulation can be as high as 30%, considerably greater than is typical with other commercially available injectable controlled release technologies. As a result, smaller injection volumes are possible with this technology.

Ease of Administration Prior to injection, SABER formulations are fairly liquid and therefore can be injected through small needles. Additionally, because of the higher drug concentration of SABER formulations, less volume is required to be injected. Small injection volumes and more liquid solutions are expected to result in easier, less painful administration.

Strong Patent Protection The SABER system, SABER-like materials, and various applications of this technology to pharmaceuticals, medical devices and drug delivery are covered by United States and foreign patents. See "Patents, Licenses and Proprietary Rights" below.

Ease of Manufacture Compared to microspheres and other polymer-based controlled release injectable systems, SABER is readily manufacturable at low cost.

The SABER Technology is the basis of POSIDUR, which recently completed a Phase III clinical trial in the U.S. In our clinical studies thus far, SABER formulations have been observed to be safe and well-tolerated, and no significant side effects or adverse events were reported.

The SABER Technology is also the basis for SucroMate[®] Equine, an injectable animal health drug utilizing our SABER technology to deliver the peptide deslorelin. This is the first FDA approved SABER injectable product and it was launched in 2011 by our collaborator, CreoSalus, Inc.

The TRANSDUR Transdermal Delivery System

Our TRANSDUR technology is a proprietary transdermal delivery system that enables delivery of drugs continuously for up to 7 days. The TRANSDUR technology is the basis for TRANSDUR-Sufentanil for which we have conducted Phase II clinical trials and for which we hold worldwide development and commercialization rights. The TRANSDUR technology is also the basis for ELADUR, for which we have conducted two Phase II clinical trials and for which we hold worldwide development and commercialization rights.

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The ORADUR Sustained Release Gel Cap Technology

We are developing ORADUR sustained release oral technology based on our SABER technology. We believe that ORADUR can transform short-acting oral capsule dosage forms into sustained release oral products. Products based on our ORADUR technology can take the form of an easy to swallow gelatin capsule that uses a high-viscosity base component such as sucrose acetate isobutyrate (SAIB) to provide controlled release of active ingredients for a period of 12 to 24 hours of drug delivery. Oral dosage forms based on the ORADUR gel-cap may also have the added benefit of being less prone to abuse (e.g., by crushing or alcohol or water extraction) than other controlled release dosage forms on the market today. These properties have the potential to make ORADUR-based products an attractive option for pharmaceutical companies that seek to develop abuse deterrent oral products.

The ORADUR technology is the basis of Remoxy, a novel long-acting oral formulation of the opioid oxycodone which is targeted to decrease the potential for oxycodone abuse. Since 2006, we also worked with Pain Therapeutics and King on the development of three additional ORADUR abuse-resistant opioid drug candidates which would address the chronic pain market. Phase I clinical trials have been conducted for two of these ORADUR-based products (hydrocodone and hydromorphone), and an IND has been accepted by the FDA for the third ORADUR-based opioid (oxymorphone). We also have an ORADUR-ADHD program for which we and Orient Pharma have conducted several Phase I clinical trials with multiple formulations in 2010 and 2011.

The DURIN Biodegradable Implant Technology

Our DURIN technology is a proprietary biodegradable implant that enables parenteral delivery of drugs from several weeks to six months or more using our LACTEL brand polymers and co-polymers of lactic and glycolic acid. The DURIN technology can deliver a wide variety of drugs including small and large molecule compounds. Our proprietary implant design allows for a variety of possible delivery profiles including constant rate delivery. Because DURIN implants are biodegradable, at the end of its delivery life, what remains of the DURIN implant is absorbed by the body.

The MICRODUR Biodegradable Microparticulate Technology

Our MICRODUR technology is a patented biodegradable microparticulate depot injectable. We have experience in microencapsulation of a broad spectrum of drugs using our LACTEL brand polymers and co-polymers of lactic and glycolic acid. In our MICRODUR process, both standard and proprietary polymers are used to entrap an active agent in solid matrices or capsules comprising particles generally between 10 and 125 microns in diameter. Through a suitable choice of polymers and processing, sustained release from a few days to many months can be achieved. As with the DURIN technology, MICRODUR particles degrade fully in the body after the active agent is released. Our range of experience extends from the manufacturing of the polymer raw material to process and product development, scale-up and cGMP manufacturing.

DURECT Strategy

Our objective is to become a specialty pharmaceutical company by developing, and in the future, commercializing pharmaceutical systems that address significant medical needs and improve patients' quality of life. To achieve this objective, our strategy includes the following key elements:

Focus on Chronic Debilitating Medical Conditions and Certain Local Pain Conditions. Many of the diseases that present the greatest challenges to medicine are chronic, debilitating diseases such as chronic pain, CNS disorders, cardiovascular disorders, cancer and degenerative neurological diseases. In addition, we have identified certain local and acute pain conditions that we believe can be addressed by improved therapeutics. Our initial efforts will focus on using our versatile drug delivery platform technologies to develop products that address these medical conditions.

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Minimize Product Development Risk. Initially, we intend to minimize product development risk by using our drug delivery platform technologies to administer drugs for which medical data on efficacy and safety are available. This strategy reduces much of the development risk that is inherent in traditional pharmaceutical product discovery. We anticipate that we can expand the medical usefulness of existing well-characterized drugs in several ways:

expand uses or create new uses for existing drugs by delivering drugs continuously for convenient long dosing intervals;

create new uses for drugs which were previously considered to be too potent to be used safely by precisely controlling dosing;

deliver drugs by injection or transdermally to eliminate the first pass effect whereby the efficacy of the active agent is impacted by digestion and deactivation;

enhance drug performance by minimizing side effects; and

expand uses of drugs by delivering them to the target site.

We anticipate that our pharmaceutical systems can be more rapidly developed at lower cost than comparable products that are developed purely based on chemical solutions to the problems of efficacy, side effects, stability and delivery of the active agent. We believe that our ability to innovate more rapidly will allow us to respond more quickly to market feedback to optimize our existing pharmaceutical systems or develop line extensions that address new market needs.

Enable the Development of Pharmaceutical Systems Based on Biotechnology and Other New Compounds. We believe there is a significant opportunity for pharmaceutical systems to add value to therapeutic medicine by administering biologics, such as proteins, peptides and genes. We believe our technologies will improve the specificity, potency, convenience and cost-effectiveness of proteins, peptides, genes and other newly discovered drugs. Our systems can enable these compounds to be effectively administered, thus allowing them to become viable medicines. We can address the stability and storage needs of these compounds through our advanced formulation technology and package them in a suitable pharmaceutical system for optimum delivery. Through continuous administration, the SABER, DURIN and MICRODUR technology platforms may eliminate or reduce the need for multiple injections of these drugs. In addition, through precise placement of our proprietary biodegradable drug formulations, proteins and genes can be delivered to specific tissues for extended periods of time, thus ensuring that large molecule agents are present at the desired site of action and minimizing the potential for adverse side effects elsewhere in the body.

Diversify Risk by Pursuing Multiple Programs in Development. In order to reduce the risks inherent in pharmaceutical product development, we have diversified our product pipeline such that, between our own programs and those where we have collaborated, we presently have one program for which a New Drug Application has been filed and a Complete Response Letter has been received, and six different disclosed programs in clinical development, including three oral drug candidates, two transdermal patch candidates and one injectable drug candidate. We believe that having multiple programs in development helps mitigate the negative consequences to us of any setbacks or delays in any one of our programs.

Enable Product Development Through Strategic Collaborations. We believe that entering into selective collaborations with respect to our product development programs can enhance the success of our product development and commercialization, mitigate our risk and enable us to better manage our operating costs. Additionally, such collaborations enable us to leverage investment by our collaborators and reduce our net cash burn, while retaining significant economic rights.

Build Our Own Commercial Organization. In the future, we may elect to build our own commercial, sales and marketing capability in order to capture more of the economic value of certain products that we may

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develop. If we choose to enter into third-party collaborations to commercialize our pharmaceutical systems, we may in the future enter into these alliances under circumstances that allow us to participate in the sales and marketing of these products.

Third-Party Collaborations

We have entered into the following agreements in connection with our third party collaborations:

Zogenix, Inc. On July 11, 2011, we and Zogenix, Inc., (Zogenix), entered into a Development and License Agreement (the License Agreement). We and Zogenix had previously been working together under a feasibility agreement pursuant to which our research and development costs were reimbursed by Zogenix. Under the License Agreement, Zogenix will be responsible for the clinical development and commercialization of a proprietary, long-acting injectable formulation of risperidone using our SABER controlled-release formulation technology in combination with Zogenix's DosePr® needle-free, subcutaneous drug delivery system. We will be responsible for non-clinical, formulation and CMC development activities. We will be reimbursed by Zogenix for our research and development efforts on the product. Zogenix paid a non-refundable upfront fee to us of \$2.25 million in July 2011. Zogenix is obligated to pay us up to \$103 million in total future milestone payments with respect to the product subject to and upon the achievement of various development, regulatory and sales milestones. Of these potential milestones, \$28 million are development-based milestones (none of which has been achieved as of December 31, 2011), and \$75 million are sales-based milestones (none of which has been achieved as of December 31, 2011). Zogenix is also required to pay a mid single-digit to low double-digit percentage patent royalty on annual net sales of the product determined on a jurisdiction-by-jurisdiction basis. The patent royalty term is equal to the later of the expiration of all DURECT technology patents or joint patent rights in a particular jurisdiction, the expiration of marketing exclusivity rights in such jurisdiction, or 15 years from first commercial sale in such jurisdiction. After the patent royalty term, Zogenix will continue to pay royalties on annual net sales of the product at a reduced rate for so long as Zogenix continues to sell the product in the jurisdiction. Zogenix is also required to pay to us a tiered percentage of fees received in connection with any sublicense of the licensed rights.

We granted to Zogenix an exclusive worldwide license, with sub-license rights, to the intellectual property rights related to the proprietary polymeric and non-polymeric controlled-release formulation technology to make and have made, use, offer for sale, sell and import risperidone products, where risperidone is the sole active agent, for administration by injection in the treatment of schizophrenia, bipolar disorder or other psychiatric related disorders in humans. We retain the right to supply Zogenix's Phase 3 clinical trial and commercial product requirements on the terms set forth in the License Agreement. We retain the right to terminate the License Agreement with respect to specific countries if Zogenix fails to advance the development of the product in such country, either directly or through a sublicensee. In addition, either party may terminate the License Agreement upon insolvency or bankruptcy of the other party, upon written notice of a material uncured breach or if the other party takes any act impairing such other party's relevant intellectual property rights. Zogenix may terminate the License Agreement upon written notice if during the development or commercialization of the product, the product becomes subject to one or more serious adverse drug experiences or if either party receives notice from a regulatory authority, independent review committee, data safety monitoring board or other similar body alleging significant concern regarding a patient safety issue. Zogenix may also terminate the License Agreement with or without cause, at any time upon prior written notice. As of December 31, 2011, the cumulative aggregate payments received by us under this agreement were \$3.4 million.

Hospira, Inc. In June 2010, we entered into a license agreement with Hospira to develop and commercialize POSIDUR in the U.S. and Canada. Under terms of the agreement, Hospira made an upfront payment of \$27.5 million, with the potential for up to an additional \$185 million in performance milestone payments based on the successful development, approval and commercialization of POSIDUR in the U.S. and Canada. Of these potential milestones, \$35 million are development-based milestones (none of which has been achieved as of December 31, 2011), and \$150 million are sales-based milestones (none of which has been achieved as of December 31, 2011). For the U.S. and Canada, the two companies will jointly direct and equally

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fund the remaining development costs for POSIDUR, while Hospira will have exclusive commercialization rights upon regulatory approval with sole funding responsibility for commercialization activities. In addition, the Company has also granted to Hospira the right to develop and commercialize in the U.S. and Canada, at Hospira's sole cost, other specified local anesthetic products, if any, based on the SABER technology, which come into existence under the Agreement. Hospira will be responsible for commercial manufacture of licensed products under the Agreement, provided that the Company will supply to Hospira a specified excipient for use in the manufacture of licensed products pursuant to a supply agreement entered into by the parties. On a product by product basis, Hospira will pay us a royalty on sales of each licensed product commercialized under the Agreement for a defined period, after which the license granted to Hospira for such product shall convert to a fully paid-up, non-royalty bearing and perpetual license. The term of the agreement shall be for the duration of Hospira's obligation to pay royalties for product sales under the Agreement. The agreement provides each party with specified termination rights, including the right of Hospira to terminate at will after a specified period and each party to terminate the agreement upon material breach of the agreement by the other party. The agreement also contains terms and conditions customary for this type of arrangement, including representations, warranties and indemnities. As of December 31, 2011, the cumulative aggregate payments received by us under this agreement were \$38.3 million.

Alpharma Ireland Limited (acquired in December 2008 by King which subsequently was acquired by Pfizer in February 2011). In September 2008, we and Alpharma entered into a development and license agreement granting Alpharma the exclusive worldwide rights to develop and commercialize ELADUR, our investigational transdermal bupivacaine patch. The agreement became effective in October 2008. Under the terms of the agreement, Alpharma paid us an upfront license fee of \$20 million. As a result of the acquisition of Alpharma by King in December 2008, King assumed Alpharma's rights and obligations under the agreement. In February 2011, Pfizer acquired King and thereby assumed the rights and obligations of King with respect to ELADUR. In February 2012, Pfizer notified us that they are returning their worldwide development and commercialization rights to ELADUR. As of December 31, 2011, the cumulative aggregate payments received by us under this agreement were \$29.0 million.

Nycomed Danmark ApS. In November 2006, we entered into a collaboration agreement with Nycomed, and this agreement was amended in February 2010 and February 2011. Under the terms of the 2010 amended agreement, we licensed to Nycomed the exclusive commercialization rights to POSIDUR for the European Union (E.U.) and certain other countries. Nycomed paid us an upfront license fee of \$14.0 million in 2006 and an \$8.0 million milestone payment in 2007 triggered by achievement of a clinical development milestone. Nycomed also paid a portion of development expenses. In January 2012, Nycomed (acquired by Takeda in October 2011) notified us that it was terminating the license agreement with us, and thereby returning their right to develop and commercialize POSIDUR (SABER -Bupivacaine) in Europe and their other licensed territories to us effective April 26, 2012. As of December 31, 2011, the cumulative aggregate payments received by us under this agreement were \$37.3 million. In addition, the cumulative aggregate payments paid by us under this agreement to Nycomed were \$9.0 million as of December 31, 2011.

Pain Therapeutics, Inc. In December 2002, we entered into an exclusive agreement with Pain Therapeutics to develop and commercialize on a worldwide basis oral sustained release, abuse deterrent opioid products incorporating four specified opioid drugs using our ORADUR technology. The agreement also provides Pain Therapeutics with the exclusive right to commercialize products developed under the agreement on a worldwide basis. In connection with the execution of the agreement, Pain Therapeutics paid us an upfront fee. In November 2005, Pain Therapeutics sublicensed the worldwide commercialization rights (except for Australia and New Zealand) to certain products developed under the agreement (including Remoxy) to King. In February 2011 Pfizer acquired King and thereby assumed the rights and obligations of King with respect to the sublicense agreement. In December 2005, we amended our agreement with Pain Therapeutics in order to specify our obligations with respect to the supply of key excipients for use in the licensed products. Under the amended agreement, we are responsible for formulation development, supply of selected key excipients used in the manufacture of licensed product and other specified tasks. We receive reimbursement for our research and development efforts on the licensed products

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and a manufacturing profit on our supply of key product excipients to Pain Therapeutics for use in the licensed products. Under the agreement with Pain Therapeutics, subject to and upon the achievement of predetermined development and regulatory milestones for the four drug candidates currently in development, we are entitled to receive milestone payments of up to \$9.3 million in the aggregate. As of December 31, 2011, we had received \$1.7 million in cumulative milestone payments. In addition, if commercialized, we will receive royalties for Remoxy and other licensed products which do not contain an opioid antagonist of between 6.0% to 11.5% of net sales of the product depending on the sales volumes. This agreement can be terminated by either party for material breach by the other party and by Pain Therapeutics without cause. As of December 31, 2011, the cumulative aggregate payments received by us from Pain Therapeutics under this agreement were \$32.8 million.

In March 2009, King assumed the responsibility for further development of Remoxy from Pain Therapeutics. As a result of this change, we will continue to perform Remoxy related activities in accordance with the terms and conditions set forth in the license agreement between us and Pain Therapeutics, but with King substituted in lieu of Pain Therapeutics with respect to interactions with us in our performance of those activities including the obligation to pay us with respect to all Remoxy related costs incurred by us. The cumulative aggregate payments received by us from King as of December 31, 2011 were \$6.3 million under this agreement.

During 2008, we began to manufacture commercial lots of certain key excipients that are included in Remoxy to meet the anticipated requirements for these components. In addition, during the second, third and fourth quarters of 2008 and the first quarter of 2009, we made shipments of these materials to meet the production requirements of King, which has rights to commercialize Remoxy upon approval by the FDA. During these periods, all product revenue and associated cost of goods sold was deferred pending the establishment of definitive final terms and conditions even though cash receipts and expenditures occurred during these periods.

Long Term Supply Agreement with King (now Pfizer). In August 2009, we entered into an exclusive long term excipient supply agreement with respect to REMOXY with King. In February 2011, Pfizer acquired King and thereby assumed the rights and obligations of King with respect to the long term excipient supply agreement. This agreement stipulates the terms and conditions under which we will supply to King, based on our manufacturing cost plus a specified percentage mark-up, two key excipients used in the manufacture of REMOXY. The term of the agreement commenced on August 5, 2009 and will continue in effect until the earlier of the expiration of all licenses granted under the development and license agreement between us and Pain Therapeutics or the termination or expiration of the 2005 development and license agreement between Pain Therapeutics and King, unless the agreement is terminated earlier in accordance with its terms. The agreement provides each party with specified termination rights, which include, but are not limited to, the right of King to terminate the agreement in the event that governmental action requires the withdrawal of REMOXY from all countries in the territory or results in the withdrawal of required manufacturing approvals, or upon a change of control of us, in which case termination will be effective one year after notice by King. We may terminate the agreement if we are unable to procure suitable and sufficient quantities of certain raw materials required to produce the excipient ingredients. Each party may terminate the agreement upon material breach of the agreement by, or the bankruptcy or insolvency of, the other party, in each case subject to a cure period. The agreement further specifies the rights and obligations of us and King with respect to plant allocation, adding additional production capacity and sourcing of raw materials, as well as other terms and conditions customary for this type of agreement, including those regarding forecasting, purchasing, invoicing, representations, warranties and indemnities. Revenue attributable to these key components aggregating \$3.0 million and cost of goods sold aggregating \$2.0 million related to shipments to King that occurred in 2008 and the first quarter of 2009 was recognized in the third quarter of 2009 upon the execution of a long term supply agreement with King such that final terms and conditions of the sales were established.

In 2010, we recognized \$551,000 of product revenue for shipments made in 2008 and 2009 related to a price settlement after all criteria of revenue recognition were met. The price settlement related to additional manufacturing cost incurred by us and certain mark-ups for the goods produced and shipped in 2008 and 2009

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pursuant to the long term excipient supply agreement. In addition, we also recognized \$410,000 of product revenue related to the shipment of another excipient that is included in Remoxy upon shipment to King in 2010. Total revenue recognized related to these excipients was \$961,000 and \$3.0 million in 2010 and 2009, respectively and the associated cost of goods sold was \$315,000 and \$2.0 million in 2010 and 2009, respectively.

In 2011, we recognized \$490,000 of product revenue related to key excipients for Remoxy and the associated cost of goods sold was \$302,000.

Endo Pharmaceuticals Inc. (TRANSDUR-Sufentanil). In March 2005, we entered into a license agreement with Endo under which we granted to Endo the exclusive right to develop, market and commercialize TRANSDUR-Sufentanil in the U.S. and Canada. We received an initial payment of \$10.0 million in connection with the execution of the agreement. In February 2009, Endo notified us that it was terminating the license agreement with us, and thereby returned their right to develop and commercialize TRANSDUR-Sufentanil in the U.S. and Canada to us effective August 26, 2009. As of December 31, 2011, the cumulative aggregate payments received by us under this agreement were \$21.5 million.

Commercial Product Lines

ALZET

The ALZET product line consists of miniature, implantable osmotic pumps and accessories used for experimental research in mice, rats and other laboratory animals. These pumps are neither approved nor intended for human use. ALZET pumps continuously deliver drugs, hormones and other test agents at controlled rates from one day to four weeks without the need for external connections, frequent handling or repeated dosing. In laboratory research, these infusion pumps can be used for systemic administration when implanted under the skin or in the body. They can be attached to a catheter for intravenous, intracerebral, or intra-arterial infusion or for targeted delivery, where the effects of a drug or test agent are localized in a particular tissue or organ. The wide use and applications of the ALZET product line is evidenced by the more than 12,000 scientific references that now exist.

We acquired the ALZET product line and assets used primarily in the manufacture, sale and distribution of this product line from ALZA in April 2000. We believe that the ALZET business provides us with innovative design and application opportunities for potential new products.

LACTEL Absorbable Polymers

We currently design, develop and manufacture a wide range of standard and custom biodegradable polymers based on lactide, glycolide and caprolactone under the LACTEL brand for pharmaceutical and medical device clients for use as raw materials in their products. These materials are manufactured and sold by us directly from our facility in Alabama and are used by us and our third-party customers for a variety of controlled-release and medical-device applications, including several FDA-approved commercial products.

Marketing and Sales

Historically, we have established strategic distribution and marketing alliances for our pharmaceutical systems to leverage the established sales organizations that certain pharmaceutical companies have in markets we are targeting. In the future, we may elect to build our own commercial, sales and marketing capability in order to capture more of the economic value of certain products that we may develop. If we choose to enter into third-party collaborations to commercialize our pharmaceutical systems, we may in the future enter into these alliances under circumstances that allow us to participate in the sales and marketing of these products. We will continue to pursue strategic alliances and collaborators from time to time consistent with our strategy to leverage the established sales organizations of third-party collaborators to achieve greater market penetration for some of our

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products than we could on our own. If we choose to enter into third-party collaborations to commercialize our pharmaceutical systems, we believe we have the flexibility to enter into these alliances under circumstances that allow us to retain greater economic participation because our pharmaceutical systems combine drugs for which medical data on efficacy and safety are available with proven technology platforms.

We market and sell our ALZET and LACTEL product lines through a direct sales force in the U.S. and through a network of distributors outside of the U.S.

Suppliers

We purchase sucrose acetate isobutyrate, a raw material for our ORADUR and SABER-based pharmaceutical systems, including POSIDUR, Remoxy and other ORADUR-based drug candidates, pursuant to a supply agreement with Eastman Chemical Company. We purchase sufentanil for TRANSDUR-Sufentanil pursuant to a supply agreement with Mallinckrodt, Inc. We have entered into a supply agreement with Corium International, Inc. for clinical and commercial supplies of ELADUR and a supply agreement with Hospira Worldwide, Inc. for clinical and commercial supplies of POSIDUR.

Our supply agreement with Eastman Chemical Company requires us to purchase a certain portion of our requirements for sucrose acetate isobutyrate from Eastman Chemical and obligates us to pay a fee per annum if our purchases do not meet specified sales targets. The agreement may be terminated by either party under certain circumstances, including any material uncured breach by, or the insolvency, liquidation or bankruptcy of, or similar proceedings involving, the other party.

Our supply agreement with Mallinckrodt, Inc. requires us to purchase a certain portion of our requirements for sufentanil from Mallinckrodt, and has no other minimum purchase requirements or exclusivity provisions. The initial term of the agreement expired on September 30, 2009 and is subject to automatic renewal for additional one-year terms unless either party provides one year notice of its intention not to renew the agreement. In addition, either party may terminate the Mallinckrodt agreement on 30 days notice for any material uncured breach by, or the bankruptcy of or similar proceedings involving, the other party. Finally, we may terminate the Mallinckrodt agreement on 60 days notice if we reasonably determine that the price being charged by Mallinckrodt is higher than the prevailing price for similar quantities of like grade or quality, or if we cease to develop or commercialize any products incorporating the products we purchase from Mallinckrodt.

We believe that these agreements will provide a sufficient supply of these raw materials and drug product to meet our needs for the foreseeable future. We do not have in place long term supply agreements with respect to all of the components of any of our pharmaceutical systems, however, and are subject to the risk that we may not be able to procure all required components in adequate quantities with acceptable quality, within acceptable time frames or at reasonable cost.

Customers

Our product revenues are derived from sale of the ALZET and LACTEL product lines as well as from the sale of certain key excipients that are included in Remoxy to our customer (Pfizer). Until such time that we are able to bring our pharmaceutical systems to market, if at all, we expect these to be our principal sources of product revenue. We also receive revenue from collaborative research and development arrangements with our third-party collaborators. In 2011, Hospira and Pfizer accounted for 34% and 16% of the Company's total revenues, respectively. In 2010, Pfizer (King) and Hospira accounted for 33% and 18% of the Company's total revenues, respectively. In 2009, Pfizer (King) accounted for 41% of our total revenues and no other customers accounted for more than 10% of total revenues.

At December 31, 2011, Hospira, Pfizer and Pain Therapeutics accounted for 27%, 22% and 22% of our net accounts receivable, respectively. At December 31, 2010, Hospira, Pfizer (King) and Pain Therapeutics accounted for 33%, 19% and 15% of our net accounts receivable, respectively.

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Manufacturing

The process for manufacturing our pharmaceutical systems is technically complex, requires special skills, and must be performed in a qualified facility. We have contracted with Hospira Worldwide and Corium International to manufacture clinical and commercial supplies of POSIDUR and ELADUR, respectively. In addition, we have a small multi-discipline manufacturing facility in California that we have used to manufacture research and clinical supplies of several of our pharmaceutical systems under GMP, including POSIDUR, Remoxy, TRANSDUR-Sufentanil, and ELADUR. In the future, we intend to develop additional manufacturing capabilities for our pharmaceutical systems and components to meet our demands and those of our third party collaborators by contracting with third party manufacturers and by construction of additional manufacturing space at our current facilities in California and Alabama. We manufacture our ALZET product line and certain key components for Remoxy at one of our California facilities and our LACTEL product line at our Alabama facility.

Patents, Licenses and Proprietary Rights

Our success depends in part on our ability to obtain patents, to protect trade secrets, to operate without infringing upon the proprietary rights of others and to prevent others from infringing on our proprietary rights. Our policy is to seek to protect our proprietary position by, among other methods, filing U.S. and foreign patent applications related to our proprietary technology, inventions and improvements that are important to the development of our business. As of February 21, 2012, we held 41 issued U.S. patents and 314 issued foreign patents (which include granted European patent rights that have been validated in various EU member states). In addition, we have 56 pending U.S. patent applications and have filed 107 patent applications under the Patent Cooperation Treaty, from which 178 national phase applications are currently pending in Europe, Australia, Japan, Canada and other countries. Our patents expire at various dates starting in 2012.

Proprietary rights relating to our planned and potential products will be protected from unauthorized use by third parties only to the extent that they are covered by valid and enforceable patents or are effectively maintained as trade secrets. Patents owned by or licensed to us may not afford protection against competitors, and our pending patent applications now or hereafter filed by or licensed to us may not result in patents being issued. In addition, the laws of certain foreign countries may not protect our intellectual property rights to the same extent as do the laws of the U.S.

The patent positions of biopharmaceutical companies involve complex legal and factual questions and, therefore, their enforceability cannot be predicted with certainty. Our patents or patent applications, or those licensed to us, if issued, may be challenged, invalidated or circumvented, and the rights granted thereunder may not provide proprietary protection or competitive advantages to us against competitors with similar technology. Furthermore, our competitors may independently develop similar technologies or duplicate any technology developed by us. Because of the extensive time required for development, testing and regulatory review of a potential product, it is possible that, before any of our products can be commercialized, any related patent may expire or remain in existence for only a short period following commercialization, thus reducing any advantage of the patent, which could adversely affect our ability to protect future product development and, consequently, our operating results and financial position.

Because patent applications in the U.S. are maintained in secrecy for at least 18 months after filing and since publication of discoveries in the scientific or patent literature often lag behind actual discoveries, we cannot be certain that we were the first to make the inventions covered by each of our issued or pending patent applications or that we were the first to file for protection of inventions set forth in such patent applications.

Our planned or potential products may be covered by third-party patents or other intellectual property rights, in which case we would need to obtain a license to continue developing or marketing these products. Any required licenses may not be available to us on acceptable terms, if at all. If we do not obtain any required

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licenses, we could encounter delays in product introductions while we attempt to design around these patents, or could find that the development, manufacture or sale of products requiring such licenses is foreclosed. Litigation may be necessary to defend against or assert such claims of infringement, to enforce patents issued to us, to protect trade secrets or know-how owned by us, or to determine the scope and validity of the proprietary rights of others. In addition, interference proceedings declared by the U.S. Patent and Trademark Office (USPTO) may be necessary to determine the priority of inventions with respect to our patent applications. Litigation or interference proceedings could result in substantial costs to and diversion of effort by us, and could have a material adverse effect on our business, financial condition and results of operations. These efforts by us may not be successful.

We may rely, in certain circumstances, on trade secrets to protect our technology. However, trade secrets are difficult to protect. We seek to protect our proprietary technology and processes, in part, by confidentiality agreements with our employees and certain contractors. There can be no assurance that these agreements will not be breached, that we will have adequate remedies for any breach, or that our trade secrets will not otherwise become known or be independently discovered by competitors. To the extent that our employees, consultants or contractors use intellectual property owned by others in their work for us, disputes may also arise as to the rights in related or resulting know-how and inventions.

Government Regulation

The Food and Drug Administration. The FDA and comparable regulatory agencies in state and local jurisdictions and in foreign countries impose substantial requirements upon the clinical development, manufacture and marketing of pharmaceutical products. These agencies and other federal, state and local entities regulate research and development activities and the testing, manufacture, quality control, safety, effectiveness, labeling, storage, distribution, record keeping, approval, advertising and promotion of our products. We believe that our initial pharmaceutical systems will be regulated as drugs by the FDA rather than as biologics or devices.

The process required by the FDA under the new drug provisions of the Federal Food, Drug and Cosmetics Act (the Act) before our initial pharmaceutical systems may be marketed in the U.S. generally involves the following:

preclinical laboratory and animal tests;

submission of an Investigational New Drug (IND) application which must become effective before clinical trials may begin;

adequate and well-controlled human clinical trials to establish the safety and efficacy of the proposed pharmaceutical in our intended use; and

FDA approval of a new drug application.

Section 505 of the Act describes three types of new drug applications: (1) an application that contains full reports of investigations of safety and effectiveness (section 505(b)(1)); (2) an application that contains full reports of investigations of safety and effectiveness but where at least some of the information required for approval comes from studies not conducted by or for the applicant and for which the applicant has not obtained a right of reference (section 505(b)(2)); and (3) an application that contains information to show that the proposed product is identical in active ingredient, dosage form, strength, route of administration, labeling, quality, performance characteristics and intended use, among other things, to a previously approved product (section 505(j)). A supplement to an application is a new drug application. We expect that most of our drug candidates will be approved by submission of a new drug application under section 505(b)(2).

The testing and approval process requires substantial time, effort, and financial resources, and we cannot be certain that any approval will be granted on a timely basis, if at all. Even though several of our pharmaceutical systems utilize active drug ingredients that are commercially marketed in the United States in other dosage forms, we need to establish safety and effectiveness of those active ingredients in the formulation and dosage forms that we are developing.

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Preclinical tests include laboratory evaluation of the product, its chemistry, formulation and stability, as well as animal studies to assess the potential safety and efficacy of the pharmaceutical system. We then submit the results of the preclinical tests, together with manufacturing information and analytical data, to the FDA as part of an IND, which must become effective before we may begin human clinical trials. Each subsequent new clinical protocol must also be submitted to the IND. An IND automatically becomes effective 30 days after receipt by the FDA, unless the FDA, within the 30-day time period, raises concerns or questions about the conduct of the trials as outlined in the IND and imposes a clinical hold. In such a case, the IND sponsor and the FDA must resolve any outstanding concerns before clinical trials can begin. Our submission of an IND may not result in FDA authorization to commence clinical trials. Further, an independent Institutional Review Board at each medical center proposing to conduct the clinical trials must review and approve any clinical study as well as the related informed consent forms and authorization forms that permit us to use individually identifiable health information of study participants.

Human clinical trials are typically conducted in three sequential phases which may overlap:

Phase I: The drug is initially introduced into healthy human subjects or patients and tested for safety, dosage tolerance, absorption, metabolism, distribution and excretion.

Phase II: Involves clinical trials in a limited patient population to identify possible adverse effects and safety risks, to determine the efficacy of the product for specific targeted diseases and to determine dosage tolerance and optimal dosage.

Phase III: When Phase II clinical trials demonstrate that a dosage range of the product is effective and has an acceptable safety profile, Phase III clinical trials are undertaken to further evaluate dosage, clinical efficacy and to further test for safety in an expanded patient population, at multiple, geographically dispersed clinical study sites.

In the case of products for severe diseases, such as chronic pain, or life-threatening diseases such as cancer, the initial human testing is often conducted in patients with disease rather than in healthy volunteers. Since these patients already have the target disease or condition, these studies may provide initial evidence of efficacy traditionally obtained in Phase II trials, and thus these trials are frequently referred to as Phase I/II clinical trials. We cannot be certain that we will successfully complete Phase I, Phase II or Phase III clinical trials of our pharmaceutical systems within any specific time period, if at all. Furthermore, the FDA or the Institutional Review Board or the sponsor may suspend clinical trials at any time on various grounds, including a finding that the subjects or patients are being exposed to an unacceptable health risk. During the clinical development of products, sponsors frequently meet and consult with the FDA in order to ensure that the design of their studies will likely provide data both sufficient and relevant for later regulatory approval; however, no assurance of approvability can be given by the FDA.

The results of product development, preclinical studies and clinical studies are submitted to the FDA as part of a new drug application, or NDA, for approval of the marketing and commercial shipment of the product. Submission of an NDA requires the payment of a substantial user fee to the FDA, and although the agency has defined user fee goals for the time in which to respond to sponsor applications, we cannot assure you that the FDA will act in any particular timeframe. The FDA may deny a new drug application if the applicable regulatory criteria are not satisfied or may require additional clinical data. Even if such data is submitted, the FDA may ultimately decide that the new drug application does not satisfy the criteria for approval. Once issued, the FDA may withdraw product approval if compliance with regulatory standards is not maintained or if safety problems occur after the product reaches the market. Requirements for additional Phase IV studies (post approval marketing studies) to confirm safety and effectiveness in a broader commercial use population may be imposed as a condition of marketing approval. In addition, the FDA requires surveillance programs to monitor approved products which have been commercialized, and the agency has the power to require changes in labeling or to prevent further marketing of a product based on the results of these post-marketing programs. Any comparative claims that we would like to make for our products vis-à-vis other dosage forms or products will need to be substantiated generally by two adequate and well-controlled head-to-head clinical trials.

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Satisfaction of FDA requirements or similar requirements of state, local and foreign regulatory agencies typically takes several years and the actual time required may vary substantially, based upon the type, complexity and novelty of the pharmaceutical product. Government regulation may delay or prevent marketing of potential products for a considerable period of time and impose costly procedures upon our activities. We cannot be certain that the FDA or any other regulatory agency will grant approval for any of our pharmaceutical systems under development on a timely basis, if at all. Success in preclinical or early stage clinical trials does not assure success in later stage clinical trials. Data obtained from preclinical and clinical activities is not always conclusive and may be susceptible to varying interpretations which could delay, limit or prevent regulatory approval. Evolving safety concerns can result in the imposition of new requirements for expensive and time consuming tests, such as for QT interval cardiotoxicity testing. Even if a product receives regulatory approval, the approval may be significantly limited to specific indications. Further, even after regulatory approval is obtained, 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. Any pharmaceutical systems that we may develop and obtain approval for would also be subject to adverse findings of the active drug ingredients being marketed in different dosage forms and formulations. Delays in obtaining, or failures to obtain regulatory approvals would have a material adverse effect on our business. Marketing our pharmaceutical systems abroad will require similar regulatory approvals and is subject to similar risks. In addition, we cannot predict what adverse governmental regulations may arise from future U.S. or foreign governmental action.

Any pharmaceutical systems manufactured or distributed by us pursuant to FDA approvals are subject to pervasive and continuing regulation by the FDA, including record-keeping requirements and reporting of adverse experiences with the drug. Drug manufacturers and their subcontractors are required to register their establishments with the FDA and state agencies, and are subject to periodic unannounced inspections by the FDA and state agencies for compliance with good manufacturing practices, which impose procedural and documentation requirements upon us and our third party manufacturers. We cannot be certain that we or our present or future suppliers will be able to comply with the GMP regulations and other FDA regulatory requirements.

The FDA regulates drug labeling and promotion activities. The FDA has actively enforced regulations prohibiting the marketing of products for unapproved uses, and federal and state authorities are also actively litigating against sponsors who promote their drugs for unapproved uses under various fraud and abuse and false claims act statutes. We and our pharmaceutical systems are also subject to a variety of state laws and regulations in those states or localities where our pharmaceutical systems are or will be marketed. Any applicable state or local regulations may hinder our ability to market our pharmaceutical systems in those states or localities. We are also subject to numerous federal, state and local laws relating to such matters as safe working conditions, manufacturing practices, environmental protection, fire hazard control, and disposal of hazardous or potentially hazardous substances. We may incur significant costs to comply with such laws and regulations now or in the future.

The FDA's policies may change and additional government regulations may be enacted which could prevent or delay regulatory approval of our potential pharmaceutical systems. Moreover, increased attention to the containment of health care costs in the U.S. and in foreign markets could result in new government regulations that could have a material adverse effect on our business. We cannot predict the likelihood, nature or extent of adverse governmental regulation that might arise from future legislative or administrative action, either in the U.S. or abroad.

On February 6, 2009, the FDA sent letters to manufacturers of certain opioid drug products, indicating that these drugs will be required to have a Risk Evaluation and Mitigation Strategy (REMS) to ensure that the benefits of the drugs continue to outweigh the risks. The affected opioid drugs include brand name and generic products and are formulated with the active ingredients fentanyl, hydromorphone, methadone, morphine, oxycodone, and oxymorphone. The FDA has authority to require a REMS under the Food and Drug Administration Amendments Act of 2007 (FDAAA) when necessary to ensure that the benefits of a drug outweigh the risks.

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On April 19, 2011, the Office of National Drug Control Policy (ONDCP) released the Obama Administration's *Epidemic: Responding to America's Prescription Drug Abuse Crisis* a comprehensive action plan to address the national prescription drug abuse epidemic. This plan includes action in four major areas to reduce prescription drug abuse: education, monitoring, proper disposal, and enforcement. In support of the action plan, the FDA announced the elements of a Risk Evaluation and Mitigation Strategy (REMS) that will require all manufacturers of long-acting and extended-release opioids to ensure that training is provided to prescribers of these medications and to develop information that prescribers can use when counseling patients about the risks and benefits of opioid use. The FDA wants drug makers to work together to develop a single system for implementing the REMS strategies.

Many of our drug candidates including Remoxy, our other ORADUR-based opioid drug candidates and TRANSDUR-Sufentanil are subject to the REMS requirement. Until the contours of required REMS programs are established by the FDA and understood by drug developers and marketers such as ourselves and our collaborators, there may be delays in marketing approvals for these drug candidates. In addition, there may be increased cost, administrative burden and potential liability associated with the marketing and sale of these types of drug candidates subject to the REMS requirement, which could negatively impact the commercial benefits to us and our collaborators from the sale of these drug candidates.

The Drug Enforcement Administration. The Drug Enforcement Administration (DEA) regulates chemical compounds as Schedule I, II, III, IV or V substances, with Schedule I substances considered to present the highest risk of substance abuse and Schedule V substances the lowest risk. Certain active ingredients in TRANSDUR-Sufentanil, and Remoxy and our other ORADUR-based opioid drug candidates, are listed by the DEA as Schedule II under the Controlled Substances Act of 1970. Consequently, their manufacture, research, shipment, storage, sale and use are subject to a high degree of oversight and regulation. For example, all Schedule II drug prescriptions must be signed by a physician, physically presented to a pharmacist and may not be refilled without a new prescription. Furthermore, the amount of Schedule II substances we can obtain for clinical trials and commercial distribution is limited by the DEA and our quota may not be sufficient to complete clinical trials or meet commercial demand. There is a risk that DEA regulations may interfere with the supply of the drugs used in our clinical trials, and, in the future, our ability to produce and distribute our products in the volume needed to meet commercial demand.

Competition

We may face competition from other companies in numerous industries including pharmaceuticals, medical devices and drug delivery. POSIDUR, TRANSDUR-Sufentanil, ELADUR, Relday, REMOXY and other ORADUR-based drug candidates, if approved, will compete with currently marketed oral opioids, transdermal opioids, local anesthetic patches, anti-psychotics, stimulants, implantable and external infusion pumps which can be used for infusion of opioids and local anesthetics. Products of these types are marketed by Purdue Pharma, Knoll, Janssen, Medtronic, Endo, AstraZeneca, Arrow International, Tricumed, I-Flow (Kimberly-Clark), Cumberland Pharmaceuticals, NeurogesX, Covidien, Shire, Johnson & Johnson, Eli Lilly, Pfizer, Novartis and others. Our ORADUR-ADHD product candidates, if approved, will compete with currently marketed products by Shire, Johnson & Johnson, UCB, Novartis, Noven, Celgene, Eli Lilly, Medice and others. Relday, if approved, will compete with currently marketed products by Johnson & Johnson, Eli Lilly, Astra Zeneca, Pfizer, Bristol-Myers Squibb and others. Numerous companies are applying significant resources and expertise to the problems of drug delivery and several of these are focusing or may focus on delivery of drugs to the intended site of action, including Alkermes, Pacira Pharmaceuticals, EpiCept, Innocoll, Nektar, I-Flow (Kimberly-Clark), NeurogesX, Flamel, Alexza, Cadence Pharmaceuticals, Hospira, Cumberland Pharmaceuticals, Egalet, Acura and others. Some of these competitors may be addressing the same therapeutic areas or indications as we are. Our current and potential competitors may succeed in obtaining patent protection or commercializing products before us. Many of these entities have significantly greater research and development capabilities than we do, as well as substantially more marketing, manufacturing, financial and managerial resources. These entities represent significant competition for us. Acquisitions of, or investments in, competing pharmaceutical or biotechnology

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companies by large corporations could increase such competitors financial, marketing, manufacturing and other resources.

Any products we develop using our pharmaceutical systems technologies will compete in highly competitive markets. Many of our potential competitors in these markets have greater development, financial, manufacturing, marketing, and sales resources than we do and we cannot be certain that they will not succeed in developing products or technologies which will render our technologies and products obsolete or noncompetitive. In addition, many of those potential competitors have significantly greater experience than we do in their respective fields.

Corporate History, Headquarters and Website Information

We were incorporated in Delaware in February 1998. We completed our initial public offering on September 28, 2000. Our principal executive offices are located at 10260 Bubb Road, Cupertino, California, 95014. Our telephone number is (408) 777-1417, and our web site address is www.durect.com. We make our annual reports on Form 10-K, quarterly reports on Form 10-Q, current reports on Form 8-K, and amendments to these reports available free of charge on our web site as soon as reasonably practicable after we file these reports with the Securities and Exchange Commission. Our Code of Ethics can be found on our website.

Employees

As of February 29, 2012 we had 106 employees, including 57 in research and development, 23 in manufacturing and 26 in selling, general and administrative. From time to time, we also employ independent contractors to support our research, development and administrative organizations. None of our employees are represented by a collective bargaining unit, and we have never experienced a work stoppage. We consider our relations with our employees to be good.

Executive Officers of the Registrant

Our executive officers and their ages as of February 29, 2012 are as follows:

| Name | Age | Position |
|--------------------------|------------|---|
| Felix Theeuwes, D.Sc. | 74 | Chairman, Chief Scientific Officer and Director |
| James E. Brown, D.V.M. | 55 | President, Chief Executive Officer and Director |
| Matthew J. Hogan, M.B.A. | 52 | Chief Financial Officer |
| Su Il Yum, Ph.D. | 72 | Executive Vice President, Pharmaceutical Systems Research and Development |

Felix Theeuwes, D.Sc. co-founded DURECT in February 1998 and has served as our Chairman, Chief Scientific Officer and a Director since July 1998. Prior to that, Dr. Theeuwes held various positions at ALZA Corporation, including President of New Ventures from August 1997 to August 1998, President of ALZA Research and Development from 1995 to August 1997, President of ALZA Technology Institute from 1994 to April 1995 and Chief Scientist from 1982 to June 1997. Dr. Theeuwes holds a D.Sc. degree in Physics from the University of Leuven (Louvain), Belgium. He also served as a post-doctoral fellow and visiting research assistant professor in the Department of Chemistry at the University of Kansas and has completed the Stanford Executive Program.

James E. Brown, D.V.M. co-founded DURECT in February 1998 and has served as our President, Chief Executive Officer and a Director since June 1998. He previously worked at ALZA Corporation as Vice President of Biopharmaceutical and Implant Research and Development from June 1995 to June 1998. Prior to that, Dr. Brown held various positions at Syntex Corporation, a pharmaceutical company, including Director of Business Development from May 1994 to May 1995, Director of Joint Ventures for Discovery Research from

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April 1992 to May 1995, and held a number of positions including Program Director for Syntex Research and Development from October 1985 to March 1992. Dr. Brown holds a B.A. from San Jose State University and a D.V.M. (Doctor of Veterinary Medicine) from the University of California, Davis where he also conducted post-graduate work in pharmacology and toxicology.

Matthew J. Hogan, M.B.A. has served as our Chief Financial Officer since September 2006. He was the Chief Financial Officer at CIPHERGEN Biosystems, Inc. from 2000 to 2006, and a consultant from March 2006. Prior to joining CIPHERGEN, Mr. Hogan was the Chief Financial Officer at Avocet Medical, Inc. from 1999 to 2000. From 1996 to 1999, Mr. Hogan was the Chief Financial Officer at Microcide Pharmaceuticals, Inc. From 1986 to 1996, he held various positions in the investment banking group at Merrill Lynch & Co., most recently as a Director focusing on the biotechnology and pharmaceutical sectors. Mr. Hogan holds a B.A. in economics from Dartmouth College and an M.B.A. from the Amos Tuck School of Business Administration.

Su Il Yum, Ph.D. has served as our Executive Vice President of Pharmaceutical Systems Research and Development since January 2007 and as our Senior Vice President of Pharmaceutical Systems Research and Development since January 2006. Previously, Dr. Yum served as our Senior Vice President, Engineering since December 2003 and as our Vice President of Engineering from December 1999 to December 2003. Prior to joining DURECT, Dr. Yum served as Senior Technical Advisor at Amira Medical in Scotts Valley, California, where he participated in the development of a pain-free blood glucose detector called AtLast[®]. Prior to joining Amira, he held a number of senior positions in project management and engineering at ALZA Corporation for 27 years. Dr. Yum earned his Ph.D. degree in Chemical Engineering from the University of Minnesota, and completed a Post-doctoral research in Biomedical Engineering at the University of Utah. Dr. Yum is a Fellow of the AAPS.

Item 1A. Risk Factors.

In addition to the other information in this Form 10-K, a number of factors may affect our business and prospects. These factors include but are not limited to the following, which you should consider carefully in evaluating our business and prospects.

Risks Related To Our Business

Development of our pharmaceutical systems is not complete, and we cannot be certain that our pharmaceutical systems will be able to be commercialized

To be profitable, we or our third-party collaborators must successfully research, develop, obtain regulatory approval for, manufacture, introduce, market and distribute our pharmaceutical systems under development. For each pharmaceutical system that we or our third-party collaborators intend to commercialize, we must successfully meet a number of critical developmental milestones for each disease or medical condition targeted, including:

selecting and developing a drug delivery platform technology to deliver the proper dose of drug over the desired period of time;

determining the appropriate drug dosage for use in the pharmaceutical system;

developing drug compound formulations that will be tolerated, safe and effective and that will be compatible with the system;

demonstrating the drug formulation will be stable for commercially reasonable time periods;

demonstrating through clinical trials that the drug and system combination is safe and effective in patients for the intended indication; and

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completing the manufacturing development and scale-up to permit manufacture of the pharmaceutical system in commercial quantities and at acceptable prices.

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The time frame necessary to achieve these developmental milestones for any individual product is long and uncertain, and we may not successfully complete these milestones for any of our products in development. We have not yet completed development of POSIDUR, TRANSDUR-Sufentanil, ELADUR, Relday, REMOXY and our other ORADUR-based drug candidates, and we have limited experience in developing such products. We may not be able to finalize the design or formulation of any of these pharmaceutical systems. In addition, we may select components, solvents, excipients or other ingredients to include in our pharmaceutical systems that have not been previously approved for use in pharmaceutical products, which may require us or our collaborators to perform additional studies and may delay clinical testing and regulatory approval of our pharmaceutical systems. Even after we complete the design of a pharmaceutical system, the pharmaceutical system must still complete required clinical trials and additional safety testing in animals before approval for commercialization. We are continuing testing and development of our pharmaceutical systems and may explore possible design or formulation changes to address issues of safety, manufacturing efficiency and performance. We and our collaborators may not be able to complete development of any pharmaceutical systems that will be safe and effective and that will have a commercially reasonable treatment and storage period. If we or our third-party collaborators are unable to complete development of POSIDUR, TRANSDUR-Sufentanil, ELADUR, Relday, REMOXY and our ORADUR-based drug candidates, or other pharmaceutical systems, we will not be able to earn revenue from them, which would materially harm our business.

We or our third-party collaborators must show the safety and efficacy of our drug candidates in animal studies and human clinical trials to the satisfaction of regulatory authorities before they can be sold, and the failure to do so according to plan would significantly harm our business, prospects and financial condition

Before we or our third-party collaborators can obtain government approval to sell any of our pharmaceutical systems, we or they, as applicable, must demonstrate through laboratory performance studies and safety testing, nonclinical (animal) studies and clinical (human) trials that each system is safe and effective for human use for each targeted indication. The clinical development status of our most advanced publicly announced development programs is as follows:

REMOXY In December 2010, King resubmitted the NDA in response to a Complete Response Letter received in December 2008 by Pain Therapeutics. On June 23, 2011, a Complete Response Letter from the FDA was received by Pfizer on the resubmission to the NDA for REMOXY. The FDA's June 2011 Complete Response Letter raised concerns related to, among other matters, the Chemistry, Manufacturing, and Controls section of the NDA for REMOXY. Pfizer has efforts underway to resolve these issues. Sufficient information does not yet exist to accurately assess the time required to resolve the concerns raised in the FDA's Complete Response Letter and they may never be resolved. On January 31, 2012, Pfizer stated that it intended to conduct two bioavailability studies in the second quarter of 2012 and anticipated meeting with the FDA during the third quarter to discuss next steps. There can be no assurance that these bioavailability studies will achieve results that will support product approval or that any regulatory meetings or product approvals will occur.

POSIDUR To date, we have completed multiple Phase II studies in various surgeries and recently completed a Phase III study (the BESST trial). BESST was conducted to measure the safety and efficacy of POSIDUR versus placebo in one abdominal surgical procedure and versus an active comparator (injections of standard bupivacaine) in two other abdominal surgical procedures. The co-primary endpoints were pain intensity as well as the use of opioid analgesics over the first 3 days following surgery. While the results trended positive for both pain reduction and reduction of supplemental opioid use in the first three days after surgery, they did not reach statistical significance. There were no signs of systemic safety issues, although local site reactions were observed more frequently in the POSIDUR and SABER-Placebo groups than in the active comparator groups. A full safety assessment is not yet available. After a complete analysis of the BESST data and preparation of integrated safety and efficacy summaries combining our previous well controlled studies, we intend to hold a pre-NDA meeting with the FDA which we expect to occur in mid-2012, with a potential NDA submission under section 505(b)2 later this year. There can be no assurance that the POSIDUR program has generated data and

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information that will be sufficient to support an NDA submission or that any such submission will be deemed sufficient for marketing approval by the FDA or other regulatory agencies.

TRANSDUR-Sufentanil Patch In February 2009, an end-of-Phase II meeting with the FDA was conducted for this program outlining a potential regulatory pathway for the Phase III program and NDA submission. In 2011, we had discussions with the FDA and regulatory agencies in several major European countries to better understand development requirements for U.S. and European countries. We are in discussions with potential partners regarding licensing development and commercialization rights to this program to which we hold worldwide rights. There can be no assurance that our planned development program for TRANSDUR-Sufentanil will generate data and information that will be deemed sufficient for marketing approval by the FDA or other regulatory agencies or that we will be able to find a collaborator with respect to the development and commercialization of this drug candidate.

ELADUR A Phase IIa clinical trial in post-herpetic neuralgia (PHN or post-shingles pain) was completed and positive efficacy trends were reported in the fourth quarter of 2007. King, which assumed worldwide development and commercialization rights for ELADUR through its acquisition of Alpharma, conducted a Phase II clinical trial to evaluate ELADUR for the treatment of chronic low back pain and reported in April 2011 that the primary efficacy endpoint for the trial was not met. In February 2012, Pfizer notified us that they are returning their worldwide development and commercialization rights to ELADUR. There can be no assurance that our planned development program for ELADUR will generate data and information that will be deemed sufficient for marketing approval by the FDA or other regulatory agencies or that we will be able to find a collaborator with respect to the development and commercialization of this drug candidate.

ORADUR-based opioids Phase I clinical trials have been conducted for two of these ORADUR-based products (hydrocodone and hydromorphone), and an IND has been accepted by the FDA for the third ORADUR-based opioid (oxymorphone). There can be no assurance that we or our collaborators will be able to successfully develop ORADUR-based formulations of hydrocodone, hydromorphone or oxymorphone to obtain marketing approval by the FDA or other regulatory agencies.

ORADUR-ADHD In 2010 and 2011, we and Orient Pharma conducted several Phase I studies to evaluate multiple formulations of ORADUR-ADHD. Based on information from these trials, we are continuing to evaluate the key formulations and are planning next steps in the ORADUR-ADHD program. There can be no assurance that we will be able to successfully develop ORADUR-ADHD to obtain marketing approval by the FDA or other regulatory agencies.

We are currently in the clinical, preclinical or research stages with respect to all our other pharmaceutical systems under development. We plan to continue extensive and costly tests, clinical trials and safety studies in animals to assess the safety and effectiveness of our pharmaceutical systems. These studies include laboratory performance studies and safety testing, clinical trials and animal toxicological studies necessary to support regulatory approval of development products in the United States and other countries of the world. These studies are costly, complex and last for long durations, and may not yield data supportive of the safety or efficacy of our drug candidates or required for regulatory approval.

Early clinical trial results may not predict the results of later trials or satisfy regulatory agencies

While some clinical trials of our product candidates have shown indications of safety and efficacy of our product candidates, there can be no assurance that these results will be confirmed in subsequent clinical trials. In addition, side effects observed in clinical trials, or other side effects that appear in later clinical trials, may adversely affect our or our collaborators' ability to obtain regulatory approval or market our product candidates. For example, in the Phase IIb hysterectomy trial and the BESST Phase III abdominal surgery trial of POSIDUR, transient local hematoma-like discolorations were observed near the surgical site. Side effects such as these, toxicity or other safety issues associated with the use of our drug candidates could require us to perform additional studies or halt development of our drug candidates. We or our collaborators may be required by regulatory agencies to conduct additional animal or human studies regarding the safety and efficacy of our

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pharmaceutical systems which we have not planned or anticipated. For example, the FDA's Complete Response Letter raised concerns related to, among other matters, the Chemistry, Manufacturing, and Controls section of the NDA for REMOXY. There can be no assurance that Pfizer will resolve these issues to the satisfaction of the FDA in a timely manner or ever, which could harm our business, prospects and financial condition. We may also be required to conduct additional clinical trials of POSIDUR, which would be expensive and could delay product approval, harming our business, prospects and financial condition.

Clinical trials and regulatory approval of our product candidates is subject to delay, which could harm our business

The length of clinical trials will depend upon, among other factors, the rate of trial site and patient enrollment and the number of patients required to be enrolled in such studies. We or our third-party collaborators may fail to obtain adequate levels of patient enrollment in our clinical trials. Delays in planned patient enrollment may result in increased costs, delays or termination of clinical trials, which could have a material adverse effect on us. In addition, even if we or our third-party collaborators enroll the number of patients we expect in the time frame we expect, such clinical trials may not provide the data necessary to support regulatory approval for the pharmaceutical systems for which they were conducted. Additionally, we or our third-party collaborators may fail to effectively oversee and monitor these clinical trials, which would result in increased costs or delays of our clinical trials. Even if these clinical trials are completed, we or our third-party collaborators may fail to complete and submit a new drug application as scheduled.

The FDA may not clear any such application in a timely manner or may deny the application entirely. Data already obtained from preclinical studies and clinical trials of our pharmaceutical systems do not necessarily predict the results that will be obtained from later preclinical studies and clinical trials. Moreover, preclinical and clinical data such as ours are susceptible to varying interpretations, which could delay, limit or prevent regulatory approval. A number of companies in the pharmaceutical industry have suffered significant setbacks in advanced clinical trials, even after promising results in earlier trials. The failure to adequately demonstrate the safety and effectiveness of a pharmaceutical system under development to the satisfaction of FDA and other regulatory agencies could delay or prevent regulatory clearance of the potential pharmaceutical system, resulting in delays to the commercialization of our pharmaceutical system, and could materially harm our business. Clinical trials may not demonstrate the sufficient levels of safety and efficacy necessary to obtain the requisite regulatory approvals for our pharmaceutical systems, and thus our pharmaceutical systems may not be approved for marketing.

Regulatory action or failure to obtain product approvals could delay or limit development and commercialization of our pharmaceutical systems and result in failure to achieve anticipated revenues

The manufacture and marketing of our pharmaceutical systems and our research and development activities are subject to extensive regulation for safety, efficacy and quality by numerous government authorities in the United States and abroad. We or our third-party collaborators must obtain clearance or approval from applicable regulatory authorities before we or they, as applicable, can perform clinical trials, market or sell our products in development in the United States or abroad. Clinical trials, manufacturing and marketing of products are subject to the rigorous testing and approval process of the FDA and equivalent foreign regulatory authorities. In particular, recent recalls of and reported adverse side effects of marketed drugs have made regulatory agencies, including the FDA, increasingly focus on the safety of drug products. Regulatory agencies are requiring more extensive and ever increasing showings of safety at every stage of drug development and commercialization from initial clinical trials to regulatory approval and beyond. These rigorous and evolving standards may delay and increase the expenses of our development efforts. The FDA or other foreign regulatory agency may, at any time, halt our and our collaborators' development and commercialization activities due to safety concerns, in which case our business will be harmed. In addition, the FDA or other foreign regulatory agency may refuse or delay approval of our or our collaborators' drug candidates for failure to collect sufficient clinical or animal safety data, and require us or our collaborators to conduct additional clinical or animal safety studies which may cause lengthy delays and increased costs to our programs.

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The Federal Food, Drug and Cosmetic Act and other federal, state and foreign statutes and regulations govern and influence the testing, manufacture, labeling, advertising, distribution and promotion of drugs and medical devices. These laws and regulations are complex and subject to change. Furthermore, these laws and regulations may be subject to varying interpretations, and we may not be able to predict how an applicable regulatory body or agency may choose to interpret or apply any law or regulation to our pharmaceutical systems. As a result, clinical trials and regulatory approval can take a number of years to accomplish and require the expenditure of substantial resources. We or our third-party collaborators, as applicable, may encounter delays or rejections based upon administrative action or interpretations of current rules and regulations. We or our third-party collaborators, as applicable, may not be able to timely reach agreement with the FDA on our clinical trials or on the required clinical or animal data we or they must collect to continue with our clinical trials or eventually commercialize our pharmaceutical systems.

We or our third-party collaborators, as applicable, may also encounter delays or rejections based upon additional government regulation from future legislation, administrative action or changes in FDA policy during the period of product development, clinical trials and FDA regulatory review. We or our third-party collaborators, as applicable, may encounter similar delays in foreign countries. Sales of our pharmaceutical systems outside the United States are subject to foreign regulatory standards that vary from country to country.

The time required to obtain approvals from foreign countries may be shorter or longer than that required for FDA approval, and requirements for foreign licensing may differ from FDA requirements. We or our third-party collaborators, as applicable, may be unable to obtain requisite approvals from the FDA and foreign regulatory authorities, and even if obtained, such approvals may not be on a timely basis, or they may not cover the clinical uses that we specify. If we or our third-party collaborators, as applicable, fail to obtain timely clearance or approval for our development products, we or they will not be able to market and sell our pharmaceutical systems, which will limit our ability to generate revenue.

Many of our drug candidates under development, including REMOXY, our other ORADUR-based opioids and TRANSDUR-Sufentanil are subject to mandatory Risk Evaluation and Mitigation Strategy (REMS) programs, which could delay the approval of these drug candidates and increase the cost, burden and liability associated with the commercialization of these drug candidates

On February 6, 2009, the FDA sent letters to manufacturers of certain opioid drug products, indicating that these drugs will be required to have a Risk Evaluation and Mitigation Strategy (REMS) to ensure that the benefits of the drugs continue to outweigh the risks. The affected opioid drugs include brand name and generic products and are formulated with the active ingredients fentanyl, hydromorphone, methadone, morphine, oxycodone, and oxymorphone.

On April 19, 2011, the Office of National Drug Control Policy (ONDCP) released the Obama Administration's *Epidemic: Responding to America's Prescription Drug Abuse Crisis* a comprehensive action plan to address the national prescription drug abuse epidemic. This plan includes action in four major areas to reduce prescription drug abuse: education, monitoring, proper disposal, and enforcement. In support of the action plan, the FDA announced the elements of a Risk Evaluation and Mitigation Strategy (REMS) that will require all manufacturers of long-acting and extended-release opioids to ensure that training is provided to prescribers of these medications and to develop information that prescribers can use when counseling patients about the risks and benefits of opioid use. The FDA wants drug makers to work together to develop a single system for implementing the REMS strategies.

Many of our drug candidates including REMOXY, our other ORADUR-opioid drug candidates and TRANSDUR-Sufentanil are subject to the REMS requirement. The FDA's REMS requirements have been evolving, and until the contours of required REMS programs are established by the FDA and understood by drug developers and marketers such as ourselves and our collaborators, there may be delays in marketing approvals

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for these drug candidates. In addition, there may be increased cost, administrative burden and potential liability associated with the marketing and sale of these types of drug candidates subject to the REMS requirement, which could negatively impact the commercial benefits to us and our collaborators from the sale of these drug candidates.

We depend to a large extent on third-party collaborators, and we have limited or no control over the development, sales, distribution and disclosure for our pharmaceutical systems which are the subject of third-party collaborative or license agreements

Our performance depends to a large extent on the ability of our third-party collaborators to successfully develop and obtain approvals for our pharmaceutical systems. We have entered into agreements with Pain Therapeutics, Hospira, Nycomed (acquired by Takeda), Alpharma (acquired by King which in turn has been acquired by Pfizer), Orient Pharma, Zogenix and others under which we granted such third parties the right to develop, apply for regulatory approval for, market, promote or distribute REMOXY and other ORADUR-based products, POSIDUR, ELADUR, Relday and other product candidates, subject to payments to us in the form of product royalties and other payments. We have limited or no control over the expertise or resources that any collaborator may devote to the development, clinical trial strategy, regulatory approval, marketing or sale of these pharmaceutical systems, or the timing of their activities. Any of our present or future collaborators may not perform their obligations as expected. These collaborators may breach or terminate their agreement with us or otherwise fail to conduct their collaborative activities successfully and in a timely manner. Enforcing any of these agreements in the event of a breach by the other party could require the expenditure of significant resources and consume a significant amount of management time and attention. Our collaborators may also conduct their activities in a manner that is different from the manner we would have chosen, had we been developing such pharmaceutical systems ourselves. Further, our collaborators may elect not to develop or commercialize pharmaceutical systems arising out of our collaborative arrangements or not devote sufficient resources to the development, clinical trials, regulatory approval, manufacture, marketing or sale of these pharmaceutical systems. If any of these events occur, we may not recognize revenue from the commercialization of our pharmaceutical systems based on such collaborations. In addition, these third parties may have similar or competitive products to the ones which are the subject of their collaborations with us, or relationships with our competitors, which may reduce their interest in developing or selling our pharmaceutical systems. We may not be able to control public disclosures made by some of our third-party collaborators, which could negatively impact our stock price.

Our near-term revenues depend on collaboration agreements with other companies. These agreements subject us to obligations which must be fulfilled and also make our revenues dependent on the performance of such third parties. If we are unable to meet our obligations or manage our relationships with our collaborators under these agreements or enter into additional collaboration agreements or if our existing collaborations are terminated, our revenues may decrease. Acquisitions of our collaborators can be disruptive

Our near-term revenues are based to a significant extent on collaborative arrangements with third parties, pursuant to which we receive payments based on our performance of research and development activities set forth in these agreements. We may not be able to fulfill our obligations or attain milestones set forth in any specific agreement, which could cause our revenues to fluctuate or be less than anticipated and may expose us to liability for contractual breach. In addition, these agreements may require us to devote significant time and resources to communicating with and managing our relationships with such collaborators and resolving possible issues of contractual interpretation which may detract from time our management would otherwise devote to managing our operations. Such agreements are generally complex and contain provisions that could give rise to legal disputes, including potential disputes concerning ownership of intellectual property under collaborations. Such disputes can delay or prevent the development of potential new pharmaceutical systems, or can lead to lengthy, expensive litigation or arbitration. In general, our collaboration agreements, including our agreements with Pain Therapeutics and King (Pfizer) with respect to REMOXY and other ORADUR-based products

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incorporating specified opioids, Hospira and Nycomed (acquired by Takeda) with respect to POSIDUR, Alpharma (acquired by King which in turn has been acquired by Pfizer) with respect to ELADUR, Orient Pharma with respect to ORADUR-ADHD and Zogenix with respect to Relday, may be terminated by the other party at will or upon specified conditions including, for example, if we fail to satisfy specified performance milestones or if we breach the terms of the agreement. From time to time, our licensees may be the subject of an acquisition by another company. For example, Alpharma was acquired by King in December 2008, in February 2011 King was acquired by Pfizer and, in October 2011 Nycomed was acquired by Takeda. Such transactions can lead to turnover of program staff, a review of development programs and strategies by the acquirer, and other events that can disrupt a program, resulting in program delays or discontinuations.

If any of our collaborative agreements are terminated or delayed, our revenues may be reduced or not materialize, and our products in development related to those agreements may not be commercialized.

Our cash flows are likely to be less than our reported revenues

Our revenues will likely differ from our cash flows from revenue-generating activities. Upfront payments received upon execution of collaborative agreements are recorded as deferred revenue and recognized on a straight-line basis over the period of our continuing involvement with the third-party collaborator pursuant to the applicable agreement. As of December 31, 2011, we have \$37.5 million of deferred revenue, which will be recognized in future periods and may cause our reported revenues to be greater than cash flows from our ongoing revenue-generating activities.

Our revenues also depend on milestone payments based on achievements by our third-party collaborators. Failure of such collaborators to attain such milestones would result in our not receiving additional revenues

In addition to payments based on our performance of research and development activities, our revenues also depend on the attainment of milestones set forth in our collaboration agreements. Such milestones are typically related to development activities or sales accomplishments. While our involvement is necessary to the achievement of development-based milestones, the performance of our third-party collaborators is also required to achieve those milestones. Under our third-party collaborative agreements, our third party collaborators will take the lead in commercialization activities and we are typically not involved in the achievement of sales-based milestones. Therefore, we are even more dependent upon the performance of our third-party collaborators in achieving sales-based milestones. To the extent we and our third-party collaborators do not achieve such development-based milestones or our third-party collaborators do not achieve sales-based milestones, we will not receive the associated revenues, which could harm our financial condition and may cause us to defer or cut-back development activities or forego the exploitation of opportunities in certain geographic territories, any of which could have a material adverse effect on our business.

Our business strategy includes the entry into additional collaborative agreements. We may not be able to enter into additional collaborative agreements or may not be able to negotiate commercially acceptable terms for these agreements

Our current business strategy includes the entry into additional collaborative agreements for the development and commercialization of our pharmaceutical systems. The negotiation and consummation of these types of agreements typically involve simultaneous discussions with multiple potential collaborators and require significant time and resources from our officers, business development, legal, and research and development staff. In addition, in attracting the attention of pharmaceutical and biotechnology company collaborators, we compete with numerous other third parties with product opportunities as well the collaborators' own internal product opportunities. We may not be able to consummate additional collaborative agreements, or we may not be able to negotiate commercially acceptable terms for these agreements. If we do not consummate additional collaborative agreements, we may have to consume money more rapidly on our product development efforts, defer development activities or forego the exploitation of certain geographic territories, any of which could have a material adverse effect on our business.

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We may have difficulty raising needed capital in the future

Our business currently does not generate sufficient revenues to meet our capital requirements and we do not expect that it will do so in the near future. We have expended and will continue to expend substantial funds to complete the research, development and clinical testing of our pharmaceutical systems. We will require additional funds for these purposes, to establish additional clinical- and commercial-scale manufacturing arrangements and facilities and to provide for the marketing and distribution of our pharmaceutical systems. Additional funds may not be available on acceptable terms, if at all. If adequate funds are unavailable from operations or additional sources of financing, we may have to delay, reduce the scope of or eliminate one or more of our research or development programs which would materially harm our business, financial condition and results of operations.

In July 2010, we entered into an equity line of credit facility with Azimuth under which we may sell to Azimuth, subject to certain limitations, up to \$50 million of our common stock over a 24-month period. Azimuth will not be obligated to purchase shares under the equity line of credit unless specified conditions are met. These include that the price per share of our common stock is greater than \$1.00. We are currently unable to access this source of financing, and if we are unable to meet the specified conditions with respect to any sale of shares under the Azimuth equity line of credit, we may not be able to access this source of financing in the future. Azimuth is also permitted to terminate the equity line of credit under certain circumstances.

We believe that our cash, cash equivalents and investments, will be adequate to satisfy our capital needs for at least the next 12 months. However, our actual capital requirements will depend on many factors, including:

regulatory actions with respect to our product candidates;

continued progress and cost of our research and development programs;

the continuation of our collaborative agreements that provide financial funding for our activities;

success in entering into collaboration agreements and meeting milestones under such agreements;

progress with preclinical studies and clinical trials;

the time and costs involved in obtaining regulatory clearance;

costs involved in preparing, filing, prosecuting, maintaining and enforcing patent claims;

costs of developing sales, marketing and distribution channels and our ability and that of our collaborators to sell our pharmaceutical systems;

costs involved in establishing manufacturing capabilities for clinical and commercial quantities of our pharmaceutical systems;

competing technological and market developments;

market acceptance of our pharmaceutical systems;

costs for recruiting and retaining employees and consultants; and

unexpected legal, accounting and other costs and liabilities related to our business.

We may consume available resources more rapidly than currently anticipated, resulting in the need for additional funding. We may seek to raise any necessary additional funds through equity or debt financings, convertible debt financings, collaborative arrangements with corporate collaborators or other sources, which may be dilutive to existing stockholders and may cause the price of our common stock to decline. In addition, in the event that additional funds are obtained through arrangements with collaborators or other sources, we may have to relinquish rights to some of our technologies or pharmaceutical systems that we would otherwise seek to develop or commercialize ourselves. If adequate funds are not available, we may be required to significantly reduce or refocus our product development efforts, resulting in loss of sales, increased costs, and reduced revenues.

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We and our third-party collaborators may not be able to manufacture sufficient quantities of our pharmaceutical systems and components to support the clinical and commercial requirements of our collaborators and ourselves at an acceptable cost or in compliance with applicable government regulations, and we have limited manufacturing experience

We or our third-party collaborators to whom we have assigned such responsibility must manufacture our pharmaceutical systems and components in clinical and commercial quantities, either directly or through third parties, in compliance with regulatory requirements and at an acceptable cost. The manufacturing processes associated with our pharmaceutical systems are complex. We and our third-party collaborators, where relevant, have not yet completed development of the manufacturing process for any pharmaceutical systems or components, including REMOXY and our other ORADUR-based drug candidates, POSIDUR, TRANSDUR-Sufentanil, ELADUR, and Relday. If we and our third-party collaborators, where relevant, fail to timely complete the development of the manufacturing process for our pharmaceutical systems, we and our third-party collaborators, where relevant, will not be able to timely produce product for clinical trials and commercialization of our pharmaceutical systems. We have also committed to manufacture and supply pharmaceutical systems or components under a number of our collaborative agreements with third-party companies. We have limited experience manufacturing pharmaceutical products, and we may not be able to timely accomplish these tasks. If we and our third-party collaborators, where relevant, fail to develop manufacturing processes to permit us to manufacture a pharmaceutical system or component at an acceptable cost, then we and our third-party collaborators may not be able to commercialize that pharmaceutical system or we may be in breach of our supply obligations to our third-party collaborators.

Our manufacturing facility in Cupertino is a multi-disciplinary site that we have used to manufacture only research and clinical supplies of several of our pharmaceutical systems, including POSIDUR, TRANSDUR-Sufentanil, ELADUR, REMOXY and other ORADUR-based drug candidates, and Relday. We have not manufactured commercial quantities of any of our pharmaceutical systems. In the future, we intend to develop additional manufacturing capabilities for our pharmaceutical systems and components to meet our demands and those of our third-party collaborators by contracting with third-party manufacturers and by construction of additional manufacturing space at our facilities in California and Alabama. We have limited experience building and validating manufacturing facilities, and we may not be able to accomplish these tasks in a timely manner.

If we and our third-party collaborators, where relevant, are unable to manufacture pharmaceutical systems or components in a timely manner or at an acceptable cost, quality or performance level, and are unable to attain and maintain compliance with applicable regulations, the clinical trials and the commercial sale of our pharmaceutical systems and those of our third-party collaborators could be delayed. Additionally, we may need to alter our facility design or manufacturing processes, install additional equipment or do additional construction or testing in order to meet regulatory requirements, optimize the production process, increase efficiencies or production capacity or for other reasons, which may result in additional cost to us or delay production of product needed for the clinical trials and commercial launch of our pharmaceutical systems and those of our third-party collaborators.

We have entered into a supply agreement with Corium International, Inc. for clinical and commercial supplies of ELADUR and a supply agreement with Hospira Worldwide, Inc. for clinical and commercial supplies of POSIDUR. These third parties are currently our sole source for drug product required for development and commercialization of these drug candidates. Furthermore, we and our third-party collaborators, where relevant, may also need or choose to subcontract with additional third-party contractors to perform manufacturing steps of our pharmaceutical systems or supply required components for our pharmaceutical systems. Where third party contractors perform manufacturing services for us, we will be subject to the schedule, expertise and performance of third parties as well as incur significant additional costs. Failure of third parties to perform their obligations could adversely affect our operations, development timeline and financial results.

If we or our third-party collaborators cannot manufacture pharmaceutical systems or components in time to meet the clinical or commercial requirements of our collaborators or ourselves or at an acceptable cost, our operating results will be harmed.

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Failure to comply with ongoing governmental regulations for our pharmaceutical systems could materially harm our business in the future

Marketing or promoting a drug is subject to very strict controls. Furthermore, clearance or approval may entail ongoing requirements for post-marketing studies. The manufacture and marketing of drugs are subject to continuing FDA and foreign regulatory review and requirements that we update our regulatory filings. Later discovery of previously unknown problems with a product, manufacturer or facility, or our failure to update regulatory files, may result in restrictions, including withdrawal of the product from the market. Any of the following or other similar events, if they were to occur, could delay or preclude us from further developing, marketing or realizing full commercial use of our pharmaceutical systems, which in turn would materially harm our business, financial condition and results of operations:

failure to obtain or maintain requisite governmental approvals;

failure to obtain approvals for clinically intended uses of our pharmaceutical systems under development; or

FDA required product withdrawals or warnings arising from identification of serious and unanticipated adverse side effects in our pharmaceutical systems.

Manufacturers of drugs must comply with the applicable FDA good manufacturing practice regulations, which include production design controls, testing, quality control and quality assurance requirements as well as the corresponding maintenance of records and documentation. Compliance with current good manufacturing practices regulations is difficult and costly. Manufacturing facilities are subject to ongoing periodic inspection by the FDA and corresponding state agencies, including unannounced inspections, and must be licensed before they can be used for the commercial manufacture of our development products. We and/or our present or future suppliers and distributors may be unable to comply with the applicable good manufacturing practice regulations and other FDA regulatory requirements. We have not been subject to a good manufacturing regulation inspection by the FDA relating to our pharmaceutical systems. If we, our third-party collaborators or our respective suppliers do not achieve compliance for our pharmaceutical systems we or they manufacture, the FDA may refuse or withdraw marketing clearance or require product recall, which may cause interruptions or delays in the manufacture and sale of our pharmaceutical systems.

We have a history of operating losses, expect to continue to have losses in the future and may never achieve or maintain profitability

We have incurred significant operating losses since our inception in 1998 and, as of December 31, 2011, had an accumulated deficit of approximately \$355.5 million. We expect to continue to incur significant operating losses over the next several years as we continue to incur significant costs for research and development, clinical trials, manufacturing, sales, and general and administrative functions. Our ability to achieve profitability depends upon our ability, alone or with others, to successfully complete the development of our proposed pharmaceutical systems, obtain the required regulatory clearances, and manufacture and market our proposed pharmaceutical systems. Development of pharmaceutical systems is costly and requires significant investment. In addition, we may choose to license from third parties either additional drug delivery platform technology or rights to particular drugs or other appropriate technology for use in our pharmaceutical systems. The license fees for these technologies or rights would increase the costs of our pharmaceutical systems.

To date, we have not generated significant revenue from the commercial sale of our pharmaceutical systems and do not expect to do so in the near future. Our current revenues are from the sale of the ALZET product line, the sale of LACTEL biodegradable polymers and certain excipient sales, and from payments under collaborative research and development agreements with third parties. We do not expect our product revenues to increase significantly in the near future, and we do not expect that collaborative research and development revenues will exceed our actual operating expenses. We do not anticipate meaningful revenues to derive from the commercialization and marketing of our pharmaceutical systems in development in the near future, and therefore do not expect to generate sufficient revenues to cover expenses or achieve profitability in the near future.

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We may develop our own sales force to market future products but we have limited sales experience and may not be able to do so effectively

We may choose to develop our own sales force to market in the United States products that we may develop in the future. Developing a sales force will require substantial expenditures. We have limited sales and marketing experience, and may not be able to effectively recruit, train or retain sales personnel. We may not be able to effectively sell our pharmaceutical systems, if approved, and our failure to do so could limit or materially harm our business.

We and our third-party collaborators may not sell our pharmaceutical systems effectively

We and our third-party collaborators compete with many other companies that currently have extensive and well-funded marketing and sales operations. Our marketing and sales efforts and those of our third-party collaborations may be unable to compete successfully against these other companies. We and our third-party collaborators, if relevant, may be unable to establish a sufficient sales and marketing organization on a timely basis, if at all. We and our third-party collaborators, if relevant, may be unable to engage qualified distributors. Even if engaged, these distributors may:

fail to satisfy financial or contractual obligations to us;

fail to adequately market our pharmaceutical systems;

cease operations with little or no notice to us;

offer, design, manufacture or promote competing product lines;

fail to maintain adequate inventory and thereby restrict use of our pharmaceutical systems; or

build up inventory in excess of demand thereby limiting future purchases of our pharmaceutical systems resulting in significant quarter-to-quarter variability in our sales.

The failure of us or our third-party collaborators to effectively develop, gain regulatory approval for, sell, manufacture and market our pharmaceutical systems will hurt our business, prospects and financial results.

We rely heavily on third parties to support development, clinical testing and manufacturing of our pharmaceutical systems

We rely on third-party contract research organizations, service providers and suppliers to provide critical services to support development, clinical testing, and manufacturing of our pharmaceutical systems. For example, we currently depend on third-party vendors to manage and monitor our clinical trials and to perform critical manufacturing steps for our pharmaceutical systems. These third parties may not execute their responsibilities and tasks competently in compliance with applicable laws and regulations or in a timely fashion. We rely on third-parties to manufacture or perform manufacturing steps relating to our pharmaceutical systems or components. We anticipate that we will continue to rely on these and other third-party contractors to support development, clinical testing, and manufacturing of our pharmaceutical systems. Failure of these contractors to provide the required services in a competent or timely manner or on reasonable commercial terms could materially delay the development and approval of our development products, increase our expenses and materially harm our business, financial condition and results of operations.

Key components of our pharmaceutical systems are provided by limited numbers of suppliers, and supply shortages or loss of these suppliers could result in interruptions in supply or increased costs

Certain components and drug substances used in our pharmaceutical systems (including POSIDUR, TRANSDUR-Sufentanil, ELADUR, REMOXY, our other ORADUR-based drug candidates, and Relday) are currently purchased from a single or a limited number of outside

sources. In particular, Eastman Chemical is the

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sole supplier, pursuant to a supply agreement entered into in December 2005, of our requirements of sucrose acetate isobutyrate, a necessary component of POSIDUR, REMOXY, our other ORADUR-based drug candidates, Relday and certain other pharmaceutical systems we have under development. The reliance on a sole or limited number of suppliers could result in:

delays associated with redesigning a pharmaceutical system due to a failure to obtain a single source component;

an inability to obtain an adequate supply of required components; and

reduced control over pricing, quality and delivery time.

We have supply agreements in place for certain components of our pharmaceutical systems, but do not have in place long term supply agreements with respect to all of the components of any of our pharmaceutical system candidates. Therefore the supply of a particular component could be terminated at any time without penalty to the supplier. In addition, we may not be able to procure required components or drugs from third-party suppliers at a quantity, quality and cost acceptable to us. Any interruption in the supply of single source components could cause us to seek alternative sources of supply or manufacture these components internally. Furthermore, in some cases, we are relying on our third-party collaborators to procure supply of necessary components. If the supply of any components for our pharmaceutical systems is interrupted, components from alternative suppliers may not be available in sufficient volumes or at acceptable quality levels within required timeframes, if at all, to meet our needs or those of our third-party collaborators. This could delay our ability to complete clinical trials and obtain approval for commercialization and marketing of our pharmaceutical systems, causing us to lose sales, incur additional costs, delay new product introductions and could harm our reputation.

If we are unable to adequately protect, maintain or enforce our intellectual property rights or secure rights to third-party patents, we may lose valuable assets, experience reduced market share or incur costly litigation to protect our rights or our third-party collaborators may choose to terminate their agreements with us

Our ability to commercially exploit our products will depend significantly on our ability to obtain and maintain patents, maintain trade secret protection and operate without infringing the proprietary rights of others.

The patent status of our lead drug candidates, REMOXY and POSIDUR, are as follows:

In the U.S., REMOXY is covered by an issued patent expiring in 2015 and two pending patent application families, which if granted, would result in patents expiring in 2023 and 2028 respectively, plus any eligible patent term adjustments and extensions. We are currently prosecuting the pending U.S. application families, and we recently received four allowances in the family having a non-adjusted expiration date in 2023. Nonetheless, there can be no assurance that the two pending U.S. patent application families covering REMOXY will be granted, in which event we will have no patent coverage after 2015 in the U.S. for REMOXY. In Europe, REMOXY is covered by two granted patents expiring in 2016 and in 2023 respectively, plus any eligible patent term extensions.

In the U.S., POSIDUR is covered by an issued patent expiring in 2015 and one pending patent application family, which if granted, will result in patents expiring in 2025 plus any eligible patent term adjustments and extensions. We recently received two allowances in the pending U.S. application family. Nonetheless, there can be no assurance that the pending U.S. patent application family covering POSIDUR will be granted, in which event we will have no patent coverage after 2015 in the U.S. for POSIDUR. In Europe, POSIDUR is covered by two granted patents expiring in 2016 and in 2025 respectively, plus any eligible patent term extensions.

As of February 21, 2012, we held 41 issued U.S. patents and 314 issued foreign patents (which include granted European patent rights that have been validated in various EU member states). In addition, we have 56 pending U.S. patent applications and have filed 107 patent applications under the Patent Cooperation Treaty, from which 178 national phase applications are currently pending in Europe, Australia, Japan, Canada and other countries. Our patents expire at various dates starting in 2012.

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The patent positions of pharmaceutical companies, including ours, are uncertain and involve complex legal and factual questions. In addition, the coverage claimed in a patent application can be significantly reduced before the patent is issued. Consequently, our patent applications or those that are licensed to us may not issue into patents, and any issued patents may not provide protection against competitive technologies or may be held invalid if challenged or circumvented. Our competitors may also independently develop products similar to ours or design around or otherwise circumvent patents issued to us or licensed by us. In addition, the laws of some foreign countries may not protect our proprietary rights to the same extent as U.S. law.

The patent laws of the U.S. have recently undergone changes through court decisions which may have significant impact on us and our industry. Decisions of the U.S. Supreme Court (e.g., *KSR v. Teleflex*, *eBay v. MercExchange*) and other courts (e.g., *In re Seagate*) with respect to the standards of patentability, enforceability, availability of injunctive relief and damages may make it more difficult for us to procure, maintain and enforce patents. In addition, the Leahy-Smith America Invents Act (HR 1249) was signed into law in September 2011, which among other changes to the U.S. patent laws, changes patent priority from first to invent to first to file, implements a post-grant opposition system for patents and provides for a prior user defense to infringement. These judicial and legislative changes have introduced significant uncertainty in the patent law landscape and may potentially negatively impact our ability to procure, maintain and enforce patents to provide exclusivity for our products.

We also rely upon trade secrets, technical know-how and continuing technological innovation to develop and maintain our competitive position. We require our employees, consultants, advisors and collaborators to execute appropriate confidentiality and assignment-of-inventions agreements with us. These agreements typically provide that all materials and confidential information developed or made known to the individual during the course of the individual's relationship with us is to be kept confidential and not disclosed to third parties except in specific circumstances, and that all inventions arising out of the individual's relationship with us will be our exclusive property. These agreements may be breached, and in some instances, we may not have an appropriate remedy available for breach of the agreements. Furthermore, our competitors may independently develop substantially equivalent proprietary information and techniques, reverse engineer our information and techniques, or otherwise gain access to our proprietary technology.

We may be unable to meaningfully protect our rights in trade secrets, technical know-how and other non-patented technology. We may have to resort to litigation to protect our intellectual property rights, or to determine their scope, validity or enforceability. In addition, interference proceedings declared by the USPTO may be necessary to determine the priority of inventions with respect to our patent applications. Enforcing or defending our proprietary rights is expensive, could cause diversion of our resources and may not prove successful. Any failure to enforce or protect our rights could cause us to lose the ability to exclude others from using our technology to develop or sell competing products.

Our collaboration agreements may depend on our intellectual property

We are party to collaborative agreements with Pfizer, Hospira and Zogenix among others. Our third-party collaborators have entered into these agreements based on the exclusivity that our intellectual property rights confer on the products being developed. The loss or diminution of our intellectual property rights could result in a decision by our third-party collaborators to terminate their agreements with us. In addition, these agreements are generally complex and contain provisions that could give rise to legal disputes, including potential disputes concerning ownership of intellectual property and data under collaborations. Such disputes can lead to lengthy, expensive litigation or arbitration requiring us to devote management time and resources to such dispute which we would otherwise spend on our business. To the extent that our agreements call for future royalties to be paid conditional on our having patents covering the royalty-bearing subject matter, the decision by the Supreme Court in the case of *MedImmune v. Genentech* could encourage our licensees to challenge the validity of our patents and thereby seek to avoid future royalty obligations without losing the benefit of their license. Should they be successful in such a challenge, our ability to collect future royalties could be substantially diminished.

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We may be sued by third parties which claim that our pharmaceutical systems infringe on their intellectual property rights, particularly because there is substantial uncertainty about the validity and breadth of medical patents

We and our collaborators may be exposed to future litigation by third parties based on claims that our pharmaceutical systems or activities infringe the intellectual property rights of others or that we or our collaborators have misappropriated the trade secrets of others. This risk is exacerbated by the fact that the validity and breadth of claims covered in medical technology patents and the breadth and scope of trade secret protection involve complex legal and factual questions for which important legal principles are unresolved. Any litigation or claims against us or our collaborators, whether or not valid, could result in substantial costs, could place a significant strain on our financial resources and could harm our reputation. We also may not have sufficient funds to litigate against parties with substantially greater resources. In addition, pursuant to our collaborative agreements, we have provided our collaborators with the right, under specified circumstances, to defend against any claims of infringement of the third party intellectual property rights, and such collaborators may not defend against such claims adequately or in the manner that we would do ourselves. Intellectual property litigation or claims could force us or our collaborators to do one or more of the following, any of which could harm our business or financial results:

cease selling, incorporating or using any of our pharmaceutical systems that incorporate the challenged intellectual property, which would adversely affect our revenue;

obtain a license from the holder of the infringed intellectual property right, which license may be costly or may not be available on reasonable terms, if at all; or

redesign our pharmaceutical systems, which would be costly and time-consuming.

Technologies and businesses which we acquire or license may be difficult to integrate, disrupt our business, dilute stockholder value or divert management attention.

We may acquire technologies, products or businesses to broaden the scope of our existing and planned product lines and technologies. Future acquisitions expose us to:

increased costs associated with the acquisition and operation of the new businesses or technologies and the management of geographically dispersed operations;

the risks associated with the assimilation of new technologies, operations, sites and personnel;

the diversion of resources from our existing business and technologies;

the inability to generate revenues to offset associated acquisition costs;

the requirement to maintain uniform standards, controls, and procedures; and

the impairment of relationships with employees and customers or third party collaborators as a result of any integration of new management personnel.

Acquisitions may also result in the issuance of dilutive equity securities, the incurrence or assumption of debt or additional expenses associated with the amortization of acquired intangible assets or potential businesses. Past acquisitions, such as our acquisitions of IntraEAR, ALZET, SBS and APT, as well as future acquisitions, may not generate any additional revenue or provide any benefit to our business.

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Some of our pharmaceutical systems contain controlled substances, the making, use, sale, importation and distribution of which are subject to regulation by state, federal and foreign law enforcement and other regulatory agencies

Some of our pharmaceutical systems currently under development contain, and our products in the future may contain, controlled substances which are subject to state, federal and foreign laws and regulations regarding

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their manufacture, use, sale, importation and distribution. The TRANSDUR-Sufentanil patch, REMOXY and our other ORADUR-based drug candidates, and other pharmaceutical systems we have under development contain active ingredients which are classified as controlled substances under the regulations of the U.S. Drug Enforcement Agency. For our pharmaceutical systems containing controlled substances, we and our suppliers, manufacturers, contractors, customers and distributors are required to obtain and maintain applicable registrations from state, federal and foreign law enforcement and regulatory agencies and comply with state, federal and foreign laws and regulations regarding the manufacture, use, sale, importation and distribution of controlled substances. These regulations are extensive and include regulations governing manufacturing, labeling, packaging, testing, dispensing, production and procurement quotas, record keeping, reporting, handling, shipment and disposal. These regulations increase the personnel needs and the expense associated with development and commercialization of drug candidates including controlled substances. Failure to obtain and maintain required registrations or comply with any applicable regulations could delay or preclude us from developing and commercializing our pharmaceutical systems containing controlled substances and subject us to enforcement action. In addition, because of their restrictive nature, these regulations could limit our commercialization of our pharmaceutical systems containing controlled substances. In particular, among other things, there is a risk that these regulations may interfere with the supply of the drugs used in our clinical trials, and in the future, our ability to produce and distribute our products in the volume needed to meet commercial demand.

Write-offs related to the impairment of long-lived assets, inventories and other non-cash charges, as well as stock-based compensation expenses may adversely impact or delay our profitability

We may incur significant non-cash charges related to impairment write-downs of our long-lived assets, including goodwill and other intangible assets. We will continue to incur non-cash charges related to amortization of other intangible assets. For example, we had a \$13.5 million non-cash write-down of deferred royalties and commercial rights related to CHRONOGESIC in the fourth quarter of 2008. We are required to perform periodic impairment reviews of our goodwill at least annually. To the extent these reviews conclude that the expected future cash flows generated from our business activities are not sufficient to recover the cost of our long-lived assets, we will be required to measure and record an impairment charge to write-down these assets to their realizable values. We completed our last review during the fourth quarter of 2011 and determined that goodwill was not impaired as of December 31, 2011. However, there can be no assurance that upon completion of subsequent reviews a material impairment charge will not be recorded. If future periodic reviews determine that our assets are impaired and a write-down is required, it will adversely impact or delay our profitability.

Inventories include certain excipients that are sold to a customer and included in products awaiting regulatory approval. These inventories are capitalized based on management's judgment of probable sale prior to their expiration date which in turn is based on non-binding forecasts from our customer. The valuation of inventory requires us to estimate the value of inventory that may become expired prior to use. We may be required to expense previously capitalized inventory costs upon a change in our judgment, due to, among other potential factors, a denial or delay of approval of our customer's product by the necessary regulatory bodies, or new information that suggests that the inventory will not be saleable. In addition, these circumstances may cause us to record a liability related to minimum purchase agreements that we have in place for raw materials.

Global credit and financial market conditions could negatively impact the value of our current portfolio of cash equivalents, short-term investments or long-term investments and our ability to meet our financing objectives

Our cash and cash equivalents are maintained in highly liquid investments with remaining maturities of 90 days or less at the time of purchase. Our short-term investments consist primarily of readily marketable debt securities with original maturities of greater than 90 days from the date of purchase but remaining maturities of less than one year from the balance sheet date. Our long-term investments consist primarily of readily marketable debt securities with maturities in one year or beyond from the balance sheet date. While, as of the date of this

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filing, we are not aware of any downgrades, material losses, or other significant deterioration in the fair value of our cash equivalents, short-term investments or long-term investments since December 31, 2011, no assurance can be given that deterioration in conditions of the global credit and financial markets would not negatively impact our current portfolio of cash equivalents, short-term investments or long-term investments or our ability to meet our financing objectives.

We depend upon key personnel who may terminate their employment with us at any time, and we may need to hire additional qualified personnel

Our success will depend to a significant degree upon the continued services of key management, technical and scientific personnel, including Felix Theeuwes, our Chairman and Chief Scientific Officer and James E. Brown, our President and Chief Executive Officer. In addition, our success will depend on our ability to attract and retain other highly skilled personnel. Competition for qualified personnel is intense, and the process of hiring and integrating such qualified personnel is often lengthy. We may be unable to recruit such personnel on a timely basis, if at all. Our management and other employees may voluntarily terminate their employment with us at any time. The loss of the services of key personnel, or the inability to attract and retain additional qualified personnel, could result in delays to product development or approval, loss of sales and diversion of management resources.

We may not successfully manage our company through varying business cycles

Our success will depend on properly sizing our company through growth and contraction cycles caused in part by changing business conditions, which places a significant strain on our management and on our administrative, operational and financial resources. To manage through such cycles, we must expand or contract our facilities, our operational, financial and management systems and our personnel. If we were unable to manage growth and contractions effectively our business would be harmed.

Our business involves environmental risks and risks related to handling regulated substances

In connection with our research and development activities and our manufacture of materials and pharmaceutical systems, we are subject to federal, state and local laws, rules, regulations and policies governing the use, generation, manufacture, storage, air emission, effluent discharge, handling and disposal of certain materials, biological specimens and wastes. Although we believe that we have complied with the applicable laws, regulations and policies in all material respects and have not been required to correct any material noncompliance, we may be required to incur significant costs to comply with environmental and health and safety regulations in the future. Our research and development involves the use, generation and disposal of hazardous materials, including but not limited to certain hazardous chemicals, solvents, agents and biohazardous materials. The extent of our use, generation and disposal of such substances has increased substantially since we started manufacturing and selling biodegradable polymers. Although we believe that our safety procedures for storing, handling and disposing of such materials comply with the standards prescribed by state and federal regulations, we cannot completely eliminate the risk of accidental contamination or injury from these materials. We currently contract with third parties to dispose of these substances generated by us, and we rely on these third parties to properly dispose of these substances in compliance with applicable laws and regulations. If these third parties do not properly dispose of these substances in compliance with applicable laws and regulations, we may be subject to legal action by governmental agencies or private parties for improper disposal of these substances. The costs of defending such actions and the potential liability resulting from such actions are often very large. In the event we are subject to such legal action or we otherwise fail to comply with applicable laws and regulations governing the use, generation and disposal of hazardous materials and chemicals, we could be held liable for any damages that result, and any such liability could exceed our resources.

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Our corporate headquarters, manufacturing facilities and personnel are located in a geographical area that is seismically active

Our corporate headquarters, primary manufacturing facilities and personnel are located in a geographical area that is known to be seismically active and prone to earthquakes. Should such a natural disaster occur, our ability to conduct our business could be severely restricted, and our business and assets, including the results of our research, development and manufacturing efforts, could be destroyed.

Risks Related To Our Industry

The market for our pharmaceutical systems is rapidly changing and competitive, and new products or technologies developed by others could impair our ability to grow our business and remain competitive

The pharmaceutical industry is subject to rapid and substantial technological change. Developments by others may render our pharmaceutical systems under development or technologies noncompetitive or obsolete, or we may be unable to keep pace with technological developments or other market factors. Technological competition in the industry from pharmaceutical and biotechnology companies, universities, governmental entities and others diversifying into the field is intense and is expected to increase.

We may face competition from other companies in numerous industries including pharmaceuticals, medical devices and drug delivery. POSIDUR, TRANSDUR-Sufentanil, ELADUR, Relday, REMOXY and other ORADUR-based drug candidates, if approved, will compete with currently marketed oral opioids, transdermal opioids, local anesthetic patches, anti-psychotics, stimulants, implantable and external infusion pumps which can be used for infusion of opioids and local anesthetics. Products of these types are marketed by Purdue Pharma, Knoll, Janssen, Medtronic, Endo, AstraZeneca, Arrow International, Tricumed, I-Flow (Kimberly-Clark), Cumberland Pharmaceuticals, NeurogesX, Covidien, Shire, Johnson & Johnson, Eli Lilly, Pfizer, Novartis and others. Our ORADUR-ADHD product candidates, if approved, will compete with currently marketed products by Shire, Johnson & Johnson, UCB, Novartis, Noven, Celgene, Eli Lilly, Medice and others. Relday, if approved, will compete with currently marketed products by Johnson & Johnson, Eli Lilly, Astra Zeneca, Pfizer, Bristol-Myers Squibb and others. Numerous companies are applying significant resources and expertise to the problems of drug delivery and several of these are focusing or may focus on delivery of drugs to the intended site of action, including Alkermes, Pacira Pharmaceuticals, EpiCept, Innocoll, Nektar, I-Flow (Kimberly-Clark), NeurogesX, Flamel, Alexza, Cadence Pharmaceuticals, Hospira, Cumberland Pharmaceuticals, Egalet, Acura and others. Some of these competitors may be addressing the same therapeutic areas or indications as we are. Our current and potential competitors may succeed in obtaining patent protection or commercializing products before us. Many of these entities have significantly greater research and development capabilities than we do, as well as substantially more marketing, manufacturing, financial and managerial resources. These entities represent significant competition for us. Acquisitions of, or investments in, competing pharmaceutical or biotechnology companies by large corporations could increase such competitors' financial, marketing, manufacturing and other resources.

We are engaged in the development of novel therapeutic technologies. Our resources are limited and we may experience technical challenges inherent in such novel technologies. Competitors have developed or are in the process of developing technologies that are, or in the future may be, the basis for competitive products. Some of these products may have an entirely different approach or means of accomplishing similar therapeutic effects than our pharmaceutical systems. Our competitors may develop products that are safer, more effective or less costly than our pharmaceutical systems and, therefore, present a serious competitive threat to our product offerings.

The widespread acceptance of therapies that are alternatives to ours may limit market acceptance of our pharmaceutical systems even if commercialized. Chronic and post-operative pain are currently being treated by oral medication, transdermal drug delivery systems, such as drug patches, and implantable drug delivery devices which will be competitive with our pharmaceutical systems. These treatments are widely accepted in the medical community and have a long history of use. The established use of these competitive products may limit the potential for our pharmaceutical systems to receive widespread acceptance if commercialized.

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We could be exposed to significant product liability claims which could be time consuming and costly to defend, divert management attention and adversely impact our ability to obtain and maintain insurance coverage

The testing, manufacture, marketing and sale of our pharmaceutical systems involve an inherent risk that product liability claims will be asserted against us. Although we are insured against such risks up to an annual aggregate limit in connection with clinical trials and commercial sales of our pharmaceutical systems, our present product liability insurance may be inadequate and may not fully cover the costs of any claim or any ultimate damages we might be required to pay. Product liability claims or other claims related to our pharmaceutical systems, regardless of their outcome, could require us to spend significant time and money in litigation or to pay significant damages. Any successful product liability claim may prevent us from obtaining adequate product liability insurance in the future on commercially desirable or reasonable terms. In addition, product liability coverage may cease to be available in sufficient amounts or at an acceptable cost. An inability to obtain sufficient insurance coverage at an acceptable cost or otherwise to protect against potential product liability claims could prevent or inhibit the commercialization of our pharmaceutical systems. A product liability claim could also significantly harm our reputation and delay market acceptance of our pharmaceutical systems.

Acceptance of our pharmaceutical systems in the marketplace is uncertain, and failure to achieve market acceptance will delay our ability to generate or grow revenues

Our future financial performance will depend upon the successful introduction and customer acceptance of our future products, including REMOXY and other ORADUR-based drug candidates, POSIDUR, TRANSDUR-Sufentanil, ELADUR and Relday. Even if approved for marketing, our pharmaceutical systems may not achieve market acceptance. The degree of market acceptance will depend upon a number of factors, including:

the receipt of regulatory clearance of marketing claims for the uses that we are developing;

the establishment and demonstration in the medical community of the safety and clinical efficacy of our products and their potential advantages over existing therapeutic products, including oral medication, transdermal drug delivery products such as drug patches, or external or implantable drug delivery products; and

pricing and reimbursement policies of government and third-party payors such as insurance companies, health maintenance organizations, hospital formularies and other health plan administrators.

Physicians, patients, payors or the medical community in general may be unwilling to accept, utilize or recommend any of our products. If we are unable to obtain regulatory approval, commercialize and market our future products when planned and achieve market acceptance, we will not achieve anticipated revenues.

If users of our products are unable to obtain adequate reimbursement from third-party payors, or if new restrictive legislation is adopted, market acceptance of our products may be limited and we may not achieve anticipated revenues

The continuing efforts of government and insurance companies, health maintenance organizations and other payors of healthcare costs to contain or reduce costs of health care may affect our future revenues and profitability, and the future revenues and profitability of our potential customers, suppliers and third-party collaborators and the availability of capital. For example, in certain foreign markets, pricing or profitability of prescription pharmaceuticals is subject to government control. In the United States, recent federal and state government initiatives have been directed at lowering the total cost of health care, and the U.S. Congress and state legislatures will likely continue to focus on health care reform, the cost of prescription pharmaceuticals and on the reform of the Medicare and Medicaid systems. While we cannot predict whether any such legislative or regulatory proposals will be adopted, the announcement or adoption of such proposals could materially harm our business, financial condition and results of operations.

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The successful commercialization of our pharmaceutical systems will depend in part on the extent to which appropriate reimbursement levels for the cost of our pharmaceutical systems and related treatment are obtained by governmental authorities, private health insurers and other organizations, such as HMOs. Third-party payors are increasingly limiting payments or reimbursement for medical products and services. Also, the trend toward managed health care in the United States and the concurrent growth of organizations such as HMOs, which could control or significantly influence the purchase of health care services and products, as well as legislative proposals to reform health care or reduce government insurance programs, may limit reimbursement or payment for our products. The cost containment measures that health care payors and providers are instituting and the effect of any health care reform could materially harm our ability to operate profitably.

If we or our third-party collaborators are unable to train physicians to use our pharmaceutical systems to treat patients' diseases or medical conditions, we may incur delays in market acceptance of our products

Broad use of our pharmaceutical systems will require extensive training of numerous physicians on the proper and safe use of our pharmaceutical systems. The time required to begin and complete training of physicians could delay introduction of our products and adversely affect market acceptance of our products. We or third parties selling our pharmaceutical systems may be unable to rapidly train physicians in numbers sufficient to generate adequate demand for our pharmaceutical systems. Any delay in training would materially delay the demand for our pharmaceutical systems and harm our business and financial results. In addition, we may expend significant funds towards such training before any orders are placed for our products, which would increase our expenses and harm our financial results.

Potential new accounting pronouncements and legislative actions are likely to impact our future financial position or results of operations

Future changes in financial accounting standards may cause adverse, unexpected fluctuations in the timing of the recognition of revenues or expenses and may affect our financial position or results of operations. New pronouncements and varying interpretations of pronouncements have occurred with frequency and may occur in the future and we may make changes in our accounting policies in the future. Compliance with changing regulation of corporate governance and public disclosure may result in additional expenses. Changing laws, regulations and standards relating to corporate governance and public disclosure, including the Sarbanes-Oxley Act of 2002, new SEC regulations, PCAOB pronouncements and NASDAQ rules, are creating uncertainty for companies such as ours and insurance, accounting and auditing costs are high as a result of this uncertainty and other factors. We are committed to maintaining high standards of corporate governance and public disclosure. As a result, we intend to invest all reasonably necessary resources to comply with evolving standards, and this investment may result in increased general and administrative expenses and a diversion of management time and attention from revenue-generating activities to compliance activities.

Risks Related To Our Common Stock

Our stock price may not meet the minimum bid price for continued listing on the Nasdaq Global Market. Our ability to publicly or privately sell equity securities and the liquidity of our common stock could be adversely affected if we are delisted from The Nasdaq Global Market or if we are unable to transfer our listing to another stock market.

On February 21, 2012, the Company received a letter from the Listing Qualifications Department of the Nasdaq Stock Market ("Nasdaq") informing the Company that because the closing bid price for the Company's common stock listed on Nasdaq was below \$1.00 for 30 consecutive trading days, the Company does not comply with the minimum closing bid price requirement for continued listing on the Nasdaq Global Market under Nasdaq Marketplace Rule 5450(a)(1).

The Company has until August 20, 2012 to regain compliance with Nasdaq's listing requirements by having the closing bid price of its common stock listed on Nasdaq be at least \$1.00 for at least 10 consecutive trading

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days. If the Company does not regain compliance within this time period, it may transfer the common stock to The Nasdaq Capital Market, provided that the Company (i) meets the applicable market value of publicly held shares requirement for continued listing and all other applicable requirements for initial listing on The Nasdaq Capital Market (except for the closing bid price requirement) based on the Company's most recent public filings and market information and (ii) notifies Nasdaq of its intent to cure this deficiency. Following a transfer to The Nasdaq Capital Market, the Company would be afforded the remainder of an additional 180 calendar day grace period in order to regain compliance with the minimum closing bid price requirement of \$1.00 per share under The Nasdaq Capital Market, unless it does not appear to NASDAQ that it would be possible for the Company to cure the deficiency.

If compliance is not demonstrated within the applicable compliance period, Nasdaq will notify the Company that its securities will be subject to delisting. The Company may appeal Nasdaq's determination to delist its securities to a Hearings Panel. During any appeal process, shares of the Company's common stock would continue to trade on the Nasdaq Global Market or Nasdaq Capital Market, as applicable.

There can be no assurance that we will regain and maintain compliance with the requirements for listing our common stock on the Nasdaq Global Market or that our common stock would be eligible for transfer to the Nasdaq Capital Market and remain in compliance with the requirements for listing on that market. Delisting from Nasdaq could adversely affect our ability to raise additional financing through the public or private sale of equity securities, would significantly affect the ability of investors to trade our securities and would negatively affect the value and liquidity of our common stock. Delisting could also have other negative results, including the potential loss of confidence by employees, the loss of institutional investor interest and fewer business development opportunities.

Our operating history makes evaluating our stock difficult

Our quarterly and annual results of operations have historically fluctuated and we expect will continue to fluctuate for the foreseeable future. We believe that period-to-period comparisons of our operating results should not be relied upon as predictive of future performance. Our prospects must be considered in light of the risks, expenses and difficulties encountered by companies with no approved pharmaceutical products, particularly companies in new and rapidly evolving markets such as pharmaceuticals, drug delivery and biotechnology. To address these risks, we must, among other things, obtain regulatory approval for and commercialize our pharmaceutical systems, which may not occur. We may not be successful in addressing these risks and difficulties. We may require additional funds to complete the development of our pharmaceutical systems and to fund operating losses to be incurred in the next several years.

Investors may experience substantial dilution of their investment

Investors may experience dilution of their investment if we raise capital through the sale of additional equity securities or convertible debt securities or grant additional stock options to employees and consultants. Any sales in the public market of the common stock issuable upon such conversion could adversely affect prevailing market prices for our common stock.

The price of our common stock may be volatile

The stock markets in general, and the markets for pharmaceutical stocks in particular, have experienced extreme volatility that has often been unrelated to the operating performance of particular companies. These broad market fluctuations may adversely affect the trading price of our common stock.

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Price declines in our common stock could result from general market and economic conditions and a variety of other factors, including:

failure of our third-party collaborators to successfully develop and commercialize the respective pharmaceutical systems they are developing;

adverse results (including adverse events or failure to demonstrate safety or efficacy) or delays in our clinical and non-clinical trials of POSIDUR, TRANSDUR-Sufentanil, ELADUR, REMOXY, our other ORADUR-based drug candidates, Relday or other pharmaceutical systems;

announcements of FDA non-approval of our pharmaceutical systems, or delays in the FDA or other foreign regulatory agency review process;

adverse actions taken by regulatory agencies or law enforcement agencies with respect to our pharmaceutical systems, clinical trials, manufacturing processes or sales and marketing activities, or those of our third party collaborators;

announcements of technological innovations, patents or new products by our competitors;

regulatory developments in the United States and foreign countries;

any lawsuit involving us or our pharmaceutical systems including intellectual property infringement or product liability suits;

announcements concerning our competitors, or the biotechnology or pharmaceutical industries in general;

developments concerning our strategic alliances or acquisitions;

actual or anticipated variations in our operating results;

changes in recommendations by securities analysts or lack of analyst coverage;

deviations in our operating results from the estimates of analysts;

sales of our common stock by our executive officers or directors or sales of substantial amounts of common stock by others;

potential delisting of our common stock from The NASDAQ Global Market;

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loss or disruption of facilities due to natural disasters;

changes in accounting principles; or

loss of any of our key scientific or management personnel.

The market price of our common stock may fluctuate significantly in response to factors which are beyond our control. The stock market in general has recently experienced extreme price and volume fluctuations. In addition, the market prices of securities of technology and pharmaceutical companies have also been extremely volatile, and have experienced fluctuations that often have been unrelated or disproportionate to the operating performance of these companies. These broad market fluctuations could result in extreme fluctuations in the price of our common stock, which could cause a decline in the value of our common stock.

In the past, following periods of volatility in the market price of a particular company's securities, litigation has often been brought against that company. If litigation of this type is brought against us, it could be extremely expensive and divert management's attention and our company's resources.

We have broad discretion over the use of our cash and investments, and their investment may not always yield a favorable return

Our management has broad discretion over how our cash and investments are used and may from time to time invest in ways with which our stockholders may not agree and that do not yield favorable returns.

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Executive officers, directors and principal stockholders have substantial control over us, which could delay or prevent a change in our corporate control favored by our other stockholders

Our directors, executive officers and principal stockholders, together with their affiliates, have substantial control over us. The interests of these stockholders may differ from the interests of other stockholders. As a result, these stockholders, if acting together, could have the ability to exercise control over all corporate actions requiring stockholder approval irrespective of how our other stockholders may vote, including:

the election of directors;

the amendment of charter documents;

the approval of certain mergers and other significant corporate transactions, including a sale of substantially all of our assets; or

the defeat of any non-negotiated takeover attempt that might otherwise benefit the public stockholders.

Our certificate of incorporation, our bylaws and Delaware law contain provisions that could discourage another company from acquiring us.

Provisions of Delaware law, our certificate of incorporation and bylaws may discourage, delay or prevent a merger or acquisition that stockholders may consider favorable, including transactions in which you might otherwise receive a premium for your shares. These provisions include:

authorizing the issuance of blank check preferred stock without any need for action by stockholders;

providing for a classified board of directors with staggered terms;

requiring supermajority stockholder voting to effect certain amendments to our certificate of incorporation and bylaws;

eliminating the ability of stockholders to call special meetings of stockholders;

prohibiting stockholder action by written consent; and

establishing advance notice requirements for nominations for election to the board of directors or for proposing matters that can be acted on by stockholders at stockholder meetings.

Item 1B. Unresolved Staff Comments.

None.

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The following chart indicates the facilities that we lease, the location and size of each such facility and their designated use.

| Location | Approximate Square Feet | Operation | Expiration |
|-----------------|--------------------------------|--------------------------------------|---|
| Cupertino, CA | 30,000 sq. ft. | Office, Laboratory and Manufacturing | Lease expires 2014 |
| Cupertino, CA | 20,000 sq. ft. | Office and Laboratory | Lease expires 2014 (with an option to renew for an additional five years) |
| Vacaville, CA | 24,634 sq. ft. | Manufacturing | Lease expires 2013 (with an option to renew for an additional five years) |
| Pelham, AL | 9,400 sq. ft. | Office, Laboratory and Manufacturing | Lease expires March 2012 |
| Birmingham, AL | 21,540 sq. ft. | Office, Laboratory and Manufacturing | Lease expires 2021 (with an option to terminate after seven years and nine months and with two options to renew the lease term for an additional five years each after the current lease expires) |

We believe that our existing facilities are adequate to meet our current and foreseeable requirements or that suitable additional or substitute space will be available as needed.

Item 3. Legal Proceedings.

We are not a party to any material legal proceedings.

Item 4. Mine Safety Disclosures.

Not applicable.

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PART II

**Item 5. Market for Registrant's Common Equity, Related Stockholder Matter and Issuer Purchases of Equity Securities.
Price Range of Common Stock**

Our common stock has been traded on the NASDAQ Global Market under the symbol "DRRX" since our initial public offering on September 28, 2000. The following table sets forth, for the periods indicated, the high and low sales prices for our common stock as reported by the NASDAQ Global Market.

| Year ended December 31, 2010 | Common Stock Price | |
|------------------------------|--------------------------|------|
| | Low | High |
| | | |