

DURECT CORP
Form 10-K
March 04, 2010
Table of Contents

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, 2009

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

94-3297098

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(State or other jurisdiction of
incorporation or organization)

(I.R.S. Employer
Identification No.)

2 Results Way

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:

None

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

Common Stock, \$0.0001 par value

Preferred Share Purchase Rights

(Title of Class)

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 \$184,167,623 as of June 30, 2009 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.

There were 86,754,768 shares of the registrant's Common Stock issued and outstanding as of February 26, 2010.

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DOCUMENTS INCORPORATED BY REFERENCE

Part III incorporates information by reference from the definitive Proxy Statement for the 2010 annual meeting of stockholders, which is expected to be filed not later than 120 days after the Registrant's fiscal year ended December 31, 2009.

Table of Contents

DURECT CORPORATION
ANNUAL REPORT ON FORM 10-K
FOR THE FISCAL YEAR ENDED DECEMBER 31, 2009

TABLE OF CONTENTS

		Page
PART I		
ITEM 1.	<u>Business</u>	1
ITEM 1A.	<u>Risk Factors</u>	27
ITEM 1B.	<u>Unresolved Staff Comments</u>	47
ITEM 2.	<u>Properties</u>	47
ITEM 3.	<u>Legal Proceedings</u>	47
ITEM 4.	<u>Reserved</u>	47
PART II		
ITEM 5.	<u>Market for the Registrant's Common Equity, Related Stockholder Matters and Issuer Purchases of Equity Securities</u>	48
ITEM 6.	<u>Selected Financial Data</u>	50
ITEM 7.	<u>Management's Discussion and Analysis of Financial Condition and Results of Operations</u>	51
ITEM 7A.	<u>Quantitative and Qualitative Disclosures About Market Risk</u>	65
ITEM 8.	<u>Financial Statements and Supplementary Data</u>	67
ITEM 9.	<u>Changes in and Disagreements with Accountants on Accounting and Financial Disclosure</u>	103
ITEM 9A.	<u>Controls and Procedures</u>	103
ITEM 9B.	<u>Other Information</u>	105
PART III		
ITEM 10.	Directors, Executive Officers and Corporate Governance	105
ITEM 11.	Executive Compensation	105
ITEM 12.	Security Ownership of Certain Beneficial Owners and Management and Related Stockholder Matters	105
ITEM 13.	Certain Relationships and Related Transactions, and Director Independence	105
ITEM 14.	Principal Accountant Fees and Services	105
PART IV		
ITEM 15.	<u>Exhibits, and Financial Statement Schedules</u>	105
	<u>Signatures</u>	112

Table of Contents

PART I

**Item 1. Business.
Overview**

We are an emerging specialty pharmaceutical company focused on the development of pharmaceutical products based on our proprietary drug delivery technology platforms. Our product pipeline currently consists of six 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), one program in Phase III, two programs in Phase II and two programs in Phase I. These more advanced programs are all 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 earlier stage research 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.

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

Table of Contents**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	King/Pain Therapeutics (worldwide)	ORADUR	NDA accepted but not approved/ Complete Response Letter received
POSIDUR (Controlled release injection of bupivacaine)	Post Operative Pain	Nycomed (Europe and other defined territories); DURECT retains rights in U.S., Canada, Japan and other countries	SABER	Phase III (U.S.) Phase II (E.U.)
ELADUR (Transdermal bupivacaine)	Pain	King (worldwide)	TRANSDUR	Phase II
TRANSDUR-Sufentanil (Transdermal sufentanil)	Chronic Pain	DURECT retains worldwide rights	TRANSDUR	Phase II
Oral controlled release opioid (active agent undisclosed)	Pain	King/Pain Therapeutics (worldwide)	ORADUR	Phase I
Oral controlled release opioid (active agent undisclosed)	Pain	King/Pain Therapeutics (worldwide)	ORADUR	Phase I
ORADUR-ADHD	Attention Deficit Hyperactivity Disorder (ADHD)	Orient Pharma (Defined Asian and South Pacific countries); DURECT retains rights in North American, Europe, Japan and all other countries	ORADUR	Preclinical/ Research Stage
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/ DUROS/ DURIN	Preclinical/ Research Stage

Table of Contents

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 approximately \$2.8 billion in worldwide sales in 2009.

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 commercialization rights of Remoxy to King Pharmaceuticals, Inc. (King) and, as of March 2009, we are working directly with King on further development of 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 painkiller, which achieved annual worldwide sales of approximately \$2.8 billion in 2009. 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. As of December 31, 2009, 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. On July 2, 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 recently announced that it has undertaken a likeability study and a pharmacokinetic trial in volunteers and plans to resubmit the NDA in the fourth quarter of 2010.

Additional ORADUR-Opioid Products in Development

During 2006, 2007 and 2008, we also worked with Pain Therapeutics and King on the development of additional ORADUR abuse-resistant opioid drug candidates which would address the chronic pain market. Phase I clinical trials have been completed for two of these ORADUR-based products. The active ingredients in these two drug candidates are opioids whose identities have not been publicly disclosed.

POSIDUR

Market Opportunity. According to data published by the Center for Disease Control and Prevention, there are approximately 72 million ambulatory and inpatient procedures performed annually in the U.S.

Table of Contents

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, transdermal opiate patches and muscle relaxants. While oral analgesics can effectively control post-surgical pain, they commonly cause side effects including drowsiness, constipation and cognitive impairment. Effective pain management can be compromised if patients fail to adhere to recommended dosing regimens because they are sleeping or disoriented. 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.

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, adequate pain control can be achieved with minimal exposure to the remainder of the body, 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.

In November 2006, we entered into a collaboration agreement with Nycomed Danmark ApS (Nycomed), which was subsequently amended in February 2010. Under the terms of the amended agreement, as amended, 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, with future potential additional milestone payments of up to \$181.0 million upon achievement of defined development, regulatory and sales milestones. Prior to the February 2010 amendment, the agreement provided for us and Nycomed to jointly direct and equally fund a development program for POSIDUR intended to secure regulatory approval in both the U.S. and the E.U. After the amendment, we now have final decision-making authority over clinical trials intended for the U.S. registration of POSIDUR. Subject to our right to initiate dispute resolution procedures in specified circumstances, Nycomed will now have final decision-making authority over clinical trials for the E. U. and other countries licensed to it. We have funding responsibility for all current and future clinical trials intended for U.S. registration of POSIDUR and, commencing April 1, 2010, Nycomed will have sole funding responsibility for all clinical trials intended for E.U. registration of POSIDUR. The final decision making authority and financial responsibility for the remainder of the development activities, such as the non-clinical and CMC activities, will be jointly managed and funded by DURECT and Nycomed. In addition, we will manufacture and supply the product to Nycomed for commercial sale in the territory licensed to Nycomed. Nycomed will pay us blended royalties on sales in the defined territory of 15-40% depending on annual sales, as well as a manufacturing markup. We retain full commercial rights to POSIDUR in the U.S., Canada, Japan and certain other countries.

Clinical Program. In 2007, we successfully completed a 122 patient Phase IIb clinical trial of POSIDUR for treatment of post-operative pain in patients undergoing inguinal hernia repair. In the Phase IIb trial, POSIDUR at a dose of 5 mL demonstrated statistically significant reductions in pain and in total consumption of supplemental opioid analgesic medications versus placebo. These successful results triggered the \$8.0 million milestone payment by Nycomed to us under our agreement with Nycomed.

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

Table of Contents

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 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

Table of Contents

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 positive 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. Nycomed is currently conducting two Phase IIb clinical trials in hysterectomy patients and in shoulder surgery patients. These trials are being conducted in a different manner than U.S. clinical trials and are designed to be suitable for European regulatory approval purposes.

U.S. Phase III Program

In January 2010, we announced that we had commenced BESST (Bupivacaine Effectiveness and Safety in SABER Trial), which is intended to be the pivotal Phase III clinical trial in the U.S. BESST is an international, multi-center, randomized, double-blind, controlled trial evaluating the safety, efficacy, effectiveness, and pharmacokinetics of POSIDUR in approximately 300 patients undergoing a variety of general abdominal surgical procedures. Eligible patients will be randomly assigned to one of three cohorts:

Cohort 1: An active comparator cohort in which patients are 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 are 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 are randomized to receive either POSIDUR 5.0 mL or SABER-Placebo after laparoscopically-assisted colectomy.

Efficacy evaluation in the BESST trial will encompass a number of parameters. The two co-primary efficacy endpoints for Cohort 3 will be 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. An adaptive feature of BESST allows for increasing the patient sample size in Cohort 3 based on pooled and blinded data. The purpose of Cohorts 1 and 2 is to give us additional experience with the use of POSIDUR in a broader group of surgeries and patients.

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, back pain, sprains, strains, and contusions) that could benefit from a locally acting pain product.

Development Strategy. We are developing a transdermal bupivacaine patch (ELADUR) based on our proprietary TRANSDUR transdermal technology 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

Table of Contents

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. Together with King, we are exploring the development of ELADUR for a variety of clinical indications.

Clinical Program. In 2007, we reported positive results from a completed 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. King has stated that it intends to initiate further studies with ELADUR in the first half of 2010.

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 approximately \$2.8 billion in worldwide sales in 2009. Another major class of drugs utilized to treat chronic pain are transdermally delivered opioids such as Duragesic®, a leading transdermal fentanyl product which accounted for approximately \$900 million in worldwide sales in 2009. 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 opioid 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. 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 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 active discussions with multiple potential collaborators regarding licensing development and commercialization rights to this program to which we hold worldwide rights.

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 detailed proposed protocols for Phase III were reviewed with the FDA at an end-of-Phase II

Table of Contents

meeting on February 19, 2009. As a result of that meeting, we believe we understand the anticipated regulatory pathway for the Phase III program and approval, which will follow a 505(b)2 pathway as discussed with FDA. This pathway 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 \$4.0 billion in 2008. 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 for ORADUR-ADHD in all territories other than the U.S. We anticipate commencing Phase I studies in 2010.

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.

Table of Contents

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 \$1 trillion spent on 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 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.

Table of Contents

The Drug Delivery Industry. In the last thirty-five 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 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

Table of Contents

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 six 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 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.

Table of Contents

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 is in Phase III clinical trials in the U.S. and Phase II clinical trials in the E.U. 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 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 an end-of-Phase II meeting with the FDA was held in February 2009, and for which we hold worldwide development and commercialization rights. The TRANSDUR technology is also the basis for ELADUR, which is currently in Phase II testing and which we have licensed worldwide development and commercialization rights to Alpharma (which was acquired by King in December 2008).

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. In December 2007, Remoxy successfully completed a pivotal Phase III clinical trial. Pain Therapeutics submitted an NDA for Remoxy to the FDA in June 2008, and in August 2008, the NDA was accepted by the FDA 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 will be required to support the approval of Remoxy but the FDA has not requested or recommended additional clinical efficacy studies prior to approval. King Pharmaceuticals assumed responsibility for further development of Remoxy from Pain Therapeutics in March 2009. On July 2, 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 has recently announced that it has undertaken a likeability study and a pharmacokinetic trial in volunteers and plans to resubmit the NDA in the fourth quarter of 2010.

We also have two other ORADUR-based opioid drug candidates for which Phase I clinical trials have been completed. According to Pain Therapeutics, the data from these Phase I trials indicate that these drug candidates are safe and well-tolerated with release profiles that appear well suited to use with a chronic pain population. The active ingredients in these two drug candidates are opioids whose identities have not been publicly disclosed.

We also have an ORADUR-ADHD program in the preclinical / research stage and we expect to commence Phase I trials in 2010.

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

Table of Contents

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 DURIN technology is the basis of Memryte for the treatment of Alzheimer's disease, with any future development controlled by Curaxis.

The DUROS Technology

The DUROS system is a miniature drug-dispensing pump which can be as small as a wooden matchstick. We have licensed the DUROS system for specified fields of use from ALZA Corporation (ALZA), pursuant to a development and commercialization agreement entered into effective April 1998. The DUROS system can be used for therapies requiring systemic or site-specific administration of drug. To deliver drugs systemically, the DUROS system is placed just under the skin, for example in the inner side of the upper arm, in an outpatient procedure that is completed in just a few minutes using local anesthetic. Removal or replacement of the product is also a simple and quick procedure completed in the doctor's office.

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.

Minimize Product Development Risk and Speed Time-to-Market. Initially, we intend to minimize product development risk and speed time-to-market 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 or by delivering them directly to the site of action;

enhance drug performance by minimizing side effects; and

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

Table of Contents

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, TRANSDUR, ORADUR, DURIN, DUROS 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 an NDA has been accepted but not approved by the FDA, and for which a Complete Response Letter has been received, and five different disclosed programs in clinical development, including two 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 Sales and Marketing Organization. Our goal is to become a specialty pharmaceutical company where we commercialize products with significant market potential. To that end, we intend, over the course of a few years, to build up commercial, sales and marketing capability and other required infrastructure in focused specialty areas. We will continue to pursue strategic alliances or collaborations 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 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.

Third-Party Collaborations

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

Alpharma Ireland Limited (acquired by King in December 2008). 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

Table of Contents

effective in October 2008. Under the terms of the agreement, upon closing of the transaction, Alharma paid us an upfront license fee of \$20 million, with possible additional payments of up to \$93 million upon the achievement of predefined development and regulatory milestones spread over multiple clinical indications and geographical territories as well as possible additional payments of up to \$150 million in sales-based milestones. If ELADUR is commercialized, we would also receive royalties on product sales. Alharma will control and fund further development of the program. The term of the agreement will continue on a jurisdiction-by-jurisdiction basis until the later of fifteen (15) years from the date of first commercial sale of ELADUR or the expiration of patent coverage or data exclusivity in each such jurisdiction. During the term of the agreement, subject to specified conditions, neither party nor their affiliates may develop or commercialize a transdermal patch containing bupivacaine. Upon expiration of the term of the agreement, the rights and licenses granted to Alharma will convert to fully paid-up, non-royalty bearing, perpetual rights and licenses. The agreement provides each party with specified termination rights, including the right of Alharma to terminate at any time without cause 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 a result of the acquisition of Alharma by King in December 2008, King assumed Alharma's rights and obligations under the agreement. As of December 31, 2009, the cumulative aggregate payments received by us under this agreement were \$24.9 million.

Nycomed Danmark ApS. In November 2006, we entered into a collaboration agreement with Nycomed, and this agreement was amended in February 2010. Under the terms of the 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, with future potential additional milestone payments of up to \$181.0 million upon achievement of defined development, regulatory and sales milestones. Prior to the February 2010 amendment, the agreement provided for us and Nycomed to jointly direct and equally fund a development program for POSIDUR intended to secure regulatory approval in both the U.S. and the E.U. After the amendment, we now have final decision-making authority over clinical trials intended for the U.S. registration of POSIDUR. Subject to our right to initiate dispute resolution procedures in specified circumstances, Nycomed will now have final decision-making authority over clinical trials for the E. U. and other countries licensed to it. We now have funding responsibility for all current and future clinical trials intended for U.S. registration of POSIDUR and, commencing April 1, 2010, Nycomed will have sole funding responsibility for all clinical trials intended for E.U. registration of POSIDUR. The final decision making authority and financial responsibility for the remainder of the development activities, such as the non-clinical and CMC activities, will be jointly managed and funded by us and Nycomed. In addition, we will manufacture and supply the product to Nycomed for commercial sale in the territory licensed to Nycomed. Nycomed will pay us blended royalties on sales in the defined territory of 15-40% depending on annual sales, as well as a manufacturing markup. We retain full commercial rights to POSIDUR in the U.S., Canada, Japan and certain other countries. The agreement will continue in effect until terminated. The agreement provides each party with specified termination rights, including the right of each party to terminate the agreement upon material breach of the agreement by the other party. In addition, Nycomed has the right to terminate the agreement after the expiration of patents covering POSIDUR in all major market countries in the E.U., for adverse product events, and within specified periods after certain clinical trials of POSIDUR. As of December 31, 2009, the cumulative aggregate payments received by us under this agreement were \$34.8 million. In addition, the cumulative aggregate payments paid by us under this agreement to Nycomed were \$6.8 million as of December 31, 2009.

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 commercialization rights to certain products developed under the agreement (including Remoxy) to King. In December 2005, we amended our agreement with Pain

Table of Contents

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 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, 2009, 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, 2009, the cumulative aggregate payments received by us from Pain Therapeutics under this agreement were \$31.2 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, 2009 were \$811,000 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.

In August 2009, we entered into an exclusive long term excipient supply agreement with respect to REMOXY with King. 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 the 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.

Endo Pharmaceuticals Inc. (TRANSDUR-Sufentanil). On March 10, 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

Table of Contents

U.S. and Canada to us effective August 26, 2009. As of December 31, 2009, the cumulative aggregate payments received by us under this agreement were \$21.5 million.

Curaxis Pharmaceutical Corporation (formerly Voyager Pharmaceutical Corporation). In July 2002, we entered into a development and commercialization agreement with Voyager Pharmaceutical Corporation (now Curaxis). Under the terms of the agreement, as amended in January 2007, we have licensed Curaxis world-wide rights to develop a product using our DURIN technology to provide sustained release of leuprolide based on Curaxis' s patented method of treatment of Alzheimer' s disease. The amended agreement also provides Curaxis with the right to commercialize the resulting product on a worldwide basis. We are responsible for preclinical development, product manufacture and other specified tasks. Under the amended agreement, subject to and upon the achievement of predetermined development and regulatory milestones, we are entitled to receive milestone payments from Curaxis of up to \$3.0 million in the aggregate. As of December 31, 2009, we had received \$500,000 in cumulative milestone payments. We are also entitled to receive reimbursement for any research and development work we perform. If Memryte is commercialized, we will receive royalties based on product sales of between ten to fourteen percent (10-14%) of the net sales of Memryte. In addition, we are entitled to receive ten percent (10%) of any upfront, milestone and other fees received by Curaxis in the event that Memryte is sublicensed to a third party. This agreement can be terminated by either party for material breach by the other party. As of December 31, 2009, the cumulative aggregate payments received by us under this agreement were \$11.6 million. Development of Memryte has been halted pending raising of additional funds by Curaxis.

ALZA Corporation. In April 1998, we entered into a development and commercialization agreement with ALZA, which has been subsequently amended and restated, most recently in October 2002. The agreement provides us with exclusive rights to develop, commercialize and manufacture products using ALZA' s patented DUROS technology in selected fields of use, and obligates us to pay ALZA a royalty on the net sales of our DUROS-based products and a percentage of upfront license fees, milestone payments, or any other payments or consideration received by us with respect to such DUROS-based products. This agreement can be terminated by either party for material breach by the other party and by us without cause.

EpiCept Corporation. In December 2006, we entered into a license agreement with EpiCept Corporation (EpiCept) that provides us with the exclusive, worldwide license to certain of EpiCept' s intellectual property for a transdermal patch containing bupivacaine for the treatment of back pain. In September 2008, the license was converted to an exclusive, worldwide, fully paid up, royalty-free, perpetual and irrevocable license for a transdermal patch containing bupivacaine under all fields of use covered by the EpiCept intellectual property. In consideration of the license, we paid EpiCept a cumulative amount of \$3.25 million in full satisfaction of all future payment obligations to EpiCept under the license agreement.

NeuroSystec Corporation. In May 2004, we entered into an exclusive license agreement with NeuroSystec Corporation (NeuroSystec), a privately-held corporation founded by Alfred E. Mann, under which we granted to NeuroSystec exclusive worldwide rights to develop and commercialize products designed for the treatment of tinnitus and to improve post-operative recovery and tolerance of surgical implantation of cochlear devices using specified DURECT proprietary drug treatment methods and drug delivery technologies to deliver precise doses of appropriate medications directly to the middle or inner ear. The first development product is currently in early clinical development. We are responsible for formulation development of products utilizing our drug delivery platforms and manufacture and supply of product components consisting of our drug delivery platforms. We will receive certain milestone payments if certain development and commercialization milestones are achieved, as well as royalties based on product sales if products are commercialized under the agreement. This agreement will remain in effect until the expiration of NeuroSystec' s royalty obligations under the agreement, which will occur when the last of our related patent rights expire or are found to be invalid, unless the agreement is otherwise terminated earlier. This agreement can be terminated by either party for material breach by the other party and by NeuroSystec without cause. In connection with the agreement, we received a minority equity ownership interest in NeuroSystec.

Table of Contents

Commercial Businesses

ALZET®

We currently make and sell the ALZET product line on a worldwide basis. We market the ALZET product line through a direct sales force in the U.S. and through a network of distributors outside the U.S.

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 11,000 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 Pelham, 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. However, our goal is to become a specialty pharmaceutical company that commercializes its own products with significant market potential. To that end, we intend, over the course of a few years, to build up commercial, sales and marketing capability and other required infrastructure in focused specialty areas, although there can be no assurance that we will be able to do so. 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 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 product line through a direct sales force in the U.S. and through a network of distributors outside of the U.S. We market and sell our LACTEL product line through a direct sales force.

Suppliers

We purchase sucrose acetate isobutyrate, a raw material for our ORADUR and SABER-based pharmaceutical systems, including POSIDUR, Remoxy and other ORADUR-based opioid drug candidates licensed to Pain Therapeutics, 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

Table of Contents

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 (King). Until such time that we are able to bring our pharmaceutical systems to market, if at all, we expect this trend to continue. We also receive revenue from collaborative research and development arrangements with our third-party collaborators. In 2009, King accounted for 41% of our total revenues and no other customers accounted for more than 10% of total revenues. In 2008, revenues from our collaborative agreements with Pain Therapeutics, Endo, Alpharma, and Nycomed represented 24%, 15%, 13% and 11% of our total revenues, respectively. In 2007, revenues from our collaborative agreements with Nycomed, Pain Therapeutics, and Endo represented 36%, 16% and 16% of our total revenues, respectively.

At December 31, 2009, Nycomed and King accounted for 39% and 11% of our net accounts receivable, respectively. At December 31, 2008, Nycomed and Alpharma accounted for 31% and 29% of our net accounts receivable, respectively. At December 31, 2007, Pain Therapeutics, Nycomed and Endo accounted for 36%, 19% and 16% of our net accounts receivable, respectively.

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 Cupertino, CA that we have used to manufacture research and clinical supplies of several of our pharmaceutical systems under GMP, including POSIDUR, Remoxy, TRANSDUR-Sufentanil, ELADUR, and Memryte. In the future, we intend to develop additional manufacturing capabilities for our pharmaceutical systems and components to meet our demands and

Table of Contents

those of our third party collaborators by contracting with third party manufacturers and by construction of additional manufacturing space at our current facilities in Cupertino, CA, Vacaville, CA and Pelham, AL. We manufacture our ALZET product line and certain key components for Remoxy at our Vacaville, CA facility and our LACTEL product line at our Pelham, AL 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. In the fourth quarter of 2007 and first quarter of 2008, in two separate tranches, we acquired from a third party a portfolio of worldwide patents relating to drug delivery technologies. This portfolio consists of approximately 22 issued and pending U.S. patents and patent applications as well as their international counterparts. We believe this portfolio will benefit our business by broadening our drug delivery technology base and strengthening our intellectual property position. As of February 26, 2010, we held 58 issued U.S. patents and 371 issued foreign patents (which include granted European patent rights that have been validated in various EU member states). In addition, we have 90 pending U.S. patent applications and have filed 107 patent applications under the Patent Cooperation Treaty, from which 532 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 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

Table of Contents

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.

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

Table of Contents

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.

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

Table of Contents

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.

According to the FDA, opioid drugs have benefit when used properly and are a necessary component of pain management for certain patients. Opioid drugs have serious risks when used improperly. The FDA, drug manufacturers, and others have taken a number of steps in the past to prevent misuse, abuse and accidental

Table of Contents

overdose of these drugs, including providing additional warnings in product labeling, implementing risk management plans, conducting inter-agency collaborations, and issuing direct communications to both prescribers and patients. Despite these efforts, the rates of misuse and abuse, and of accidental overdose of opioids, have risen over the past decade. The FDA believes that establishing a REMS for opioids will reduce these risks, while still ensuring that patients with legitimate need for these drugs will continue to have appropriate access.

According to the FDA, it recognizes the need to achieve balance between appropriate access and risk mitigation, and believes an effective strategy would benefit from input from industry, patient advocacy groups, the pain and addiction treatment communities, the general public, and other stakeholders. In the first of a series of meetings with stakeholders, the FDA invited those companies that market the affected opioid drugs to a meeting with the agency on March 3, 2009 to discuss REMS development. Additional steps will include discussions with other federal agencies and non-government institutions, including patient and consumer advocates, representatives of the pain and addiction treatment communities, other health care professionals, and other interested parties. The FDA also held a public meeting on May 27 and 28, 2009 to allow for broader public input and participation. On December 4, 2009, FDA held a public meeting with the drug company sponsors to hear from them about the status of the development of a proposed REMS and their views regarding the specific features of the REMS. Through this process, FDA hopes to gain valuable information that will lead to practical and effective solutions for development of a REMS and for appropriate use of these opioid drug products.

Many of our drug candidates including Remoxy, our other ORADUR-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, Remoxy and the other ORADUR- based opioid drug candidates licensed to Pain Therapeutics, if approved, will compete with currently marketed oral opioids, transdermal opioids, local anesthetic patches, and 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, King, Knoll, Janssen, Medtronic, Endo, AstraZeneca, Arrow International, Tricumed, I-Flow 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, NeurogesX, Alexza, I-Flow (Kimberly-Clark), Javelin

Table of Contents

Pharmaceuticals, Cadence Pharmaceuticals, 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.

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 2 Results Way, 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 26, 2010 we had 127 employees, including 77 in research and development, 22 in manufacturing and 28 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 26, 2010 are as follows:

Name	Age	Position
Felix Theeuwes, D.Sc.	72	Chairman, Chief Scientific Officer and Director
James E. Brown, D.V.M.	53	President, Chief Executive Officer and Director
Matthew J. Hogan, M.B.A.	50	Chief Financial Officer
Joseph Stauffer, D.O., M.B.A.	43	Chief Medical Officer and Executive Vice President, Corporate Strategy
Jean I Liu, J.D., M.S.	41	Senior Vice President, General Counsel and Secretary
Paula Mendenhall, Pharm.D.	66	Executive Vice President, Operations and Administration
Su Il Yum, Ph.D.	70	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.

Table of Contents

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 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.

Joseph Stauffer, D.O., M.B.A. joined DURECT in June 2009 as Chief Medical Officer and Executive Vice President, Corporate Strategy. Prior to joining DURECT, Dr. Stauffer was at Alpharma Inc. from 2004 to 2009, where his latest position was as Chief Medical Officer and Senior Vice President of Clinical Research & Medical Affairs. Prior to joining Alpharma, Dr. Stauffer was employed at Abbott Laboratories from 2002 to 2004 as Global Medical Director. Prior to Abbott, he worked at the FDA from 2000 to 2002 as a Medical Review Officer in the Analgesic Division of the Center for Drug Evaluation and Research. Dr. Stauffer is a founding member of the Initiative on Methods, Measurement and Pain Assessment in Clinical Trials (IMMPACT). This on-going collaboration between pharma, FDA, NIH, academia and patient advocacy groups helps to develop core domains and outcomes for chronic pain clinical trials. Dr. Stauffer graduated from the Philadelphia College of Osteopathic Medicine and completed residency training in Anesthesiology at the Johns Hopkins University Hospital, where he is currently an Adjunct Assistant Professor in the Department of Anesthesiology and Critical Care Medicine. Dr. Stauffer is a veteran of the U.S. Navy, honorably discharged as a Lieutenant Commander after serving eight years as a Naval Medical Officer. He completed his MBA in September 2009 as part of the TRIUM Global Executive MBA Program, a joint degree granted by NYU Stern School of Business, HEC School of Management (Paris) and the London School of Economics and Political Science.

Jean I Liu, J.D., M.S. has served as our Senior Vice President and General Counsel since February 2003. She was appointed Secretary of the corporation in March 2004. She served as our Vice President of Legal and General Counsel from February 1999 to February 2003. Previously, from October 1998, Ms. Liu served as our Vice President of Legal. Prior to that, Ms. Liu worked as an attorney at Venture Law Group, a law firm, from May 1997 to October 1998. Ms. Liu worked as an attorney at Pillsbury Madison & Sutro LLP, a law firm, from September 1993 to May 1997. Ms. Liu holds a B.S. in Cellular & Molecular Biology from University of Michigan, an M.S. in Biology from Stanford University and a J.D. from Columbia University School of Law. Ms. Liu is a member of the State Bar of California and is admitted to practice before the USPTO.

Paula Mendenhall, Pharm.D. has served as our Executive Vice President of Operations and Administration since January 2007 and as Senior Vice President of Operations since January 2005. Prior to joining DURECT, Dr. Mendenhall was an independent consultant for various pharmaceutical companies for in-house and outsourcing of pharmaceutical manufacturing, including development of manufacturing strategies and plans and development and training of personnel. From 1997 to 2000, Dr. Mendenhall served as Vice President, Group Vice President and President of Oread Pharmaceutical Manufacturing at Oread Inc. From 1979 to 1997, Dr. Mendenhall served in a variety of roles for Hoffmann-La Roche Inc./Syntex, including in the areas of manufacturing, quality assurance, finance, planning and facilities, as well as provided technical assistance and support to Syntex Global Operations for marketed products and new product launches. Dr. Mendenhall received

Table of Contents

a Pharm D. degree from the University of California, San Francisco, and is a member of the American Association of Pharmaceutical Scientists (AAPS) and the Parenteral Drugs Association.

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 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

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

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 selected the drug dosages nor finalized the formulation or the system design of POSIDUR, TRANSDUR-Sufentanil, ELADUR, our ORADUR-based drug candidates other than Remoxy, 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

Table of Contents

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, Remoxy and our ORADUR-based drug candidates other than Remoxy, 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 conduct and satisfactorily complete required laboratory performance and safety testing, animal studies and clinical trials for our pharmaceutical systems before they can be sold

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 2007, Pain Therapeutics and King reported positive results from the pivotal Phase III trial submitted under an approved Special Protocol Assessment (SPA) with the FDA; the NDA was submitted to the FDA in June 2008, and in August 2008, the NDA was accepted by the FDA 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 had not requested or recommended additional clinical efficacy studies prior to approval. In March 2009, King assumed the responsibility for further development of Remoxy from Pain Therapeutics. In July 2009, King met with the FDA to discuss the Complete Response Letter for Remoxy. 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 recently announced that it has undertaken a likeability study and a pharmacokinetic trial in volunteers and plans to resubmit the NDA in the fourth quarter of 2010. There can be no assurance that any resubmission of the NDA by King will be timely or sufficient to gain approval of Remoxy.

POSIDUR A successful Phase IIb clinical trial in hernia surgery was completed and an end-of-Phase II meeting has been held with the FDA. In 2009, we completed a successful Phase IIb clinical study in 60 shoulder surgery patients, and Nycomed is conducting Phase IIb studies in hysterectomy patients and shoulder surgery patients. These trials are being conducted by Nycomed in a different manner than U.S. studies and are designed to be suitable for European regulatory approval purposes. In January 2010, we announced that we had commenced BESST (Bupivacaine Effectiveness and Safety in SABER Trial), which is intended to be the pivotal Phase III clinical trial in the U.S. BESST is an international, multi-center, randomized, double-blind, controlled trial evaluating the safety, efficacy, effectiveness, and pharmacokinetics of POSIDUR in approximately 300 patients undergoing a variety of general abdominal surgical procedures. There can be no assurance that these trials will be successful. Furthermore, there can be no assurance that our planned development program for POSIDUR will generate data and information that will be deemed sufficient for marketing approval by the FDA or other regulatory agencies.

TRANSDUR-Sufentanil Patch Our license agreement with Endo to develop and commercialize TRANSDUR-Sufentanil in the U.S. and Canada was terminated effective August 26, 2009. Prior to the termination of the license agreement, Endo successfully completed a Phase II program for TRANSDUR-Sufentanil in which they evaluated the conversion of patients on oral and transdermal

Table of Contents

opioids to TRANSDUR-Sufentanil. The most recent Phase II study 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 detailed proposed protocols for Phase III were reviewed with the FDA at an end-of-Phase II meeting on February 19, 2009. As a result of that meeting, we believe we understand the anticipated regulatory pathway for the Phase III program and approval, which will follow a 505(b)2 pathway as discussed with FDA. This pathway would allow us to reference third-party data, potentially reducing time and expense. 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 was completed and positive results were reported in the fourth quarter of 2007. In 2008, we conducted manufacturing scale-up and processing activities 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. Effective October 2008, we entered into a development and license agreement with Alpharma, granting it the exclusive worldwide rights to develop and commercialize ELADUR. Alpharma was acquired by King in December 2008 and, as a result, Alpharma's rights and obligations under the agreement have now been assumed by King. Our main activities since December 2008 have involved interacting with the King team on details associated with next steps in the clinical program, which King expects to initiate in the first half of 2010. There can be no assurance that King will be able to successfully develop ELADUR 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 the data required for regulatory approval. We and our collaborators may not be permitted to begin or continue our planned clinical trials for our potential pharmaceutical systems. If our trials are permitted, our potential pharmaceutical systems may not prove to be safe or produce their intended effects. In addition, we or our collaborators may be required by regulatory agencies to conduct additional animal or human studies regarding the safety and efficacy of our pharmaceutical systems which we have not planned or anticipated. For example, according to Pain Therapeutics, the FDA has indicated that additional non-clinical data will be required prior to regulatory approval for Remoxy. This additional data could delay commercialization of Remoxy and harm our business and financial condition.

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

Table of Contents

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 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 data which may cause lengthy delays and increased costs to our programs.

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

Table of Contents

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 and TRANSDUR-Sufentanil are subject to mandatory Risk Evaluation and Mitigation Strategy (REMS) programs, a new requirement by the FDA, 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. 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.

According to the FDA, opioid drugs have benefit when used properly and are a necessary component of pain management for certain patients. Opioid drugs have serious risks when used improperly. The FDA, drug manufacturers, and others have taken a number of steps in the past to prevent misuse, abuse and accidental overdose of these drugs, including providing additional warnings in product labeling, implementing risk management plans, conducting inter-agency collaborations, and issuing direct communications to both prescribers and patients. Despite these efforts, the rates of misuse and abuse, and of accidental overdose of opioids, have risen over the past decade. The FDA believes that establishing a REMS for opioids will reduce these risks, while still ensuring that patients with legitimate need for these drugs will continue to have appropriate access.

According to the FDA, it recognizes the need to achieve balance between appropriate access and risk mitigation, and believes an effective strategy would benefit from input from industry, patient advocacy groups, the pain and addiction treatment communities, the general public, and other stakeholders. In the first of a series of meetings with stakeholders, the FDA invited those companies that market the affected opioid drugs to a meeting with the agency on March 3, 2009 to discuss REMS development. Additional steps will include discussions with other federal agencies and non-government institutions, including patient and consumer advocates, representatives of the pain and addiction treatment communities, other health care professionals, and other interested parties. The FDA also held a public meeting on May 27 and 28, 2009 to allow for broader public input and participation. On December 4, 2009, FDA held a public meeting with the drug company sponsors to hear from them about the status of the development of a proposed REMS and their views regarding the specific features of the REMS. Through this process, the FDA hopes to gain valuable information that will lead to practical and effective solutions for development of a REMS and for appropriate use of these opioid drug products.

Many of our drug candidates including Remoxy, our other ORADUR-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.

Table of Contents

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, Nycomed, Alparma (acquired by King), Orient Pharma 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 and other product candidates, respectively, 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. They 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

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 with respect to Remoxy and other ORADUR-based products incorporating specified opioids, Nycomed with respect to POSIDUR, Alparma (acquired by King) with respect to ELADUR and Orient Pharma with respect to ORADUR-ADHD, 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.

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

Table of Contents

Our near-term 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 clinical trial developments, regulatory approvals or sales accomplishments. To the extent third-party collaborators do not achieve such 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 type 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.

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.

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:

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;

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

Table of Contents

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.

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. Except with respect to Remoxy, we and our third-party collaborators, where relevant, have not yet completed development of the manufacturing process for any pharmaceutical systems or components including POSIDUR, TRANSDUR-Sufentanil, ELADUR, and other ORADUR-based drug candidates. 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 under good manufacturing practices (GMP), including POSIDUR, TRANSDUR-Sufentanil, ELADUR, Remoxy and other ORADUR-based drug candidates. 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 current facilities in Cupertino, CA, Vacaville, CA and Pelham, AL. We have limited experience building and validating manufacturing facilities, and we may not be able to accomplish these tasks in a timely manner.

Table of Contents

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 tes