DURECT CORP
Form 10-K
March 16, 2006
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UNITED STATES

SECURITIES AND EXCHANGE COMMISSION

Washington, D.C. 20549

Form 10-K

(Mark One)

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

For the fiscal year ended December 31, 2005

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
(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

(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 x

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 x

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 x 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. x

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

Large accelerated filer ¨	Accelerated filer x	Non-accelerated filer ¨

Indicate by check mark whether the registrant is a shell company (as defined in Rule 12b-2 of the Act). YES ¨ NO x

The aggregate market value of the voting stock held by non-affiliates of the registrant was approximately $207,087,561 as of June 30, 2005 based upon the closing sale price on the Nasdaq National 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 61,954,889 shares of the registrant s Common Stock issued and outstanding as of February 28, 2006.

DOCUMENTS INCORPORATED BY REFERENCE

Part III incorporates information by reference from the definitive Proxy Statement for the 2006 annual meeting of stockholders, which is expected to be filed not later than 120 days after the Registrant s fiscal year ended December 31, 2005.

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DURECT CORPORATION

ANNUAL REPORT ON FORM 10-K

FOR THE FISCAL YEAR ENDED DECEMBER 31, 2005

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PART I

Item 1. Business.

Overview

We are an emerging specialty pharmaceutical company focused on the development of pharmaceutical products based on proprietary drug delivery technology platforms. We are developing and commercializing pharmaceutical systems that will deliver the right drug to the right place in the right amount at the right time to treat chronic or episodic diseases and conditions. By integrating chemistry and engineering advancements, we can achieve what drugs or devices alone cannot. Our pharmaceutical systems enable optimized therapy for a given disease or patient population by controlling the rate and duration of drug administration. Our proprietary drug delivery technology platforms include:

- SABER Delivery System a patented and versatile depot injectable useful for protein and small molecule delivery that can be formulated for systemic or local administration. The advantages of SABER may include reduced side effects, longer duration and smaller injection volume. Our first application is for controlled delivery of bupivacaine for post-operative pain relief (SABER-Bupivacaine), for which we own all worldwide rights. SABER-Bupivacaine is currently in Phase II clinical trials.

- ORADUR an oral sustained release gel-cap technology. We believe that ORADUR can transform short-acting oral capsule forms into oral sustained release technology products with the added benefit of being less prone to abuse. Our first application is Remoxy , a novel long-acting, abuse deterrent oral formulation of the opioid oxycodone, for which we have licensed worldwide rights to Pain Therapeutics, Inc. (Pain Therapeutics), which has in turn sublicensed the commercialization rights to King Pharmaceuticals, Inc. (King). Remoxy is currently in Phase III clinical trials. King and Pain Therapeutics have announced that they will commence a pivotal Phase III clinical trial in the first half of 2006.

- TRANSDUR Delivery System a proprietary transdermal patch technology. The advantages of TRANSDUR may include less potential for abuse, longer use per patch and smaller patch size. Our first application is for a transdermal sufentanil patch (TRANSDUR-Sufentanil) which we have licensed to Endo Pharmaceuticals for the U.S. and Canada. TRANSDUR-Sufentanil is currently in Phase II clinical trials.

- DURIN Biodegradable Implant a proprietary biodegradable drug-loaded implant that is absorbed into the body. DURIN enables parenteral (injectable) delivery over a period of weeks or months of both large and small molecules using our proprietary polymers. The advantages of DURIN may include small size, longer duration and constant rate of delivery. Our first application is Memryte, a novel long-acting potential therapy for the treatment of Alzheimer s disease using leuprolide, for which we have licensed worldwide rights to Voyager Pharmaceutical Corporation. Memryte is currently in Phase III clinical trials.

- DUROS® System an osmotic implant technology licensed to us for specified fields from ALZA Corporation, a Johnson & Johnson Company. DUROS is a miniature drug-dispensing subcutaneous pump which can be as small as a matchstick that can be used for therapies requiring systemic or site-specific administration of drug. The advantages of DUROS may include precise constant drug delivery of potent molecules. Our first application is CHRONOGESIC, designed to deliver sufentanil for a period of three months for treatment of chronic pain, which we have licensed to Endo Pharmaceuticals for the U.S. and Canada. CHRONOGESIC completed a pilot Phase III clinical trial. Clinical trials have been suspended pending system redesign.

- MICRODUR Biodegradable Microparticulates a microsphere injectable system.

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

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Our pharmaceutical systems combine engineering with proprietary small molecule pharmaceutical and biotechnology drug formulation 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 target the delivery of the drug to its intended site of action, allowing our pharmaceutical systems to meet the special challenges associated with treating medical conditions over an extended period of time. Our pharmaceutical systems can enable new drug therapies or optimize existing therapies based on a broad range of compounds, including small molecule pharmaceuticals as well as biotechnology molecules 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 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.

In addition to developing our own proprietary products, we also collaborate with pharmaceutical companies to develop and commercialize proprietary and enhanced pharmaceutical products based on our technologies.

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, or CNS, disorders, cardiovascular disease and other chronic diseases. Our ongoing product research and development efforts in these areas are set forth in the following table:

Disease/Indication	Product	Collaborator	Technology Platform	Stage
Post Operative Pain	Controlled Release Injection of Local Anesthetic (SABER-Bupivacaine)	DURECT retains worldwide rights	SABER	Phase II
Chronic Pain	Transdermal sufentanil (TRANSDUR-Sufentanil)	Endo (U.S. & Canada)	TRANSDUR	Phase II
Chronic Pain	Oral controlled release oxycodone (Remoxy)	King/ Pain Therapeutics	ORADUR	Phase III
Alzheimer s Disease	Controlled Release Leuprolide Implant (Memryte)	Voyager	DURIN	Phase III
Chronic Pain	Systemic sufentanil (CHRONOGESIC)	Endo (U.S. & Canada)	DUROS	System redesign
Central Nervous System Disorders	Various	DURECT retains worldwide rights	SABER/DUROS/DURIN	Preclinical/Research Stages
Cardiovascular Disorders	Various	DURECT retains worldwide rights	SABER/DUROS/DURIN	Preclinical/Research Stage

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Local Post-Operative Pain

Market Opportunity. According to data published by the Center for Disease Control and Prevention, there are over 72 million ambulatory and inpatient procedures performed in the United States. We believe that more than 60% of patients who undergo surgery experience moderate to extreme post-operative pain. 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 such as drowsiness, constipation, cognitive impairment and other possible side effects. Effective pain management can be compromised if patients fail to adhere to recommended dosing regimens because they are sleeping or disoriented. We believe that the majority of post-surgical pain can be localized to the surgical site. Post-surgical pain can be treated effectively with local anesthetics; however, the usefulness of these current conventional medications is limited by their short duration of action.

Development Strategy. We are developing SABER-Bupivacaine, a sustained-release formulation of bupivacaine, a local anesthetic, using our SABER delivery system for the treatment of post-surgical pain. The physician would administer SABER-Bupivacaine at the time of surgery. Placed in the tissues immediately adjacent 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, and hence minimal side effects. SABER-Bupivacaine is intended to provide local analgesia of 3 days or more, which we believe coincides with the time period of greatest need for post-surgical pain control in most patients. We retain the full commercialization rights to SABER-Bupivacaine.

Clinical Program. We are currently conducting Phase II dose escalation trials in Australia and the United Kingdom designed for dose optimization of SABER-Bupivacaine. The Australian trial includes three cohorts, and the United Kingdom trial has two cohorts. Each trial will evaluate safety, pharmacokinetics and efficacy. We have completed dosing and analysis of all three cohorts in the Australian Phase II clinical trial, consisting of an aggregate of 81 patients, and we have announced positive preliminary results from this trial. Enrollment in the United Kingdom trial is ongoing.

The following summarizes the preliminary data from the Australian Phase II study as of December 2005:

Six patients were enrolled in cohort 1, fifteen patients were enrolled in cohort 2 and sixty patients in cohort 3.

Preliminary data indicate that all primary endpoints for the study were achieved, which include:

- Pharmacokinetic Evaluation of plasma bupivacaine concentrations showed that SABER-Bupivacaine achieved its target delivery profile of providing a delivery duration of over 72 hours with no burst upon injection.

- Safety No significant clinical adverse events or local or systemic toxicity were observed, and the injections were well tolerated by the patients.

- Established dose range for the product.

Other Preliminary Observations (Cohort 2 and Cohort 3, N=75)

- Using a standardized pain evaluation methodology that has been recognized by regulatory authorities to measure pain relief, patients treated with SABER-Bupivacaine reported a trend for better overall mean pain relief over the four days following treatment compared with patients treated with commercial bupivacaine (control).

- The SABER-Bupivacaine group had less pain intensity and required less supplemental opioid analgesics over the four days following treatment as compared to the control group.

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- The total numbers of doses of supplemental medication (opiate and non-opiate) were approximately the same in both the treatment and control groups; however, the SABER-Bupivacaine group utilized fifty percent (50%) less supplemental opioid medication for post-operative pain over the four days following treatment compared with the control group.

In the first quarter of 2006, the FDA accepted our Investigational New Drug (IND) application for SABER-Bupivacaine. In 2006, we intend to initiate additional Phase II studies in the U.S. for soft tissue and orthopedic surgical procedures, as well as continue our clinical studies outside of the U.S. We intend to initiate the Phase III clinical program in the second half of 2006.

Chronic Pain (Systemic)

Market Opportunity. Chronic pain, defined as lasting six months or longer, 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 34 million Americans annually. Worldwide opioid sales to treat chronic pain exceeded approximately $3.9 billion in 2004, of which OxyContin®, a brand name narcotic painkiller, and Duragesic®, a leading transdermal opioid product, accounted for approximately $1.8 billion and $2.1 billion in sales, respectively.

Development Strategy. We are developing several products for the chronic pain market:

- TRANSDUR-sufentanil, our proprietary transdermal patch licensed to Endo Pharmaceuticals (Endo) in the U.S. and Canada that is intended to provide sufentanil for a period of seven days from a single application;

- ORADUR-based oral sustained release, abuse deterrent opioid products, including Remoxy, licensed to Pain Therapeutics, which has in turn sublicensed the commercialization rights of these products to King; and

- CHRONOGESIC, a subcutaneous, implantable DUROS-based system licensed to Endo Pharmaceuticals in the U.S. and Canada that delivers sufentanil systemically at a constant rate for three months.

TRANSDUR-Sufentanil Patch

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 three days of relief provided by currently available opioid patches. Sufentanil is an off-patent, highly potent opioid that is currently used in hospitals as an analgesic. 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. Worldwide sales for Duragesic®, a leading transdermal fentanyl product, exceeded $2.1 billion in 2004.

In March 2005, we entered into an agreement with Endo granting Endo exclusive rights to develop, market and commercialize TRANSDUR-Sufentanil in the U.S. and Canada. We have received an initial payment of $10 million, and we will receive up to $35 million in

additional milestone payments if specified development and commercialization milestones are achieved. If commercialized, we will also receive royalties based on the sale of TRANSDUR-Sufentanil in the U.S. and Canada. We have also retained limited co-promotion rights to TRANSDUR-Sufentanil in the U.S. and Canada and full commercialization rights in the rest of the world. We continued to perform development activities for Endo with respect to TRANSDUR-Sufentanil throughout 2005.

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Clinical Program. In October 2004, we initiated a Phase I clinical trial for TRANSDUR-Sufentanil, consisting of a pharmacokinetic study in normal, healthy volunteers in Europe. The objectives of the clinical study were to determine the safety and tolerability of TRANSDUR-Sufentanil as well as to evaluate the pharmacokinetics of sufentanil following administration of TRANSDUR-Sufentanil. The study evaluated 24 subjects using TRANSDUR-Sufentanil. No clinically significant adverse events were reported. Some slight to moderate redness at patch site was observed by patients in the trial. Other results from the Phase I trial were as follows:

- the preliminary pharmacokinetics showed a rapid onset of the drug and the targeted plasma level over a 7-day period was achieved, and
- the clinical patches performed as designed.

We commenced the first clinical trial of the Phase II program for TRANSDUR-Sufentanil in February 2005. The clinical trial was an open-label study that was designed to evaluate the transition of chronic pain patients from Duragesic® (commercial fentanyl patch) to the TRANSDUR-Sufentanil patch. The clinical study also evaluated the pharmacokinetics and safety of repetitive applications of TRANSDUR-Sufentanil in patients for a period of up to four weeks. The clinical trial was conducted at two clinical sites (one in the United States and the other in Europe) and enrolled 13 adult patients in the primary study with malignant or non-malignant chronic pain. In December 2005, we announced positive preliminary results from this trial as follows:

Preliminary data indicate that all primary endpoints for the clinical trial were achieved, which include:

- Pharmacokinetic Evaluation of plasma level data indicate that TRANSDUR-Sufentanil performed as designed by achieving its target delivery profile of providing a rapid onset of drug and a delivery duration of over seven days. Targeted plasma levels over the consecutive four-week period (repetitive applications of TRANSDUR-Sufentanil) were achieved as intended.
- Safety The product was tolerated well with no apparent safety issues over the four-week treatment period.

Preliminary Efficacy Observations:

As this was an open label study, conclusions on efficacy cannot be drawn; on average, pain levels remained stable after the transition to TRANSDUR-Sufentanil.

Endo intends to conduct additional development activities, including clinical studies of TRANSDUR-Sufentanil in 2006.

ORADUR-Opioid Products In Development

Remoxy (ORADUR-Oxycodone)

Remoxy is an oral, long-acting oxycodone gelatin capsule under development with Pain Therapeutics, to which we have licensed exclusive, worldwide, development and commercialization rights under a development and license agreement entered into in December 2002. Pain Therapeutics has in turn sublicensed the commercialization rights of Remoxy to King. 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 narcotic painkiller with annual sales exceeding $1.8 billion in 2004. We will receive payments if certain development and regulatory milestones are achieved. We also receive reimbursement for our research and development efforts on Remoxy and a manufacturing profit on our supply of key product excipients to Pain Therapeutics for use in Remoxy. In addition, if Remoxy is commercialized, we will receive royalties for Remoxy of between 6.0% to 11.5% of net sales depending the sales volumes.

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Clinical Program. Pain Therapeutics began the first Phase III clinical trial for Remoxy in December 2004 and in September 2005 announced positive results from this trial. Pain Therapeutics reported the following with respect to the trial:

- The study consisted of a randomized, double-blinded study designed to compare the safety and efficacy of Remoxy against placebo in osteoarthritic patients with moderate-to-severe chronic pain. Over 209 patients were enrolled in over 20 U.S. clinical sites. Patients were treated with Remoxy 20 mg or matching placebo twice daily over a four-week study period.

- The results demonstrated a statistically significant percent decrease in pain scores for patients using Remoxy as compared to placebo, as measured by a standard Likert Pain Scale. Patients also reported a statistically significant difference in quality of life using Remoxy as compared to placebo, as measured by as measured by a standard SF-12 Health Survey and in patients self-reported Quality of Analgesia. No drug-related safety issues were noted in the study. As expected, opioid-related adverse events (including nausea/vomiting, dizziness, pruritis (itching) and somnolence/sedation) and drop-out rates were higher in the Remoxy arm compared to placebo.

In February 2006, Pain Therapeutics and its commercialization sublicensee King reported that Remoxy had successfully completed a Special Protocol Assessment (SPA) with the FDA and that the parties were commencing a pivotal Phase III trial on Remoxy in 400 patients with severe chronic pain. According to Pain Therapeutics and King, under the terms of the SPA for Remoxy, one pivotal Phase III trial is required to file a New Drug Application. The randomized, double-blinded, placebo-controlled, multi-center pivotal trial will enroll 400 patients with moderate-to-severe osteoarthritic pain in multiple U.S. clinical sites. Following a titration period, patients will be randomized to either Remoxy (10-80 mg daily) or placebo for 12 weeks. The primary endpoint is reduction in pain scores over three months compared to baseline. King and Pain Therapeutics have announced that patient accrual is expected to begin shortly and continue through end of 2006.

Additional ORADUR- Opioid Products in Development

King and Pain Therapeutics have announced their intention to initiate Phase I clinical testing for the second ORADUR-based abuse deterrent sustained release oral formulation of an undisclosed opioid during the second half of 2006.

CHRONOGESIC

CHRONOGESIC, based on the DUROS technology, is intended for patients with chronic pain that is stable and opioid responsive and results from a variety of causes. CHRONOGESIC consists of a small titanium pump, about the size of a match stick, which is implanted under the skin of a patient in a simple out-patient procedure. Once implanted, CHRONOGESIC is designed to deliver sufentanil for period of up to three months from a single application. If approved for marketing and sale, CHRONOGESIC will provide an alternative to current therapies for the treatment of chronic pain such as pills and patches, as well as providing the potential advantages of physician controlled dosing, improved patient compliance and convenience and reduced potential for opioid abuse. We intend to develop a family of dosage strengths, tailored to meet market needs. CHRONOGESIC is being developed for the U.S. and Canadian markets in collaboration with Endo Pharmaceutics, to which we have granted exclusive commercialization rights pursuant to a development, commercialization and supply license agreement entered into effective November 2002. We will receive from Endo milestone payments if specified development milestones are achieved, and, if commercialized, we will receive royalties based on sale of CHRONOGESIC in the U.S. and Canada.

Clinical Program. We have completed an initial Phase I clinical trial, a Phase II clinical trial, a pilot Phase III clinical trial and a pharmacokinetic trial for CHRONOGESIC. In September 2001, DURECT presented data from a Phase II trial that enrolled 66 patients

experiencing chronic pain due to failed back surgery, cancer and other malignant and non-malignant causes. Patients were transitioned from their pre-study opioid medication to a six-week period of CHRONOGESIC therapy. In a post-study survey, 60% of patients indicated a preference

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for CHRONOGESIC over their pre-study medication and 35% of patients preferred their previous medication (5% of patients indicated no preference). CHRONOGESIC also demonstrated improvements in select side effects when compared to pre-study medication. In an 18 patient pilot Phase III study, the results of which were presented in March 2002, patients were successfully converted from the Duragesic® product, a 3-day transdermal fentanyl patch, to CHRONOGESIC without observing clinically-relevant side effects or adverse events.

In August 2002, the FDA requested that we delay enrolling new patients in our Phase III clinical trial initiated in June 2002 until the clinical trial protocol is revised and approved by the FDA to provide for additional patient monitoring and data collection. These requested protocol changes were not in response to any observed patient safety or adverse event. We subsequently discontinued all patients from the clinical trial at our discretion in September 2002. Independently from the FDA s request for protocol changes, in October 2002, we started to implement manufacturing process enhancements to the CHRONOGESIC product to permit terminal sterilization of the product and system design enhancements to prevent a premature shutdown in the delivery of drug prior to the end of the intended three-month delivery period which was observed in a small fraction of units utilizing the previous system design. We are presently working to redesign the delivery system to address performance problems. We have stopped all clinical testing of CHRONOGESIC and will not resume clinical testing until the system design is completed.

Alzheimer s Disease

Market Opportunity. Alzheimer s disease is a progressive, degenerative and ultimately terminal brain disorder that gradually destroys a person s memory and ability to learn, reason, make judgments, communicate and carry out daily activities. There is currently no treatment that stops or materially slows the progression of Alzheimer s disease. As a result, it is one of the world s largest unmet medical needs. The global market for currently available Alzheimer s disease drugs is growing rapidly and was over $3 billion in 2004. The American Health Assistance Foundation estimates that approximately 18 million people worldwide, including approximately 4.5 million people in the United States, suffer from Alzheimer s disease.

Development Strategy. We are developing Memryte for the treatment of Alzheimer s disease in collaboration with Voyager, to which we have licensed exclusive, worldwide development and commercialization rights under a development and license agreement entered into in July 2002. Memryte uses our proprietary DURIN technology to provide sustained release of the peptide leuprolide acetate and is based on Voyager s patented method of treatment of Alzheimer s disease. We will receive from Voyager milestone payments if specified development milestones are achieved, and, if commercialized, royalties based on sale of the resulting product anywhere in the world.

Clinical Program. In December 2004, the FDA accepted an IND application and clinical protocol submitted by Voyager for Memryte. The trial consists of a pharmacokinetic study in normal, healthy volunteers, the objectives of which are to determine the safety and tolerability of the DURIN implant, as well as to evaluate the pharmacokinetic profile of the active agent (leuprolide acetate) following administration of the development product. Voyager completed enrollment of the clinical trial in January 2005. Voyager has completed dosing of one Phase I trial for Memryte, has performed one Phase II proof of concept trial using the active pharmaceutical agent for Memryte and has another such trial ongoing. Voyager has announced that the FDA has agreed to Voyager s clinical development plan and indicated that the results from Voyager s clinical trials to date were adequate to initiate Phase III trials. Voyager has initiated dosing for pivotal Phase III clinical studies using Memryte as an adjunctive therapy with acetyl cholinesterase inhibitors (ACIs) for the treatment of mild to moderate Alzheimer s disease. Voyager has stated its intention to complete patient enrollment for the first Phase III clinical study in the second half of 2006.

Central Nervous System Disorders

Market Opportunity. Millions of people suffer from chronic diseases and disorders of the central nervous system (CNS), including brain and spinal cord tumors, chronic pain, psychosis, epilepsy, spasticity, spinal meningitis, Parkinson s disease, and multiple sclerosis.

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We believe that there are over 39,000 new brain tumors diagnosed in the United States every year and approximately 350,000 patients living with primary brain tumors in the U.S., of which, about 170,000 are malignant. Current treatments for CNS tumors include radiation, resection and chemotherapy. Treatment success rates vary by tumor type, but are generally low, and the risk of side effects or disability is high. It is generally recognized that improvements in treating primary metastatic brain tumors are needed, particularly for those which are inoperable.

Schizophrenia, a disease of the brain that manifests itself through multiple signs and symptoms involving thought, perception and behavior, is another CNS disorder estimated to affect about 2.5 million patients in the U.S.; worldwide, the incidence is about 51 million. Patients typically begin exhibiting symptoms early in life and the illness is usually severe and long lasting, requiring lifelong treatment. Adherence to prescribed drug regimens is recognized as a significant treatment obstacle in the schizophrenic population. According to IMS, global sales of antipsychotics increased more than ten-fold following the introduction of the new drugs, from less than $500 million in 1991 to almost $5 billion in 2000. Opportunities exist to apply our pharmaceutical systems for treatment of these and other CNS disorders.

Development Strategy. We are developing our platform technologies for systemic and targeted delivery of drugs to treat select CNS disorders.

We are conducting preclinical research on a SABER-based injectable controlled release product to deliver a potent antipsychotic agent systemically in a controlled fashion, with a goal to deliver medication for 30 days from a single injection. We view our research activities as a proof-of-concept application of our drug delivery technologies to treat CNS disorders. Once we have demonstrated proof-of-concept, our long-term plan is to use our platform technologies with therapeutic agents to develop products for CNS disorders.

Cardiovascular Disease

Market Opportunity. Cardiovascular disease, principally heart disease and stroke, accounts for 41% of all deaths, or 960,000 fatalities, annually in the U.S. The aggregate annual cost of cardiovascular disease in the U.S., including treatment and lost productivity, is estimated at $287 billion.

Ischemic heart disease, one of the major forms of cardiovascular disease, is the leading cause of death worldwide. Existing treatments for ischemia, or insufficient blood flow to the heart muscle, include cardiovascular bypass, angioplasty and the use of cardiovascular stents and similar medical devices. While effective, these treatments are invasive, and ischemia returns in a significant number of patients. There is a need for less invasive and more long lasting treatments for ischemic heart disease.

Development Strategy. In collaboration with the University of Maastricht in The Netherlands, we are working to develop methods for treating ischemic heart disease and other chronic cardiovascular diseases through continuous delivery of drugs to the pericardial sac of the heart, a thin membrane that envelops the heart. To date, our research in animal models suggests that ischemic heart disease may be treated by the induction of new blood vessel growth as a way of regenerating normal blood flow to the heart and thereby restoring function to the diseased heart. Our research data showed that the delivery of a proprietary angiogenic factor directly to the pericardial sac of a test animal resulted in the growth of new blood vessels and increased bloodflow in the heart. Should we choose to develop and commercialize a pharmaceutical system using such proprietary angiogenic factor or other proprietary agent, we may be required to obtain a license to use such agent in our pharmaceutical system. Any required licenses may not be available to us on acceptable terms, if at all. See Risk Factors We may be required to obtain rights to certain drugs.

Other Development Programs

We intend to complete a Phase I clinical study for a new development project during the second half of 2006. DURECT retains full rights to this new development project.

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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 Centers for Disease Control estimates that the major chronic diseases are responsible for approximately 70% of all deaths in the U.S., and medical care costs for these conditions totaled more than $400 billion annually. Currently, more than 60% of total health care spending in the U.S. is devoted to the treatment of chronic diseases. Demographic trends suggest that, as the U.S. population ages, the cost of treating chronic diseases as a proportion of total health care spending 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.

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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 drug itself. However, drug delivery products on the market today can still be improved, for example, by providing reduced abuse potential, targeted delivery to minimize system effects and longer delivery durations where useful. Furthermore, traditional drug delivery products are generally not capable of administering biotechnology agents such as proteins, peptides and genes.

The Medical Device Industry. Advances in the field of medical device technology have dramatically improved device miniaturization and sophistication and allowed minimally invasive surgical access to remote locations within the body. For example, a coronary bypass patient can be treated with a stent in a procedure with a relatively short recovery, rather than with major surgery. Most devices, however, apply only mechanical solutions, rather than delivering chemical or biological agents.

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 at the right time to treat chronic and episodic diseases and conditions. By integrating chemistry and engineering advancements, we can achieve what drugs or devices alone cannot. 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 otherwise would 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 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 one year, without the fluctuations in drug levels 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 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.

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DURECT Pharmaceutical Systems Technology

DURECT s pharmaceutical systems combine technology innovations from the drug delivery and medical device industries with proprietary pharmaceutical and biotechnology drug formulations. These capabilities can enable new drug therapies or optimize existing therapies based on a broad range of compounds, including small molecule pharmaceuticals as well as biotechnology molecules such as proteins, peptides and genes. 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 the drug. When the high viscosity SAIB is formulated with drug, a biocompatible solvent and other additives, the resulting formulation is liquid enough to inject easily with standard syringes and needles. After injection of a SABER formulation, the solvent diffuses away, leaving a viscous depot. Depending on how it is formulated, the SABER system can successfully deliver therapeutic levels of a wide spectrum of drugs from one day to three months from a single injection. Based on research and development work to date, our SABER technology has shown the following advantages:

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

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

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

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

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

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

The SABER Technology is the basis of SABER-Bupivacaine, which is currently in Phase II clinical testing. 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, which is currently in Phase II testing and which we have licensed to Endo in the U.S. and Canada.

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The ORADUR Sustained Release Gel Cap Technology

We are developing ORADUR sustained release oral technology based on our SABER technology. We believe that ORADUR can transform short-acting oral capsule dosage forms into sustained release oral products. Products based on our ORADUR technology (previously referred to as SABER oral gel cap 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. ORADUR-based products can be manufactured by a simple process using conventional methods making them readily scalable. These properties have the potential to make ORADUR-based products an attractive option for pharmaceutical companies that seek to develop abuse resistant 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 currently under Phase III clinical testing by Pain Therapeutics and its commercialization sublicensee, King.

The DURIN Biodegradable Implant Technology

Our DURIN technology is a proprietary biodegradable implant that enables parenteral delivery of drugs from several weeks to six months or more using our Lactel® brand polymers and co-polymers of lactic and glycolic acid. The DURIN technology can deliver a wide variety of drugs including small and large molecule compounds. Our proprietary implant design allows for a variety of possible delivery profiles including constant rate delivery. Because DURIN implants are biodegradable, at the end of its delivery life, what remains of the DURIN implant is absorbed by the body. DURECT is researching and developing products based on the DURIN technology for a variety of chronic disease applications. The DURIN technology is the basis of Memryte for the treatment of Alzheimer s disease currently under Phase III clinical trials by Voyager.

The DUROS Technology

The DUROS system is a miniature drug-dispensing pump made out of titanium which can be as small as a wooden matchstick. We have licensed the DUROS system for specified fields of use from ALZA Corporation, a Johnson & Johnson Company, pursuant to a development and commercialization agreement entered into effective April 1998. The potential of the DUROS technology as a platform for providing drug therapy was demonstrated by the FDA s approval in March 2000 of ALZA s VIADUR® product (leuprolide acetate implant), a once-yearly implant for the palliative treatment of prostate cancer, the first approved product to incorporate the DUROS implant technology. The DUROS system can be used for therapies requiring systemic or site-specific administration of drug. To deliver drugs systemically as in our CHRONOGESIC product, 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. To deliver drug to a specific site, we are developing proprietary miniaturized catheter technology that can be attached to the DUROS system to direct the flow of drug directly to a target organ, tissue or synthetic medical structure, such as a graft. The DUROS system is the basis of CHRONOGESIC under development in collaboration with Endo in the U.S. and Canada. Clinical trials have been suspended pending the redesign of the delivery system to address performance issues.

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 suitable choice of polymers and processing, sustained release from a few days to

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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 manufacture of the polymer raw material to process and product development, scale up and cGMP manufacture.

DURECT Strategy

Our objective is to become a specialty pharmaceutical company by developing and 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. Many of the diseases that present the greatest challenges to medicine are chronic, debilitating diseases such as chronic pain, central nervous system disorders, cardiovascular disorders, cancer and degenerative neurological diseases. Our initial efforts will focus on using our versatile drug delivery platform technologies to develop products that address these diseases.

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.

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 biotechnology products, 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 the need for multiple injections of these drugs. In addition, through the use of our proprietary miniature catheter technology or by 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.

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, diversify our product portfolio and enable us to better manage our operating costs. Additionally, such collaborations enables us to leverage investment by our collaborators and reduce our net cash burn, while retaining significant economic rights.

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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 may still choose to enter into strategic alliances 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 collaboration agreements:

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 products developed under the agreement to King. In December 2005, we amended our agreement with Pain Therapeutics in order to specify our obligations with respect to the supply of key excipients for use in the licensed products. Under the agreement, as amended, we are responsible for formulation development, supply of selected key excipients used in the manufacture of licensed product and other specified tasks. We will receive additional payments if certain development and regulatory milestones are achieved. 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. 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.

Voyager Pharmaceutical Corporation. In July 2002, we entered into a development and commercialization agreement with Voyager. Under the terms of the agreement, we will collaborate with Voyager to develop a product using our DURIN technology to provide sustained release of leuprolide based on Voyager s patented method of treatment of Alzheimer s disease. The agreement also provides Voyager with the right to commercialize the resulting product on a worldwide basis. We are responsible for preclinical development, product manufacture and other specified tasks. We will receive payments if certain development and regulatory milestones are achieved, and receive payments for our research and development efforts. If Memryte is commercialized, we will receive royalties based on product sales. This agreement can be terminated by either party for material breach by the other party and by Voyager without cause.

Endo Pharmaceuticals Inc. (CHRONOGESIC). In November 2002, we entered into a development, commercialization and supply license agreement with Endo under which the companies will collaborate on the development and commercialization of CHRONOGESIC for the U.S. and Canada. The agreement was amended in January 2004, in November 2004 and again in January 2006 to take into account the increase in the CHRONOGESIC development program timeline due to DURECT s implementation of necessary design and manufacturing enhancements. In connection with the execution of the agreement in November 2002, Endo purchased 1,533,742 shares of newly issued common stock of DURECT at an aggregate purchase price of approximately $5.0 million. Under the terms of the agreement, as amended, we will be responsible for the CHRONOGESIC product s design and development. Endo shall not be responsible for any development costs for CHRONOGESIC prior to May 1, 2007. Commencing on May 1, 2007, unless the agreement is earlier terminated by Endo, Endo will fund 50% of the ongoing development costs and will reimburse us for a portion of

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our prior development costs for CHRONOGESIC upon the achievement of certain milestones. Development- based milestone payments made by Endo under this agreement could total up to $52 million. Under the agreement, Endo has licensed exclusive promotional rights to CHRONOGESIC in the U.S. and Canada. Endo will be responsible for marketing, sales and distribution, including providing specialty sales representatives dedicated to supplying technical and training support for CHRONOGESIC therapy and will pay for product launch costs. We will be responsible for the manufacture of CHRONOGESIC. If commercialized, we will share profits from the commercialization of CHRONOGESIC in the U.S. and Canada with Endo based on the financial performance of CHRONOGESIC. Based on our projected financial performance of CHRONOGESIC in the U.S. and Canada, we anticipate that our share of such profits, if CHRONOGESIC is commercialized, will be approximately 50%. Our agreement with Endo provides each party with specified termination rights. In particular, our agreement can be terminated by Endo in the event that (i) we have not delivered to Endo on or before March 31, 2007 a written notice that a human pharmacokinetic trial had been completed with CHRONOGESIC, together with a full study report of the results of the trial or (ii) Endo, determines, in its sole discretion, to terminate the agreement during the sixty-day period after our delivery of our notice, provided, that, in each case Endo delivers to us its written notice of termination prior to April 30, 2007.

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. Under the terms of the agreement, Endo will assume all remaining development and regulatory filing responsibility in the U.S. and Canada, including the funding thereof. We will perform all formulation development for Endo unless we default on such obligations and we will be reimbursed for our fully allocated cost in performance of such work. Endo will also be responsible and pay for the manufacture, marketing, sales and distribution of TRANSDUR-Sufentanil in the U.S. and Canada. Endo has paid us an upfront fee of $10 million, and we will receive additional payments of up to approximately $35 million in the aggregate if predetermined regulatory and commercial milestones are achieved. If commercialized, Endo will also pay us product royalties based on the net sales of TRANSDUR-Sufentanil under the agreement. We have the right to co-promote TRANSDUR-Sufentanil under terms specified in the agreement. The agreement also contains terms and conditions customary for this type of arrangement, including representations, warranties and indemnities. The agreement shall 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, Endo shall have the right to terminate the agreement at any time without cause subject to a specified notice period and due to adverse product events, legal impediment or the issuance of a final, non-appealable court order enjoining Endo from selling TRANSDUR-Sufentanil in the U.S. and Canada as a result of an action for patent infringement by a third party, provided that in the latter instance, we will be required to pay Endo a termination fee ranging from $5 million to $10 million, depending on the date of termination. We have the right to terminate the agreement in the event that Endo pursues directly or indirectly any proceeding seeking to have any of our TRANSDUR-Sufentanil related patents revoked or declared invalid, unpatentable or unenforceable.

NeuroSystec Corporation. In May 2004, we entered into an exclusive license agreement with NeuroSystec Corporation (NeuroSystec), a privately held corporation founded by Al 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 pre-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 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 equity constituting a minority ownership interest in NeuroSystec.

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Commercial Businesses

ALZET

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

The ALZET product is a miniature, implantable osmotic pump 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.

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

Polymer Supply

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. Until December 31, 2004, this business was conducted by our wholly owned subsidiary, Absorbable Polymers International Corporation (API), formerly known as Birmingham Polymers Inc., an Alabama corporation. API was merged with and into DURECT on December 31, 2004.

Marketing and Sales

Historically, we have established strategic distribution and marketing alliances for our pharmaceutical systems to take advantage of 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 may still choose to enter into strategic alliances 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 a proven technology platform.

We market and sell our ALZET product in the U.S. through a direct sales force, and we have a network of distributors for this product outside of the U.S.

Suppliers

We purchase sucrose acetate isobutyrate, a raw material for our SABER-based pharmaceutical systems, including SABER-Bupivacaine and Remoxy, pursuant to a supply agreement with Eastman Chemical Company. We also purchase sufentanil for CHRONOGESIC pursuant to a supply agreement with Mallinckrodt, Inc. We believe that these agreements will provide a sufficient supply of these raw materials to meet our needs for the

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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, within acceptable time frames or at reasonable cost.

Customers

A substantial portion of our product revenues is derived from sale of the ALZET product line. 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. For the year ended December 31, 2005, revenues from our collaborative agreements with Pain Therapeutics (Remoxy), Endo (TRANSDUR-Sufentanil) and Voyager (DURIN-Leuprolide (Memryte)) represented 17%, 26% and 25% of our total revenues, respectively. At December 31, 2005, three customers accounted for 27%, 26% and 23% of our gross accounts receivables. At December 31, 2004, two customers accounted for 40% and 26% of our gross accounts receivables.

Manufacturing

The process for manufacturing our pharmaceutical systems is technically complex, requires special skills, and must be performed in a qualified facility. Our manufacturing facility in Cupertino, CA is a functional multi-discipline site that we have used to manufacture research and clinical supplies of several of our pharmaceutical systems under GMP, including SABER-Bupivacaine, Memryte, TRANSDUR-sufentanil, Remoxy and CHRONOGESIC. We have recently made significant site improvements and equipment installations to upgrade and expand our manufacturing capabilities. 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 manufacture our ALZET product at our Vacaville, CA facility.

Patents, Licenses and Proprietary Rights

Our success depends in part on our ability to obtain patents, to protect trade secrets, to operate without infringing upon the proprietary rights of others and to prevent others from infringing on our proprietary rights. Our policy is to seek to protect our proprietary position by, among other methods, filing U.S. and foreign patent applications related to our proprietary technology, inventions and improvements that are important to the development of our business. As of February 28, 2006, we held 26 issued U.S. patents and 69 issued foreign patents (which include granted European patent rights that have been validated in various EU member states). In addition, we have 36 pending U.S. patent applications and have filed 55 patent applications under the Patent Cooperation Treaty, from which 101 national phase applications are currently pending in Europe, Australia, Japan, Canada, Mexico, New Zealand, Brazil, Israel, India, Hong Kong and China. Our patents expire at various dates starting in the year 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.

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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 may be necessary to determine the priority of inventions with respect to our patent applications. Litigation or interference proceedings could result in substantial costs to and diversion of effort by us, and could have a material adverse effect on our business, financial condition and results of operations. These efforts by us may not be successful.

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

Government Regulation

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

The process required by the FDA under the new drug provisions of the Federal Food, Drug and Cosmetics 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 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.

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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 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 studies 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 evaluations demonstrate that a dosage range of the product is effective and has an acceptable safety profile, Phase III 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 trials. We cannot be certain that we will successfully complete Phase I, Phase II or Phase III testing 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

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occur after the product reaches the market. Requirements for additional Phase IV 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.

In addition to the drug approval requirements applicable through the Center for Drug Evaluation and Research (CDER), the FDA, through its Office of Combination Products, may require an intercenter consultation review by the Center for Devices and Radiological Health (CDRH), in order to determine a product s Primary Method of Action (PMOA). This request for consultation may be based on the device-like nature of a number of aspects of the DUROS technology.

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

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

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

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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.

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, Remoxy and CHRONOGESIC 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. SABER-Bupivacaine, TRANSDUR-Sufentanil, Remoxy and CHRONOGESIC, if approved, will compete with currently marketed oral opioids, transdermal opioid patches, and implantable and external infusion pumps which can be used for infusion of opioids. Products of these types are marketed by Purdue Pharma, Knoll, Janssen, Medtronic, Endo Pharmaceuticals, AstraZeneca, Arrow International, Tricumed and others, including compounding pharmacies operating under state pharmacy licensure. 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, Atrix, Inovio, The Liposome Company, Focal, I-Flow 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.

If approved, Memryte will compete against the five drugs currently approved for the treatment of Alzheimer s disease. Four of the drugs are ACIs, including: Aricept, marketed by Pfizer, Inc. and Eisai Company, Ltd.; Exelon, marketed by Novartis AG; Reminyl, marketed by Shire Pharmaceuticals Group plc and Janssen Pharmaceutical Products, LP; and Cognex, marketed by First Horizon Pharmaceutical Corporation. The fifth drug, Namenda, marketed by Forest Pharmaceuticals, Inc., is an NMDA receptor antagonist. In addition, Memryte could face competition from other leuprolide acetate products that are already on the market or may later be approved for other indications, if they are used or prescribed off label for Alzheimer s disease.

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.

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Corporate History, Headquarters and Website Information

DURECT Corporation was 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 those 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. Durect Corporation s Code of Ethics can be found free of charge on our website.

Employees

As of December 31, 2005 we had 138 employees, including 86 in research and development, 20 in manufacturing and 32 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.

The executive officers of DURECT Corporation and their ages as of February 28, 2006 are as follows:

Name	Age	Position
Felix Theeuwes, D.Sc.	68	Chairman, Chief Scientific Officer and Director
James E. Brown, D.V.M.	49	President, Chief Executive Officer and Director
Jean I Liu	37	Senior Vice President, General Counsel and Secretary
Paula Mendenhall, Ph.D.	62	Senior Vice President, Operations
Su Il Yum, Ph.D.	66	Senior Vice President, Engineering
Steven Halladay, Ph.D.	58	Vice President, Clinical and Regulatory
Jian Li	35	Vice President, Finance and Corporate Controller
Andrew R. Miksztal, Ph.D.	54	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, a pharmaceutical and drug delivery company which is an affiliate of us, 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 is also a director of Inovio Biomedical Corporation, a medical device company. Dr. Theeuwes holds a D.Sc. degree in Physics from the University of Leuven (Louvain), Belgium. He also served as a post-doctoral fellow and visiting research assistant professor in the Department of Chemistry at the University of Kansas and has completed the Stanford Executive Program.

James E. Brown, D.V.M. co-founded DURECT in February 1998 and has served as our President, Chief Executive Officer and a Director since June 1998. He previously worked at ALZA Corporation as Vice President of Biopharmaceutical and Implant Research and Development from

June 1995 to June 1998. Prior to that, Dr. Brown held various positions at Syntex Corporation, a pharmaceutical company, including Director of Business Development from May 1994 to May 1995, Director of Joint Ventures for Discovery Research from 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.

Jean I Liu 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

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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 United States Patent and Trademark Office.

Paula Mendenhall, Ph.D. has served as our 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 a Pharm D. degree from the University of California, San Francisco, and is a member of the American Association of Pharmaceutical Scientists (AAPS), the American Pharmaceutical Association and the Society of Cosmetic Chemists.

Dr. Su IL Yum, Ph.D. has served as our Senior Vice President, Engineering since December 2003. Previously, Dr. Yum served 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. 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.

Steven Halladay, Ph.D. has served as Vice President of Clinical and Regulatory since April 2003. Prior to that, Dr. Halladay served as our Medical Director from November 2002 and April 2003. Prior to joining DURECT, Dr. Halladay held various positions at Clingenix, Inc., Research Services, Inc., Hoffmann-La Roche, Syntex Laboratories, ALZA Corporation and Dynapol. Following 20 years with Syntex and Hoffmann-La Roche, Dr. Halladay founded Research Services, Inc., an innovative pharmaceutical research company. After 5 years as President and CEO, Research Services merged with Clingenix, Inc. As Senior Executive Vice President at Clingenix his corporate responsibilities included pharmacogenomic program development, new business development, strategic alliances/relationships, and all aspects associated with clinical research and pharmacogenomic medical application. Dr. Halladay holds a B.S. from Southern Utah University, M.S. in Toxicology from University of Arizona and a Ph.D. from the Arizona Medical Center, Tucson, Arizona in Clinical Pharmacology.

Jian Li has served as our Vice President of Finance and Corporate Controller since December 2003. Previously, Ms. Li served as our Corporate Controller from April 2001 to December 2003, Assistant Controller from December 2000 to April 2001 and our Accounting Manager from March 2000 to December 2000. Prior to joining DURECT, she held various positions at Elan Pharmaceuticals in California and GTE Hawaiian Telephone in Honolulu, Hawaii in the roles of Financial Analyst, Accountant and Marketing Analyst. Ms. Li holds an M.B.A. from the University of Hawaii at Manoa. She is also a Certified Public Accountant and a member of American Institute of Certified Public Accountants.

Andrew R. Miksztal, Ph.D. has served as our Vice President of Pharmaceutical Research and Development since January 2006. Dr. Miksztal joined DURECT in March 2000 as Senior Director of Pharmaceutical Development and was promoted to Executive Director of Pharmaceutical Development in October 2000. Prior to joining DURECT, Dr. Miksztal was the Associate Director of the Pharmaceutical Analysis Department at Oread

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Laboratories from 1996 to 2000, a Senior Scientist in Pharmaceutical Research at Roche Bioscience from 1995 to 1996, and a Scientist in the Preformulation and Pharmaceutical Analysis Departments at Syntex Research from 1987 to 1995. Dr. Miksztal earned his Ph.D. degree in Chemistry from Rutgers University, and completed an NIH postdoctoral research fellowship in the Chemistry Department at the University of California, San Diego. Dr. Miksztal is a member of the American Association of Pharmaceutical Scientists, the Parenteral Drug Association and the American Chemical Society.

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;
- selecting and developing catheter or other targeting technology, if appropriate, to deliver the drug to a specific location within the body; and
- demonstrating through clinical trials that the drug and system combination is safe and effective in patients for the intended indication.

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. Other than for Remoxy, we have not yet selected the drug dosages nor finalized the formulation or the system design of any of our pharmaceutical systems, including our SABER-Bupivacaine, TRANSDUR-Sufentanil, Memryte and CHRONOGESIC, 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 to perform additional studies and may delay clinical testing and regulatory approval of our pharmaceutical systems. Even after we complete the design of a pharmaceutical system, the pharmaceutical system must still complete required clinical trials and additional safety testing in animals before approval for commercialization. See We must conduct and satisfactorily complete required laboratory performance and safety testing, animal studies and clinical trials for our pharmaceutical systems before we can sell them. 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 may not be able to complete development of any pharmaceutical

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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 SABER-Bupivacaine, TRANSDUR-Sufentanil, Remoxy, Memryte, CHRONOGESIC 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, preclinical (animal) studies and clinical (human) trials that each system is safe and effective for human use for each targeted disease. The clinical development status of our most advanced programs is as follows:

- SABER-Bupivacaine Phase I trial completed and Phase II trials initiated in Australia and the United Kingdom. Dosing of all three cohorts consisting of an aggregate of 81 patients in the Phase II clinical trial in Australia completed as of September 2005. Positive preliminary results from Phase II trial in Australia announced in October 2005. Dosing for the United Kingdom trial is ongoing.

- TRANSDUR-Sufentanil Patch Dosing of Phase I trial completed and first trial of Phase II program initiated as of February 2005. Positive preliminary results from first Phase II trial announced in December 2005.

- Remoxy Phase I and Phase III trials completed by Pain Therapeutics. Pain Therapeutics announced positive results from the first Phase III study in September 2005. In February 2006, Pain Therapeutics and its commercialization sublicensee King announced that Remoxy had successfully completed a Special Protocol Assessment (SPA) with the FDA and that the parties were going to commence a pivotal Phase III trial on Remoxy in 400 patients with severe chronic pain.

- Memryte Dosing completed in one Phase I trial by Voyager. One Phase II proof of concept trial using the drug but not our DURIN-based dosage form (Memryte) completed and a second such trial ongoing by Voyager. Voyager has initiated dosing for pivotal Phase III clinical studies using Memryte as an adjunctive therapy with acetyl cholinesterase inhibitors (ACIs) for the treatment of mild to moderate Alzheimer s disease.

- CHRONOGESIC Phase I, Phase II and Pilot Phase III completed. Redesigning the system to address performance problems and will resume clinical trials when system design is completed.

We are currently in the 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 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 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 that could delay commercialization of such pharmaceutical systems and harm our business and financial conditions.

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

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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 Food and Drug Administration (FDA) may not clear any such application in a timely manner or may deny the application entirely.

Data already obtained from preclinical studies and clinical trials of our pharmaceutical systems do not necessarily predict the results that will be obtained from later preclinical studies and clinical trials. Moreover, preclinical and clinical data such as ours is 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.

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 manufacture processes associated with our pharmaceutical systems are complex. We and our third-party collaborators, where relevant, have not yet completed development of the manufacturing process for any pharmaceutical systems or components including SABER Bupivacaine, TRANSDUR-Sufentanil, Remoxy, Memryte and CHRONOGESIC. 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 systems or component at an acceptable cost, then we and our third-party collaborators may not be able to commercialize that pharmaceutical systems or we may be in breach of our supply obligations to our third-party collaborators.

Our manufacturing facility in Cupertino is a functional multi-discipline site that we have used to manufacture only research and clinical supplies of several of our pharmaceutical systems under good manufacturing practices (GMP), including SABER-Bupivacaine, TRANSDUR-Sufentanil, DURIN-Leuprolide (Memryte), Remoxy and CHRONOGESIC. 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 timely accomplish these tasks.

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 attain and maintain

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compliance with applicable regulations, the clinical trials and the commercial sale of our pharmaceutical systems and those of our third-party collaboratorss could be delayed. Additionally, we may need to alter our facility design or manufacturing processes, install additional equipment or do additional construction or testing in order to meet regulatory requirements, optimize the production process, increase efficiencies or production capacity or for other reasons, which may result in additional cost to us or delay production of product needed for the clinical trials and commercial launch of our pharmaceutical systems and those of our third-party collaborators. We and our third-party collaborators, where relevant, may also need or choose to subcontract with third-party contractors to perform manufacturing steps of our pharmaceutical systems or supply required components for our pharmaceutical systems in which case we will be subject to the schedule, expertise and performance of third parties as well as incur significant additional costs. See We rely heavily on third parties to support development, clinical testing and manufacturing of our development products and Key Components of our pharmaceutical systems are provided by limited numbers of suppliers, and supply shortages or loss of these suppliers could result in interruptions in supply or increased costs. Under our development and commercialization agreement with ALZA, we cannot subcontract the manufacture of subassemblies of the DUROS system components of our DUROS-based pharmaceutical systems to third parties which have not been approved by ALZA.

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

Failure to obtain product approvals could delay or limit introduction 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 market or sell our development products 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.

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 trial protocols or on the required 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

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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.

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

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

- failure to obtain or maintain requisite governmental approvals;
- failure to obtain approvals for clinically intended uses of our pharmaceutical systems under development; or
- identification of serious and unanticipated adverse side effects in our pharmaceutical systems under development.

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

Our near-term revenues depend on collaboration agreements with other companies. These agreements subject us to obligations which must be fulfilled and require us to manage complex relationships with 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 and the attainment of milestones set forth in the 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 relationship with such collaborators and resolving possible issues of contractual interpretation which may detract from time our management would otherwise devote to our 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 Endo with respect to

CHRONOGESIC and TRANSDUR-Sufentanil,

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Pain Therapeutics with respect to Remoxy and Voyager with respect to Memryte, 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.

In addition to customary termination rights, our agreement with Endo for the development and commercialization of CHRONOGESIC in the United States and Canada can be terminated by Endo in the event that (i) we have not delivered to Endo on or before March 31, 2007 a written notice that a human pharmacokinetic trial had been completed with CHRONOGESIC, together with a full study report of the results of the trial or (ii) Endo, determines, in its sole discretion, to terminate the agreement during the sixty-day period after our delivery of the notice, provided, that, in each case Endo delivers to us its written notice of termination prior to April 30, 2007.

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

We depend to a large extent on third-party collaborators, and we do not have or have limited control over the development, sales, distribution and disclosure for our pharmaceutical systems which are the subject of third-party collaborative or license agreements

Our future 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 Endo related to the development, promotion and distribution of CHRONOGESIC and TRANSDUR-Sufentanil in the United States and Canada once such products are approved for commercialization. In addition, we have entered into agreements with Pain Therapeutics and Voyager under which we granted such third parties the right to develop, apply for regulatory approval for, market, promote or distribute Remoxy and Memryte, 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, 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. 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, manufacture, marketing or sale of these pharmaceutical systems. If any of these events occur, we may not be able to develop our technologies or 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.

We may develop our own sales force to market our SABER-Bupivacaine and to co-promote along with Endo TRANSDUR-Sufentanil in the United States but we have limited sales experience and may not be able to do so effectively

We currently plan to develop our own sales force to market SABER-Bupivacaine and to co-promote, along with Endo, TRANSDUR-Sufentanil in the United States, if such pharmaceutical systems are approved for marketing by the FDA. Developing a sales force will require substantial expenditures. DURECT has limited sales and marketing experience, and may not be able to effectively recruit, train or retain sales personnel. We may not be able to effectively sell our pharmaceutical systems, if approved, and our failure to do so could materially harm our business.

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

We and our third-party collaborators compete with many other companies that currently have extensive and well-funded marketing and sales operations. Our marketing and sales efforts and those of our third-party

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collaborations may be unable to compete successfully against these other companies. We and our third-party collaborators, if relevant, may be unable to establish a sufficient sales and marketing organization on a timely basis, if at all. We and our third-party collaborators, if relevant, may be unable to engage qualified distributors. Even if engaged, these distributors may:

- fail to satisfy financial or contractual obligations to us;
- fail to adequately market our pharmaceutical systems;
- cease operations with little or no notice to us;
- offer, design, manufacture or promote competing product lines;
- fail to maintain adequate inventory and thereby restrict use of our pharmaceutical systems; or
- build up inventory in excess of demand thereby limiting future purchases or our pharmaceutical systems resulting in significant quarter-to-quarter variability in our sales.

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

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

We rely on third-party contract research organizations, service providers and suppliers to provide critical services to support development, clinical testing, and manufacturing of our pharmaceutical systems. For example, we currently depend on third-party vendors to manage and monitor our clinical trials and to perform critical manufacturing steps for our pharmaceutical systems. We rely on third-parties to manufacture or perform manufacturing steps relating to our pharmaceutical systems or components. See We may not be able to manufacture sufficient quantities of our development products to support our clinical and commercial requirements at an acceptable cost, and we have limited manufacturing experience. We anticipate that we will continue to rely on these and other third-party contractors to support development, clinical testing, and manufacturing of our pharmaceutical systems. Failure of these contractors to provide the required services in a timely manner or on reasonable commercial terms could materially delay the development and approval of our development products, increase our expenses and materially harm our business, financial condition and results of operations.

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

Certain components and drug substances used in our pharmaceutical systems (including SABER-Bupivacaine, TRANSDUR-Sufentanil, Remoxy, Memryte and CHRONOGESIC) are currently purchased from a single or a limited number of outside sources. The reliance on a sole or limited number of suppliers could result in:

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

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

- reduced control over pricing, quality and time delivery.

We have supply agreements in place for certain components of our pharmaceuticals systems, but do not have in place long term supply agreements with respect to all of the components of any of our pharmaceutical system candidates. Therefore the supply of a particular component could be terminated at any time without penalty to the supplier. In addition, we may not be able to procure required components or drugs from third-party suppliers at a quantity, quality and cost acceptable to us. Any interruption in the supply of single source

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components could cause us to seek alternative sources of supply or manufacture these components internally. Furthermore, in some cases, we are relying on our third-party collaborators to procure supply of necessary components. If the supply of any components for our pharmaceutical systems is interrupted, components from alternative suppliers may not be available in sufficient volumes or at acceptable quality levels within required timeframes, if at all, to meet our needs or those of our third-party collaborators. This could delay our ability to complete clinical trials and obtain approval for commercialization and marketing of our pharmaceutical systems, causing us to lose sales, incur additional costs and delay new product introductions and could harm our reputation.

If we do not generate sufficient cash flow through increased revenues or raising additional capital, then we may not be able to meet our substantial debt obligations that become due in 2008

As of December 31, 2005, we had approximately $57.3 million in long-term convertible subordinated notes which mature in June 2008, $27,000 in non-current lease obligations and $675,000 in non-current bonds payable. Our substantial indebtedness, which totals $58.0 million, has impacted and will continue to impact us by:

- making it more difficult to obtain additional financing;
- requiring interest payments to service the debt; and
- constraining our ability to react quickly in an unfavorable economic climate.

Currently we are not generating positive cash flow. Adverse occurrences related to our product development efforts will adversely impact our ability to meet our obligations to repay the principal amounts on our convertible subordinated notes when due in June 2008. In addition, if the market price of our common stock on the due date of our notes is below $3.15 per share, the approximate equity conversion price of the notes, it will be highly unlikely that the holders of a large percentage of our outstanding convertible subordinated notes will convert such securities to equity in accordance with their existing terms. If we are unable to satisfy our debt service requirements, substantial liquidity problems could result. As of December 31, 2005, we had cash and investments valued at approximately $91.0 million. We expect to use substantially all of these assets to fund our on-going operations over the next few years. We may not generate sufficient cash from operations to repay our convertible subordinated notes or satisfy any other of these obligations when they become due and may have to raise additional financing from the sale of equity or debt securities or otherwise restructure our obligations in order to do so. There can be no assurance that any such financing or restructuring will be available to us on commercially acceptable terms, if at all. If we are unable to restructure our obligations, we may be forced to seek protection under applicable bankruptcy laws. Any restructure or bankruptcy could materially impair the value of our common stock.

We may be required to redeem our outstanding convertible subordinated notes before maturity, and we may not have sufficient funds to do so. The redemption rights in our outstanding convertible subordinated notes could discourage a potential acquirer

If a fundamental change occurs, we may be required to redeem all or part of the remaining $57.3 million in outstanding principal, plus any accrued but unpaid interest on our outstanding convertible promissory notes. A fundamental change is defined as:

- any transaction or event in connection with which all or substantially all of our common stock is exchanged for, converted into, acquired for or constitutes solely the right to receive consideration which is not all or substantially all common stock listed on a United

States national securities exchange or approved for quotation on the NASDAQ National Market or any similar United States system of automated dissemination of quotations of securities prices, or,

- if for any reason, our common stock is no longer listed for trading on a United States national securities exchange nor approved for trading on the NASDAQ National Market.

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If there is a fundamental change, we may not have enough funds to pay the redemption price for all tendered notes. In addition, any credit agreement or other agreements relating to our indebtedness may contain provisions prohibiting redemption of the notes under certain circumstances, or expressly prohibit our redemption of the notes upon a designated event or may provide that a designated event constitutes an event of default under that agreement. Our failure to redeem tendered notes would constitute an event of default under the indenture, which might also constitute a default under the terms of our other indebtedness. Any such default could cause us to seek to restructure our indebtedness or seek protection under applicable bankruptcy laws, either of which could materially impair the value of our common stock.

This redemption feature upon fundamental change could also discourage a potential acquirer. However, this redemption feature is not the result of management s knowledge of any specific effort to obtain control of us by means of a merger, tender offer or solicitation, or part of a plan by management to adopt a series of anti-takeover provisions. The term fundamental change is limited to specified transactions and may not include other events that might adversely affect our financial condition or business operations.

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

We have incurred significant operating losses since our inception in 1998 and, as of December 31, 2005, had an accumulated deficit of approximately $182.0 million. We expect to continue to incur significant operating losses over the next several years as we continue to incur costs for research and development, clinical trials and manufacturing. Our ability to achieve profitability depends upon our ability, alone or with others, to successfully complete the development of our proposed pharmaceutical systems, obtain the required regulatory clearances and manufacture and market our proposed pharmaceutical systems. Development of pharmaceutical systems is costly and requires significant investment. In addition, we may choose to license either additional drug delivery platform technology or rights to particular drugs or other appropriate technology for use in our pharmaceutical systems. The license fees for these technologies or rights would increase the costs of our pharmaceutical systems.

To date, we have not generated significant revenue from the commercial sale of our pharmaceutical systems and do not expect to receive significant revenue in the near future. Our current product revenues are from the sale of the ALZET product we acquired in April 2000 from ALZA and the sale of biodegradable polymers. We do not expect these product revenues to increase significantly in future periods. We do not anticipate commercialization and marketing of our pharmaceutical systems in development in the near future, and therefore do not expect to generate sufficient revenues to cover expenses or achieve profitability in the near future.

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;

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

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- progress with preclinical studies and clinical trials;
- the time and costs involved in obtaining regulatory clearance;
- costs involved in preparing, filing, prosecuting, maintaining and enforcing patent claims;
- costs of developing sales, marketing and distribution channels and our ability to sell our pharmaceutical systems;
- costs involved in establishing manufacturing capabilities for clinical and commercial quantities of our pharmaceutical systems;
- competing technological and market developments;
- market acceptance of our pharmaceutical systems; and
- costs for recruiting and retaining employees and consultants.

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 collaboratorss 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.

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

Our success will depend in part on our ability to obtain patents, maintain trade secret protection and operate without infringing the proprietary rights of others. As of February 28, 2006, we held 26 issued U.S. patents and 69 issued foreign patents (which include granted European patent rights that have been validated in various EU member states). In addition, we have 36 pending U.S. patent applications and have filed 55 patent applications under the Patent Cooperation Treaty, from which 101 national phase applications are currently pending in Europe, Australia, Japan, Canada, Mexico, New Zealand, Brazil, Israel, India, Hong Kong and China. Our patents expire at various dates starting in the year 2012.

Under our agreement with ALZA, we must assign to ALZA any intellectual property rights relating to the DUROS system and its manufacture and any combination of the DUROS system with other components, active agents, features or processes. In addition, ALZA retains the right to enforce and defend against infringement actions relating to the DUROS system, and if ALZA exercises these rights, it will be entitled to the proceeds of these infringement actions.

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

We are party to several collaborative agreements. See Our near-term revenues depend on collaboration agreements with other companies. These agreements subject us to obligations which must be fulfilled and require

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us to manage complex relationships with 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 third-party collaborators have entered into these agreement based on the exclusivity that our intellectual property rights confer on the products being developed. The loss or diminishment of our intellectual property rights could result in a decision by our third-party collaborators to terminate their agreements with us. In addition, these agreements are generally complex and contain provisions that could give rise to legal disputes, including potential disputes concerning ownership of intellectual property under collaborations. Such disputes can lead to lengthy, expensive litigation or arbitration requiring us to devote management time and resources to such dispute which we would otherwise spend on our business. To the extent that our agreements call for future royalties to be paid conditional on our having patents covering the royalty-bearing subject matter, a decision by the Supreme Court adverse to the patent holder in the case of MedImmune, Inc. v. Genentech, Inc., U.S. Supreme Court No. 05-608 (Feb. 21, 2006) could encourage our licensees to challenge the validity of our patents and thereby seek to avoid future royalty obligations without losing the benefit of their license. Should they be successful in such a challenge, our ability to collect future royalties could be substantially diminished.

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

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

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

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

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

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

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

We may be required to obtain rights to certain drugs

Some of the pharmaceutical systems that we are currently developing require the use of proprietary drugs to which we do not have commercial rights. For example, our research collaboration with the University of Maastricht has demonstrated that the use of a proprietary angiogenic factor in a pharmaceutical system can lead to elevated local concentration of the angiogenic factor in the pericardial sac of the heart, resulting in physical changes, including the growth of new blood vessels. We do not currently have a license to develop or commercialize a pharmaceutical system containing such proprietary angiogenic factor.

To complete the development and commercialization of pharmaceutical systems containing drugs to which we do not have commercial rights, we will be required to obtain rights to those drugs. We may not be able to do this at an acceptable cost, if at all. If we are not able to obtain required rights to commercialize certain drugs, we may not be able to complete the development of pharmaceutical systems which require use of those drugs. This could result in the cessation of certain development projects and the potential write-off of certain assets.

Technologies and businesses which we have acquired may be difficult to integrate, disrupt our business, dilute stockholder value or divert management attention. We may also acquire additional businesses or technologies in the future, which could have these same effects

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

- increased costs associated with the acquisition and operation of the new businesses or technologies and the management of geographically dispersed operations;
- the risks associated with the assimilation of new technologies, operations, sites and personnel;
- the diversion of resources from our existing business and technologies;
- the inability to generate revenues to offset associated acquisition costs;
- the requirement to maintain uniform standards, controls, and procedures; and
- the impairment of relationships with employees and customers or third party collaborators as a result of any integration of new management personnel.

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

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

Some of our pharmaceutical systems currently under development contain, and our products in the future may contain, controlled substances which are subject to state, federal and foreign laws and regulations regarding their manufacture, use, sale, importation and distribution. TRANSDUR-Sufentanil patch, Remoxy and CHRONOGESIC and other pharmaceutical systems we have under development contain opioids which are classified as Schedule II controlled substances under the regulations of the U.S. Drug Enforcement Agency. For our pharmaceutical systems containing controlled substances, we and our suppliers, manufacturers, contractors, customers and distributors are required to obtain and maintain applicable registrations from state, federal and foreign law enforcement and regulatory agencies and comply with state, federal and foreign laws and regulations regarding the manufacture, use, sale, importation and distribution of controlled substances. These regulations are

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extensive and include regulations governing manufacturing, labeling, packaging, testing, dispensing, production and procurement quotas, record keeping, reporting, handling, shipment and disposal. Failure to obtain and maintain required registrations or comply with any applicable regulations could delay or preclude us from developing and commercializing our pharmaceutical systems containing controlled substances and subject us to enforcement action. In addition, because of their restrictive nature, these regulations could limit our commercialization of our pharmaceutical systems containing controlled substances.

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

We may incur significant non-cash charges related to impairment write-downs of our long-lived assets, including goodwill and other intangible assets.

We will continue to incur non-cash charges related to amortization of other intangible assets. We are required to perform periodic impairment reviews of our goodwill at least annually. To the extent these reviews conclude that the expected future cash flows generated from our business activities are not sufficient to recover the cost of our long-lived assets, we will be required to measure and record an impairment charge to write down these assets to their realizable values. We completed our last review during the fourth quarter of 2005 and determined that goodwill was not impaired as of December 31, 2005. However, there can be no assurance that upon completion of subsequent reviews a material impairment charge will not be recorded. If future periodic reviews determine that our assets are impaired and a write down is required, it will adversely impact or delay our profitability.

In December 2004, the FASB issued Statement No. 123 (revised 2004, or SFAS 123R), Share-Based Payment, which was originally effective for annual or interim periods beginning after June 15, 2005. SFAS 123R supersedes APB Opinion No. 25, Accounting for Stock Issued to Employees, and will require companies to recognize compensation expense, using a fair-value based method, for costs related to share-based payments including stock options and stock issued under our employee stock purchase plans. We adopted SFAS 123R using the modified prospective basis on January 1, 2006. We expect that our adoption of SFAS 123R will have a material adverse impact on our consolidated results of operations and will adversely impact or delay our profitability. Furthermore, we have issued to ALZA common stock and a warrant to purchase common stock with an aggregate value of approximately $13.5 million, which will be amortized over time based on sales of our DUROS-based products and which will also adversely impact or delay our profitability.

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

Our success will depend to a significant degree upon the continued services of key management, technical and scientific personnel, including Felix Theeuwes, our Chairman and Chief Scientific Officer and James E. Brown, our President and Chief Executive Officer. Although we have obtained key man life insurance policies for each of Messrs. Theeuwes and Brown in the amount of $1.0 million, this insurance may not adequately compensate us for the loss of their services. In addition, our success will depend on our ability to attract and retain other highly skilled personnel. Competition for qualified personnel is intense, and the process of hiring and integrating such qualified personnel is often lengthy. We may be unable to recruit such personnel on a timely basis, if at all. Our management and other employees may voluntarily terminate their employment with us at any time. The loss of the services of key personnel, or the inability to attract and retain additional qualified personnel, could result in delays to product development or approval, loss of sales and diversion of management resources.

We may not successfully manage our growth

Our success will depend on the timely expansion of our operations and the effective management of growth, which will place a significant strain on our management and on our administrative, operational and financial

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resources. To manage such growth, we must expand our facilities, augment our operational, financial and management systems and hire, train and supervise additional qualified personnel. If we were unable to manage growth effectively our business would be harmed.

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

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

Our agreement with ALZA limits our fields of operation for our DUROS-based pharmaceutical systems and gives ALZA a first right to negotiate to distribute selected products for us

Our agreement with ALZA gives us exclusive rights to develop, commercialize and manufacture products using ALZA s DUROS technology to deliver by catheter:

- drugs to the central nervous system to treat select nervous system disorders;
- drugs to the middle and inner ear;
- drugs to the pericardial sac of the heart; and
- select drugs into vascular grafts.

We also have the right to use the DUROS technology to deliver systemically and by catheter:

- sufentanil to treat chronic pain; and

- select cancer antigens.

We may not develop, manufacture or commercialize DUROS-based pharmaceutical systems outside of these specific fields without ALZA s prior approval. In addition, if we develop or commercialize any drug delivery technology for use in a manner similar to the DUROS technology in a field covered in our license agreement with ALZA, then we may lose our exclusive rights to use the DUROS technology in such field as well as the right to develop new pharmaceutical systems using DUROS technology in such field. In order to maintain commercialization rights for our products on a worldwide basis, we must diligently develop our pharmaceutical systems, procure required regulatory approvals and commercialize the pharmaceutical systems in selected major market countries. If we fail to meet commercialization diligence requirements, we may lose rights for products in

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some or all countries, including the United States. These rights would revert to ALZA, which could then develop DUROS-based pharmaceutical products in such countries itself or license others to do so. In addition, in the event that our rights terminate with respect to any product or country, or this agreement terminates or expires in its entirety (except for termination by us due to a breach by ALZA), ALZA will have the exclusive right to use all of our data, rights and information relating to the products developed under the agreement as necessary for ALZA to commercialize these products, subject to the payment of a royalty to us based on the net sales of the products by ALZA.

Our agreement with ALZA gives us the right to perform development work and manufacture the DUROS pump component of our DUROS-based pharmaceutical systems. In the event of a change in our corporate control, including an acquisition of us, our right to manufacture and perform development work on the DUROS pump would terminate and ALZA would have the right to manufacture and develop DUROS systems for us so long as ALZA can meet our specification and supply requirements following such change in control.

Under the ALZA agreement, we must pay ALZA royalties on sales of DUROS-based pharmaceutical systems we commercialize and a percentage of any up-front license fees, milestone or special fees, payments or other consideration we receive, excluding research and development funding. In addition, commencing upon the commercial sale of a product developed under the agreement, we are obligated to make minimum product payments to ALZA on a quarterly basis based on our good faith projections of our net product sales of the product. These minimum payments will be fully credited against the product royalty payments we must pay to ALZA.

ALZA may obtain from us, for its own behalf or on behalf of one of its affiliates, the exclusive right to develop and commercialize a product in a field of use exclusively licensed to us, provided that such product does not incorporate a drug in the same drug class and is not intended for the same therapeutic indication as a product which is then being developed or commercialized by us or for which we have made commitments to a third-party. In the event that ALZA or an affiliate commercializes such a product, ALZA or its affiliate will pay us a royalty on sales of such product at a specified rate.

ALZA also has an exclusive option to distribute any DUROS-based pharmaceutical system we develop to deliver non-proprietary cancer antigens worldwide. The terms of any distribution arrangement have not been set and are to be negotiated in good faith between ALZA and us. ALZA s option to acquire distribution rights limits our ability to negotiate with other distributors for these products and may result in lower payments to us than if these rights were subject to competitive negotiations. We must allow ALZA an opportunity to negotiate in good faith for commercialization rights to our products developed under the agreement prior to granting these rights to a third-party. These rights do not apply to products that are subject to ALZA s option or products for which we have obtained funding or access to a proprietary drug from a third-party to whom we have granted commercialization rights prior to the commencement of human clinical trials.

ALZA has the right to terminate the agreement in the event that we breach a material obligation under the agreement and do not cure the breach in a timely manner. In addition, ALZA has the right to terminate the agreement if at any time prior to July 2006, we solicit for employment or hire, without ALZA s consent, a person who is or within the previous 180 days has been an employee of ALZA in the DUROS technology group.

We do not control ALZA s ability to develop and commercialize DUROS technology outside of fields licensed to us, and problems encountered by ALZA could result in negative publicity, loss of sales and delays in market acceptance of our DUROS-based pharmaceutical systems

ALZA retains complete rights to the DUROS technology for fields outside the specific fields licensed to us. Accordingly, ALZA may develop and commercialize DUROS-based products or license others to do so, so long as there is no conflict with the rights granted to us. ALZA received FDA approval to market its first DUROS-based product, VIADUR (leuprolide acetate implants) for the palliative treatment of advanced prostate cancer in

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March 2000. If ALZA or its commercialization collaborators, Bayer, fails to commercialize this product successfully, or encounters problems associated with this product, negative publicity could be created about all DUROS-based products, which could result in harm to our reputation and cause reduced sales of our DUROS-based pharmaceutical systems. In addition, if any third party that may be licensed by ALZA fails to develop and commercialize DUROS-based products successfully, the success of all DUROS-based systems could be impeded, including ours, resulting in delay or loss of revenue or damage to our reputation, any one of which could harm our business.

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

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

Risks Related To Our Industry

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

The pharmaceutical industry is subject to rapid and substantial technological change. Developments by others may render our pharmaceutical systems under development or technologies noncompetitive or obsolete, or we may be unable to keep pace with technological developments or other market factors. Technological competition in the industry from pharmaceutical and biotechnology companies, universities, governmental entities and others diversifying into the field is intense and is expected to increase. Many of these entities have significantly greater research and development capabilities than we do, as well as substantially more marketing, manufacturing, financial and managerial resources. These entities represent significant competition for us. Acquisitions of, or investments in, competing pharmaceutical or biotechnology companies by large corporations could increase such competitors financial, marketing, manufacturing and other resources.

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

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

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

The testing, manufacture, marketing and sale of our pharmaceutical systems involve an inherent risk that product liability claims will be asserted against us. Although we are insured against such risks up to an annual aggregate limit in connection with clinical trials and commercial sales of our pharmaceutical systems, our present

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product liability insurance may be inadequate and may not fully cover the costs of any claim or any ultimate damages we might be required to pay. Product liability claims or other claims related to our pharmaceutical systems, regardless of their outcome, could require us to spend significant time and money in litigation or to pay significant damages. Any successful product liability claim may prevent us from obtaining adequate product liability insurance in the future on commercially desirable or reasonable terms. In addition, product liability coverage may cease to be available in sufficient amounts or at an acceptable cost. An inability to obtain sufficient insurance coverage at an acceptable cost or otherwise to protect against potential product liability claims could prevent or inhibit the commercialization of our pharmaceutical systems. A product liability claim could also significantly harm our reputation and delay market acceptance of our pharmaceutical systems.

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

Our future financial performance will depend upon the successful introduction and customer acceptance of our future products, including SABER-Bupivacaine, TRANSDUR-Sufentanil, Remoxy, DURIN-Leuprolide (Memryte) and CHRONOGESIC. Even if approved for marketing, our pharmaceutical systems may not achieve market acceptance. The degree of market acceptance will depend upon a number of factors, including:

- the receipt of regulatory clearance of marketing claims for the uses that we are developing;
- the establishment and demonstration in the medical community of the safety and clinical efficacy of our products and their potential advantages over existing therapeutic products, including oral medication, transdermal drug delivery products such as drug patches, or external or implantable drug delivery products; and
- pricing and reimbursement policies of government and third-party payors such as insurance companies, health maintenance organizations, hospital formularies and other health plan administrators.

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

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

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

The successful commercialization of our pharmaceutical systems will depend in part on the extent to which appropriate reimbursement levels for the cost of our pharmaceutical systems and related treatment are obtained by governmental authorities, private health insurers and other organizations, such as HMOs. Third-party payors are increasingly limiting payments or reimbursement for medical products and services. Also, the trend toward managed health care in the United States and the concurrent growth of organizations such as HMOs, which could control or significantly influence the purchase of health care services and products, as well as legislative

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proposals to reform health care or reduce government insurance programs, may limit reimbursement or payment for our products. The cost containment measures that health care payors and providers are instituting and the effect of any health care reform could materially harm our ability to operate profitably.

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

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

Legislative actions, potential new accounting pronouncements and higher insurance costs are likely to impact our future financial position or results of operations

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

In December 2004, the FASB issued Statement No. 123 (revised 2004, or SFAS 123R), *Share-Based Payment*, which was originally effective for annual or interim periods beginning after June 15, 2005. SFAS 123R supersedes APB Opinion No. 25, *Accounting for Stock Issued to Employees*, and will require companies to recognize compensation expense, using a fair-value based method, for costs related to share-based payments including stock options and stock issued under our employee stock purchase plans. We adopted SFAS 123R using the modified prospective basis on January 1, 2006. We expect that our adoption of SFAS 123R will have a material adverse impact on our consolidated results of operations.

In March 2005, the SEC issued SAB No. 107 regarding the interaction between SFAS 123R which was revised in December 2004, and certain SEC rules and regulations and provides the SEC s staff views regarding the valuation of share-based payment arrangements for public companies. We expect that this guidance will have a material adverse impact on our consolidated results of operations.

In June 2005, the FASB ratified the consensus reached by the Emerging Issues Task Force No. 05-6 (EITF 05-6). The Task Force reached a consensus that leasehold improvements that are placed in service significantly after and not contemplated at or near the beginning of the lease term should be amortized over the shorter of the useful life of the assets or a term that includes required lease periods and renewals that are

deemed to be reasonably assured at the date the leasehold improvements are purchased. In addition, leasehold improvements acquired in a business combination should be amortized over the shorter of the useful lives of the assets or a term that includes required lease periods and renewals that are deemed to be reasonably assured at the date of

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acquisition. EITF 05-6 is effective for leasehold improvements (within the scope of this issue) that are purchased or acquired in the reporting period beginning after June 29, 2005. Adoption of EITF 05-6 did not have an impact on our consolidated financial condition or results of operations.

Risks Related To Our Common Stock

Our operating history makes evaluating our stock difficult

We have engaged primarily in research and development, licensing technology, raising capital and recruiting scientific and management personnel and, to a lesser extent, sales and marketing of products that we do not consider core to our business. We have no approved pharmaceutical system products. This history does not enable investors to fully assess our ability to successfully develop our pharmaceutical systems, achieve market acceptance of our pharmaceutical systems and respond to competition. Furthermore, we anticipate that our quarterly and annual results of operations will fluctuate for the foreseeable future. We believe that period-to-period comparisons of our operating results should not be relied upon as predictive of future performance. Our prospects must be considered in light of the risks, expenses and difficulties encountered by companies with no approved pharmaceutical products, particularly companies in new and rapidly evolving markets such as pharmaceuticals, drug delivery and biotechnology. To address these risks, we must, among other things, obtain regulatory approval for and commercialize our pharmaceutical systems, which may not occur. We may not be successful in addressing these risks and difficulties. We may require additional funds to complete the development of our pharmaceutical systems and to fund operating losses to be incurred in the next several years.

Investors may experience substantial dilution of their investment

In the past, we have issued and have assumed, pursuant to the SBS acquisition, options and warrants to acquire common stock. To the extent these outstanding options are ultimately exercised, there will be dilution to investors. In addition, conversion of some or all of the remaining $57.3 million aggregate principal amount of convertible subordinated notes that we issued in June and July 2003 will dilute the ownership interests of investors. Investors may experience further dilution of their investment if we raise capital through the sale of additional equity securities or convertible debt securities. Any sales in the public market of the common stock issuable upon such conversion could adversely affect prevailing market prices for our common stock.

We may choose to purchase a portion of our convertible subordinated notes in exchange for shares of our common stock in the open market. These transactions could dilute existing stockholders and increase the volatility of our stock

To the extent we are able to do so on terms favorable to us, we may choose to purchase a portion of our outstanding 6.25% Convertible Subordinated Notes due June 2008 from time to time in privately negotiated transactions under Section 3(a)(9) of the Securities Act of 1933. On July 21, 2005, we entered into an agreement for such a transaction for notes with an aggregate principal amount of up to $5.0 million. The issuance of shares of our common stock in such transactions will dilute our existing investors. To the extent such shares are resold, such transactions may increase the volatility of our stock.

The price of our common stock may be volatile

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

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

- failure of our third-party collaborators (such as Endo Pharmaceuticals, Pain Therapeutics or Voyager Pharmaceuticals) to develop and commercialize successfully the respective pharmaceutical systems they are developing;

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- adverse results or delays in our clinical trials of SABER-Bupivacaine, TRANSDUR-Sufentanil, Remoxy, Memryte, CHRONOGESIC or other pharmaceutical systems;

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

- adverse actions taken by regulatory agencies with respect to our pharmaceutical systems or our or our third-party collaborator s clinical trials, manufacturing processes or sales and marketing activities;

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

- regulatory developments in the United States and foreign countries;

- any lawsuit involving us or our pharmaceutical systems;

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

- developments concerning our strategic alliances or acquisitions;

- actual or anticipated variations in our operating results;

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

- deviations in our operating results from the estimates of analysts;

- sales of our common stock by our executive officers, directors and five percent stockholders or sales of substantial amounts of common stock;

- changes in accounting principles; and

- loss of any of our key scientific or management personnel.

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

Our trading volume is relatively low and may contribute to its volatility

The average daily trading volume of our common stock for the year ended December 31, 2005, was 338,817 shares. The limited trading volume of our stock may contribute to its volatility, and an active trading market in our stock might not continue. Pursuant to a Purchase Agreement with Morgan Stanley & Co., Incorporated, we filed a registration statement on August 29, 2003 with the SEC on Form S-3 to register an aggregate of $60.0 million in convertible subordinated notes and the shares of common stock issuable upon conversion of the notes for resale. The registration statement was declared effective by the SEC on November 3, 2003. The convertible subordinated notes are convertible into shares of our common stock at a conversion rate of 317.4603 shares per $1,000 principal amount of notes, subject to adjustment and will bear interest at a rate of 6.25% per annum. So long as this registration is effective, shares covered thereunder are tradable without limitation. If substantial amounts of our common stock issued upon conversion of our promissory notes or otherwise were to be sold in the public market, the market price of our common stock could fall. In addition, the existence of our convertible subordinated notes may encourage short selling by market participants. The market price of our common stock may fluctuate significantly in response to factors which are beyond our control. The stock market in general has recently experienced extreme price and volume fluctuations. In addition, the market prices of securities of technology and pharmaceutical companies have also been extremely volatile, and have experienced fluctuations that often have been unrelated or disproportionate to the operating performance of these companies. These broad market fluctuations could result in extreme fluctuations in the price of our common stock, which could cause a decline in the value of our investors stock.

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

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

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

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

- the election of directors;
- the amendment of charter documents;
- the approval of certain mergers and other significant corporate transactions, including a sale of substantially all of our assets; or
- the defeat of any non-negotiated takeover attempt that might otherwise benefit the public stockholders.

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

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

- authorizing the issuance of blank check preferred stock without any need for action by stockholders;
- providing for a dividend on our common stock, commonly referred to as a poison pill , which can be triggered after a person or group acquires 17.5% or more of common stock;
- providing for a classified board of directors with staggered terms;
- requiring supermajority stockholder voting to effect certain amendments to our certificate of incorporation and bylaws;

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

- prohibiting stockholder action by written consent; and

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

Item 1B. Unresolved Staff Comments.

None.

Item 2. Properties.

We are headquartered in Cupertino, California, where we lease four buildings: a building consisting of approximately 30,000 square feet of office, laboratory and manufacturing space, under a lease expiring in February 2009 with an option to extend for up to an additional five years; a building consisting of approximately

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20,000 square feet of office and laboratory space, under a lease expiring in February 2009 with an option to extend for up to an additional five years; and a building consisting of approximately 40,560 square feet of office space, under a lease expiring in December 2012 with an option to extend for up to an additional six years.

We also lease approximately 7,800 square feet of manufacturing space in Vacaville, California under a lease expiring in August 2008 with an option to extend for three years. We lease approximately 2,500 square feet of office and laboratory space in Birmingham, Alabama, under a lease which expires in April 2006. In addition, we lease approximately 9,400 square feet of office and laboratory space in Pelham, Alabama, under a lease expiring in September 2009 with one option to extend for five years.

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

Item 3. Legal Proceedings.

We are not a party to any material legal proceedings.

Item 4. Submission of Matters to a Vote of Security Holders.

Not applicable**.**

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PART II

Item 5. Market for Registrant s Common Equity, Related Stockholder Matter and Issuer Purchases of Equity Securities.

Price Range of Common Stock

Our common stock has been listed for quotation on the Nasdaq National Market under the symbol DRRX since our initial public offering on September 28, 2000. The following table shows the high and low sales prices of our common stock as reported by the Nasdaq National Market for the period indicated.

	Common Stock Price	
Year ended December 31, 2004	**Low**	**High**
First Quarter	$ 2.51	$ 3.49
Second Quarter	3.25	4.23
Third Quarter	1.26	3.36
Fourth Quarter	1.41	3.45
Year ended December 31, 2005	**Low**	**High**
First Quarter	$ 2.64	$ 3.78
Second Quarter	2.73	5.09
Third Quarter	4.85	7.15
Fourth Quarter	4.85	7.18

The closing sale price of the common stock as reported on the Nasdaq National Market on February 28, 2006 was $5.69 per share. As of that date there were approximately 184 holders of record of the common stock. This does not include the number of persons whose stock is in nominee or street name accounts through brokers. The market price of our common stock has been and may continue to be subject to wide fluctuations in response to a number of events and factors, such as progress in our development programs, quarterly variations in our operating results, announcements of technological innovations or new products by us or our competitors, changes in financial estimates and recommendations by securities analysts, the operating and stock performance of other companies that investors may deem comparable to us, and news reports relating to trends in our markets. These fluctuations, as well as general economic and market conditions, may adversely affect the market price for our common stock.

Dividend Policy

We have never paid cash dividends on our common stock. We currently intend to retain any future earnings to fund the development and growth of our business. Therefore, we do not currently anticipate paying any cash dividend