

DURECT CORP  
Form 424B2  
October 27, 2005  
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*Filed Pursuant to Rule 424(b)(2) under the Securities Act of 1933  
in connection with Registration No. 333-128979*

**The information in this prospectus supplement is not complete and may be changed. A registration statement relating to the offer and sale of these securities has been filed with the Securities and Exchange Commission and has been declared effective. This prospectus is not an offer to sell these securities and we are not soliciting offers to buy these securities in any jurisdiction where the offer or sale is not permitted.**

*PROSPECTUS SUPPLEMENT (Subject to Completion)  
(To Prospectus dated October 25, 2005)*

*Issued October 26, 2005*

*7,400,000 Shares*

*COMMON STOCK*

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*We are offering 7,400,000 shares of our common stock and the selling stockholders are offering 32,256 shares of our common stock. We will not receive any of the proceeds from the sale of the shares being sold by the selling stockholders.*

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*Our common stock is quoted on the Nasdaq National Market under the symbol **DRRX** . On October 25, 2005, the reported last sale price of the common stock on the Nasdaq National Market was \$6.84 per share.*

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*Investing in our securities involves risks. See Risk Factors beginning on page S-7 of this prospectus supplement and on page 3 of the accompanying prospectus.*

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*PRICE \$      A SHARE*

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	<u>Price to Public</u>	<u>Underwriting Discounts and Commissions</u>	<u>Proceeds to DURECT</u>	<u>Proceeds to Selling Stockholders</u>
<i>Per Share</i>	\$	\$	\$	\$
<i>Total</i>	\$	\$	\$	\$

*We and a selling stockholder have granted the underwriters the right to purchase an aggregate of up to an additional 1,114,838 shares of common stock to cover over-allotments. We will not receive any proceeds from the sale of the shares being sold by the selling stockholder.*

*The Securities and Exchange Commission and state securities regulators have not approved or disapproved these securities or determined if this prospectus is truthful or complete. Any representation to the contrary is a criminal offense.*

*Morgan Stanley & Co. Incorporated expects to deliver the shares to purchasers on November , 2005.*

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***MORGAN STANLEY***

***JPMORGAN***

***CIBC WORLD MARKETS***

***WR HAMBRECHT + CO***

, 2005

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SABER<sup>®</sup>, TRANSDUR<sup>®</sup>, DURIN<sup>®</sup>, MICRODUR<sup>®</sup>, ORADUR<sup>®</sup>, CHRONOCISIZET<sup>®</sup> and LACTEL<sup>®</sup> are trademarks of DURECT Corporation. Remoxy<sup>®</sup> is a trademark of Pain Therapeutics, Inc. DUROS<sup>®</sup> is a trademark of ALZA Corporation, a Johnson & Johnson Company. Memryte<sup>®</sup> is a trademark of Voyager Pharmaceutical Corporation. Other referenced trademarks belong to their respective owners.

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This prospectus supplement and the accompanying prospectus are part of a registration statement that we filed with the Securities and Exchange Commission (SEC) using a shelf registration process. The shelf registration statement was declared effective by the SEC on October 25, 2005.

## Edgar Filing: DURECT CORP - Form 424B2

This document is in two parts. The first part is the prospectus supplement, which describes the specific terms of the common shares we are offering and also adds to and updates the information contained in the accompanying prospectus and the documents incorporated by reference into the accompanying prospectus. The second part, the prospectus, including the documents incorporated by reference therein, provides more general information. Generally, when we refer to this prospectus, we are referring to both parts of this document combined. To the extent there is a conflict between the information contained in this prospectus supplement, on the one hand, and the information contained in the accompanying prospectus or any document incorporated by reference therein, on the other hand, you should rely on the information in this prospectus supplement.

You should rely only on the information contained in this prospectus supplement and contained, or incorporated by reference, in the accompanying prospectus. We have not authorized and the underwriters have not authorized anyone to provide you with information that is different. We are offering to sell, and seeking offers to buy, shares of our common stock only in jurisdictions where offers and sales are permitted. The information contained in this prospectus supplement and contained, or incorporated by reference, in the accompanying prospectus is accurate only as of the respective dates thereof, regardless of the time of delivery of this prospectus supplement and the accompanying prospectus, or of any sale of our common stock. It is important for you to read and consider all information contained in this prospectus supplement and the accompanying prospectus, including the documents incorporated by reference therein, in making your investment decision. You should also read and consider the information in the documents we have referred you to in the section entitled "Where You Can Find Additional Information" in the accompanying prospectus.

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**PROSPECTUS SUPPLEMENT SUMMARY**

*This summary provides an overview of selected information and does not contain all the information you should consider. You should carefully read both this prospectus supplement and the accompanying prospectus, including the information under Risk Factors, together with the additional information described under Where You Can Find Additional Information in the accompanying prospectus before buying securities in this offering. When used in this prospectus supplement, unless otherwise indicated, the terms we, our, and us refer to DURECT Corporation.*

**DURECT CORPORATION**

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 and providing sustained drug delivery. Our proprietary drug delivery technology platforms include:

**SABER** 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, for which we own all worldwide rights. This product candidate is currently in Phase II clinical trials.

**TRANSDUR** 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 which we have licensed to Endo Pharmaceuticals for the U.S. and Canada. This product candidate 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 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. This product candidate is currently in Phase III 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. This product candidate is currently in Phase III clinical trials.

**DUROS®** 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 and can be used for therapies requiring systemic or site-specific administration of drug. The advantages of DUROS may include precise and 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. This product candidate completed a pilot Phase III clinical trial. Clinical trials have been suspended pending system redesign.

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Our pharmaceutical systems combine engineering innovations and delivery technology with our proprietary pharmaceutical and biotechnology drug formulations. By integrating these technologies, 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 partner with pharmaceutical companies to develop and commercialize proprietary and enhanced pharmaceutical products based on our technologies. We have five disclosed on-going development programs of which four are in collaboration with pharmaceutical partners. The following are our most advanced product candidates in development:

### *SABER-Bupivacaine*

Our post-operative pain relief depot product candidate (SABER-Bupivacaine) is a sustained release injectable using our SABER delivery system to deliver bupivacaine. SABER is a patented controlled drug delivery technology that can be formulated for systemic or local administration of drugs via the parenteral (i.e., injectable) route. This product candidate is designed to be administered around a surgical site after surgery for post-operative pain relief and is intended to provide local analgesia for 3 days or more, which we believe coincides with the time period of the greatest need for post-surgical pain control in most patients. Bupivacaine, the active agent for the product candidate, is currently FDA-approved for use as a local anesthetic in the post-surgical setting.

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 and cognitive impairment. 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 incision 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.

We are currently conducting Phase II dose escalation trials in Australia and the United Kingdom designed for dose optimization of the product candidate. The Australian trial includes three cohorts, and the United Kingdom trial has two cohorts. Each trial will evaluate safety, pharmacokinetics and efficacy. As of October 2005, we have completed dosing of all three cohorts in the Australian Phase II trial, consisting of an aggregate of



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81 patients, and we have announced positive preliminary results from this trial. Dosing for the United Kingdom trial is ongoing.

### *TRANSDUR-Sufentanil*

Our transdermal sufentanil product candidate (TRANSDUR-Sufentanil) uses our proprietary TRANSDUR delivery system to deliver sufentanil, an opioid medication. This product candidate is designed to provide extended chronic pain relief for up to seven days, as compared to the three days of relief provided with currently available opiate patches. We anticipate that the small size of our sufentanil patch (potentially as small as 1/5<sup>th</sup> the size of currently marketed transdermal fentanyl patches for a therapeutically equivalent dose) may offer improved convenience and compliance for patients.

Chronic pain, defined as lasting 6 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<sup>®</sup>, a brand name narcotic painkiller, and Duragesic<sup>®</sup>, a leading transdermal opioid product, accounted for \$1.8 billion and \$2.1 billion in sales, respectively.

We commenced the first clinical trial of the Phase II program for our TRANSDUR-sufentanil product candidate in February 2005. In March 2005, we entered into an agreement with Endo Pharmaceuticals Inc. (Endo) granting Endo exclusive rights to develop, market and commercialize TRANSDUR-Sufentanil in the U.S. and Canada. We have also retained limited co-promotion rights to this product candidate in the U.S. and Canada. In the second quarter of 2005, we continued to perform development activities for Endo with respect to this product candidate. We expect to announce data from the first Phase II trial by the end of 2005.

### *ORADUR-Oxycodone (Remoxy )*

In December 2002, we entered into an agreement with Pain Therapeutics, Inc. (Pain Therapeutics) under which we granted Pain Therapeutics the exclusive, worldwide right to develop and commercialize selected long-acting oral opioid products using our ORADUR technology. ORADUR is our SABER-based oral gel cap technology. Products based on the ORADUR technology can take the form of an easy to swallow gelatin capsule that provides controlled release of active ingredients for a period of 12 to 24 hours of drug delivery. Oral dosage forms based on the ORADUR technology may also have the added benefit of being less prone to abuse than other sustained release dosage forms on the market today. The first product candidate being developed under the collaboration is Remoxy, a novel long-acting oral formulation of the opioid oxycodone targeted to decrease the potential for oxycodone abuse. This product candidate is intended for patients with chronic pain.

Oxycodone is the active drug ingredient in OxyContin<sup>®</sup>, a brand name narcotic painkiller. According to IMS Health Services, there were over 7 million prescriptions written for OxyContin in fiscal year 2004, generating sales exceeding \$1.8 billion. Drug abusers attempt to extract oxycodone from the OxyContin tablets in order to induce a quick euphoric high, while risking respiratory depression, which can be fatal, and opioid addiction. The U.S. Drug Enforcement Administration (DEA) and the national media have linked illicit oxycodone use to widespread patterns of drug abuse, addiction, diversion and drug overdose. In the United States, the Department of Health and Human Services Drug Abuse Warning Network (DAWN) reported over 22,000 oxycodone-specific drug-abuse related emergency room visits in 2002.





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Pain Therapeutics began its first Phase III clinical trial for Remoxy in December 2004. In September 2005, Pain Therapeutics announced that it achieved positive results for this clinical trial, and that it intends to initiate a second Phase III clinical trial by year-end 2005.

### *DURIN-Leuprolide (Memryte®)*

In July 2002, we entered into a development and commercialization agreement with Voyager Pharmaceutical Corporation (Voyager) under which we granted Voyager the exclusive, worldwide right to develop and commercialize a product candidate using the DURIN implant system to deliver the peptide leuprolide acetate to treat Alzheimer's disease based on Voyager's patented method of treatment. DURIN is our proprietary biodegradable polymeric implant drug delivery technology which can deliver a wide variety of drugs from several weeks to six months or more.

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.

Voyager has completed dosing of one Phase I trial for this product candidate, has performed one Phase II proof of concept trial using the active pharmaceutical agent for this product candidate and has another such trial ongoing. 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® (sufentanil) Pain Therapy System*

The CHRONOGESIC (sufentanil) Pain Therapy System is an osmotic implant that is intended to continuously deliver sufentanil for an extended duration. This product candidate is intended to treat chronic pain, and is based on the DUROS System, a miniature osmotic pump capable of continuously delivering drugs for up to a year in duration. We have granted to Endo exclusive commercialization rights for the CHRONOGESIC product candidate in the U.S. and Canada.

To date, we have completed a Phase I clinical trial, a Phase II clinical trial, a pharmacokinetic trial and a pilot Phase III clinical trial for the CHRONOGESIC product candidate. We are presently working to redesign the delivery system to address performance issues. We have stopped all clinical testing of the product candidate and will not resume clinical testing until the system redesign is completed.

### *DURECT Research Programs*

We are also currently researching and developing additional pharmaceutical systems in a variety of therapeutic areas, including chronic pain, central nervous system disorders and cardiovascular diseases based on our proprietary drug delivery platform technologies.

We were incorporated in Delaware in February 1998. Our principal executive offices are located at 10240 Bubb Road, Cupertino, California 95014 and our telephone number at that address is (408) 777-1417. Our website is [www.direct.com](http://www.direct.com). The information contained or incorporated in our website is not part of this prospectus supplement or the accompanying prospectus.

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**THE OFFERING**

Common stock offered by us	7,400,000 shares
Common stock offered by the selling stockholders	32,256 shares
Common stock to be outstanding after this offering	60,709,664 shares
Use of proceeds	For general corporate purposes, including clinical trials, research and development activities, capital expenditures, facilities expansion and to meet working capital needs. We may purchase, exchange or induce conversion of some or all of our convertible notes or acquire businesses, products or technologies. We will not be receiving any proceeds from the sale of shares by the selling stockholders. See Use of Proceeds.
Risk Factors	You should read the Risk Factors sections of this prospectus supplement and the accompanying prospectus for a discussion of factors to consider before deciding to purchase shares of our common stock.
Nasdaq National Market symbol	DRRX

The number of shares to be outstanding after this offering is based on 53,309,664 shares outstanding as of October 25, 2005 and excludes:

7,562,810 shares of common stock issuable upon the exercise of stock options outstanding under our stock option plans at a weighted average exercise price of \$3.92 per share and 5,299,905 additional shares of common stock reserved for issuance under our stock option plans;

175,933 shares reserved for future issuance under our employee stock purchase plan; and

18,202,221 shares of common stock issuable upon conversion of our 6.25% convertible notes due 2008 at a conversion price of approximately \$3.15 per share.

Unless otherwise stated, information herein assumes that the underwriters will not exercise their over-allotment option.

**Table of Contents****SUMMARY FINANCIAL DATA**

The statement of operations data for each of the three years ended December 31, 2004, 2003 and 2002 have been derived from our consolidated audited financial statements. The statement of operations data for the nine months ended September 30, 2005 and 2004, and the balance sheet data as of September 30, 2005, are unaudited but include, in the opinion of management, all adjustments, consisting of only normal recurring adjustments, necessary for a fair presentation of such data. You should read the data presented below in conjunction with Management's Discussion and Analysis of Financial Condition and Results of Operations and our financial statements and related footnotes incorporated by reference in this prospectus supplement and the accompanying prospectus.

	Year ended December 31,					Nine Months ended	
	2002			2003		September 30,	
	2002	2003	2004	2004	2005		
(in thousands, except per share information)							
<b>Consolidated Condensed Statement of Operations Data:</b>							
Product revenue, net	\$ 6,314	\$ 6,691	\$ 6,416	\$ 4,901	\$ 5,299		
Revenue from sale of intellectual property rights					1,600		
Collaborative research and development and other revenue	871	5,144	7,437	4,929	15,896		
<b>Total revenues</b>	<b>7,185</b>	<b>11,835</b>	<b>13,853</b>	<b>9,830</b>	<b>22,795</b>		
Operating expenses:							
Cost of revenue	3,086	2,427	2,729	2,117	1,933		
Research and development	29,554	20,948	24,233	18,020	21,195		
Selling, general and administrative	10,970	8,498	9,747	6,825	8,015		
Amortization of intangible assets	1,340	1,343	1,249	946	909		
Stock-based compensation	1,204	(102)	204	178	453		
<b>Total operating expenses</b>	<b>46,154</b>	<b>33,114</b>	<b>38,162</b>	<b>28,086</b>	<b>32,505</b>		
Loss from operations	(38,969)	(21,279)	(24,309)	(18,256)	(9,710)		
Net other income (expense)	1,796	(1,419)	(3,310)	(2,427)	(2,373)		
Loss before income taxes	(37,173)	(22,698)	(27,619)	(20,683)	(12,083)		
Income tax provision			18		4		
<b>Net loss</b>	<b>\$ (37,173)</b>	<b>\$ (22,698)</b>	<b>\$ (27,637)</b>	<b>\$ (20,683)</b>	<b>\$ (12,087)</b>		
Net loss per share, basic and diluted	\$ (0.77)	\$ (0.45)	\$ (0.54)	\$ (0.40)	\$ (0.23)		
Shares used in computing basic and diluted net loss per share	48,318	50,510	51,507	51,397	52,240		
					<b>As of September 30, 2005</b>		
					<b>Actual</b>	<b>As Adjusted</b>	
<b>Balance Sheet Data:</b>							
Cash and cash equivalents and investments				\$ 59,240	\$ 106,479		
Working capital				50,039	97,278		

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Total assets	85,544	132,783
Long-term debt and equipment financing obligations, net of current portion	58,241	58,241
Stockholders' equity	10,881	58,120

The preceding table summarizes our balance sheet data at September 30, 2005:

on an actual basis; and

as adjusted to reflect our sale of 7,400,000 shares of common stock offered by us at an assumed public offering price of \$6.84 (the reported last sale price on October 25, 2005), after deducting estimated underwriting discounts and commissions and estimated offering expenses payable by us.

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**RISK FACTORS**

*An investment in our securities involves a high degree of risk. You should consider carefully the following risk factors, along with other information contained or incorporated by reference in this prospectus supplement and the accompanying prospectus, in deciding whether to invest in our securities. These factors, among others, may cause actual results, events or performances to differ materially from those expressed in any forward-looking statements we made in this prospectus supplement and the accompanying prospectus, resulting in a decline in the value of our securities and a loss of all or part of your investment.*

**Risks related to this offering**

*Our management will have broad discretion with respect to the use of proceeds of this offering, and may not apply the proceeds to uses that will benefit stockholders*

Our management will have broad discretion as to how to use the proceeds of this offering. You will be relying on the judgment of our management and Board of Directors regarding the application of the proceeds of this offering. The results and effectiveness of the uses of proceeds is uncertain.

*If a significant number of shares of our common stock are sold into the market, the market price of our common stock could significantly decline, even if our business is doing well*

In connection with this offering, our officers, directors and a stockholder owning an aggregate of approximately 11.3 million shares of our common stock have agreed to not sell any of these shares, subject to specified exemptions, for a period of 90 days from the date of this prospectus, subject to extension in certain circumstances. Sales of a substantial number of these shares of our common stock in the public market could depress the market price of our common stock and impair our ability to raise capital through the sale of additional equity securities.

*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*

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 October 25, 2005, we held 25 issued U.S. patents and 18 issued foreign patents. In addition, we have 38 pending U.S. patent applications and have filed 54 patent applications under the Patent Cooperation Treaty, from which 105 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.

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The patent positions of pharmaceutical companies, including ours, are uncertain and involve complex legal and factual questions. In addition, the coverage claimed in a patent application can be significantly reduced before the patent is issued. Consequently, our patent applications or those 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 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 contractors to execute appropriate confidentiality and assignment-of-inventions agreements with us. These agreements typically

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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. Enforcing or defending our proprietary rights is expensive, could cause diversion of our resources and may not prove successful. Any failure to enforce or protect our rights could cause us to lose the ability to exclude others from using our technology to develop or sell competing products.

Our 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.

## **CAUTIONARY NOTE REGARDING FORWARD LOOKING INFORMATION**

All statements included or incorporated by reference in this prospectus, other than statements of historical facts, that address activities, events or developments that we intend, expect, project, believe or anticipate will or may occur in the future are forward looking statements. Such statements are typically characterized by terminology such as believe, anticipate, should, intend, plan, will, expect, estimate, project, strategy, and similar expressions. These statements are based on assumptions and assessments made by our management in light of its experience and its perception of historical trends, current conditions, expected future developments and other factors our management believes to be appropriate. These forward looking statements are subject to a number of risks and uncertainties, including those risks described or incorporated by reference in this prospectus supplement and in the accompanying prospectus under Risk Factors. Any such forward looking statements are not guarantees of future performance and actual results, developments and business decisions may differ from those contemplated by such forward looking statements. We disclaim any duty to update any forward looking statements. You should also carefully consider other information set forth in reports or other documents that we file with the Securities and Exchange Commission.

**Table of Contents****USE OF PROCEEDS**

We estimate that the net proceeds from the sale of the 7,400,000 shares of common stock that we are offering will be approximately \$47.2 million, based upon an assumed public offering price of \$6.84 per share (the reported last sale price on October 25, 2005), after deducting estimated underwriting discounts and commissions and our estimated offering expenses. If the underwriters exercise their option to purchase an additional 820,368 shares from us in the offering, we estimate the aggregate net proceeds to us will be approximately \$52.5 million.

We anticipate that the net proceeds from the sale of securities offered by this prospectus will be used for general corporate purposes, including clinical trials, research and development activities, capital expenditures, facilities expansion and to meet working capital needs. We may also use all or a portion of the proceeds from the sale of securities offered by this prospectus to purchase, exchange or induce conversion of some or all of our 6.25% convertible notes due June 2008 in open market or privately negotiated transactions. We expect from time to time to evaluate the acquisition of businesses, products and technologies for which a portion of the net proceeds may be used, although we currently are not planning or negotiating any such transactions. Pending such uses, we may invest the net proceeds in investment-grade interest-bearing securities. We will not receive any proceeds from the sale of the shares of our common stock by the selling stockholders.

The amounts actually expended for each purpose may vary significantly depending upon numerous factors, including the amount and timing of the proceeds from this offering and progress with the commercial development of our products as well as our clinical development programs. Expenditures will also depend upon the establishment of collaborative arrangements with other companies, the availability of additional financing and other factors. Investors will be relying on the judgment of our management regarding the application of the proceeds of any sale of securities.

**DILUTION**

Our net tangible book value as of September 30, 2005 was \$3.6 million or approximately \$0.07 per share. The per share amount results from dividing total assets less goodwill and intangible assets and total liabilities by the 53,283,459 shares of our common stock outstanding on September 30, 2005. After giving effect to the sale of the 7,400,000 shares of common stock at the assumed public offering price of \$6.84 per share, and after deducting the underwriting discounts and commissions and estimated offering expenses, our net tangible book value as of September 30, 2005 would have been \$50.9 million, or \$0.84 per share. This represents an immediate increase in net tangible book value of \$0.77 per share to existing stockholders and an immediate dilution of \$6.00 per share to new investors in this offering. The following table illustrates this dilution on a per share basis:

Assumed public offering price per share		\$ 6.84
Net tangible book value per share as of September 30, 2005	\$ 0.07	
Increase per share attributable to new investors	0.77	
	<hr/>	
Net tangible book value per share after this offering		0.84
	<hr/>	
Dilution per share to new investors		\$ 6.00
		<hr/>

**Table of Contents****PRICE RANGE OF CAPITAL STOCK**

Our common stock is quoted on the Nasdaq National Market under the symbol DRRX . The following table sets forth, for the periods indicated, the reported high and low sale prices per share of our common stock on the Nasdaq National Market:

	<b>Common Stock Price</b>	
	<b>Low</b>	<b>High</b>
<b>Year ending December 31, 2003</b>		
First Quarter	\$ 1.12	\$ 2.31
Second Quarter	1.41	4.00
Third Quarter	1.87	3.55
Fourth Quarter	2.15	3.99
<b>Year ended December 31, 2004</b>		
First Quarter	\$ 2.51	\$ 3.49
Second Quarter	3.25	4.23
Third Quarter	1.26	3.36
Fourth Quarter	1.41	3.45
<b>Year ended December 31, 2005</b>		
First Quarter	\$ 2.64	\$ 3.78
Second Quarter	2.73	5.09
Third Quarter	4.85	7.15
Fourth Quarter (through October 25, 2005)	6.10	7.00

On October 25, 2005, the reported last sale price of the common stock on the Nasdaq National Market was \$6.84 per share. As of October 25, 2005, there were approximately 187 stockholders of record of our common stock.

**DIVIDEND POLICY**

We have never declared or paid any cash dividends on our common stock and we anticipate that we will continue to retain any earnings for use in the operation of our business and that we will not pay cash for any dividends in the foreseeable future.

**Table of Contents****CAPITALIZATION**

The following table sets forth our cash, cash equivalents and investments and our capitalization as of September 30, 2005:

on an actual basis; and

on an as adjusted basis to give effect to the sale by us of 7,400,000 shares of our common stock in this offering based on an assumed public offering price of \$6.84 per share (the reported last sale price on October 25, 2005), after deducting estimated underwriting discounts and commissions and our estimated offering expenses.

You should read this table in conjunction with Management's Discussion and Analysis of Financial Condition and Results of Operations and our financial statements and related footnotes incorporated by reference to this prospectus.

	<b>As of September 30, 2005</b>	
	<b>Actual</b>	<b>As adjusted</b>
	<b>(in thousands)</b>	
Cash, cash equivalents and investments	\$ 59,240	\$ 106,479
Long-term debt and equipment financing obligations, net of current portion	\$ 58,241	\$ 58,241
Stockholders' equity:		
Common stock, \$0.0001 par value: 110,000,000 shares authorized; 53,283,459 shares issued and outstanding, actual; 60,683,459 shares issued and outstanding, as adjusted	5	6
Additional paid-in capital	200,611	247,849
Deferred compensation	(1)	(1)
Deferred royalties and commercial rights	(13,480)	(13,480)
Accumulated other comprehensive loss	(276)	(276)
Accumulated deficit	(175,978)	(175,978)
Total stockholders' equity	10,881	58,120
Total capitalization	\$ 69,122	\$ 116,361

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### **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 and providing sustained drug delivery. 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, for which we own all worldwide rights. This product candidate is currently in Phase II clinical trials.

**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 which we have licensed to Endo Pharmaceuticals for the U.S. and Canada. This product candidate 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. This product candidate is currently in Phase III 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. This product candidate 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. This product candidate completed a pilot Phase III clinical trial. Clinical trials have been suspended pending system redesign.

**MICRODUR Biodegradable Microparticulates** a microsphere injectable system.

Our pharmaceutical systems combine engineering innovations and delivery technology with our proprietary pharmaceutical and biotechnology drug formulations. By integrating these technologies, 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



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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 partner 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 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:

<b>Disease/Indication</b>	<b>Product</b>	<b>Partner</b>	<b>Technology Platform</b>	<b>Stage</b>
Post Operative Pain	Controlled Release Injection of Local Anesthetic	None	SABER	Phase II
Chronic Pain	Transdermal sufentanil	Endo	TRANSDUR	Phase II
Chronic Pain	Oral controlled release opioid (Remoxy)	Pain Therapeutics	ORADUR	Phase III
Chronic Pain	Systemic sufentanil (CHRONOGESIC)	Endo	DUROS	System redesign
Alzheimer's Disease	Controlled Release Implant (Memryte)	Voyager	DURIN	Phase III
Central Nervous System Disorders	Various	None	SABER/DUROS/DURIN	Preclinical/Research Stages
Cardiovascular Disorders	Various	None	SABER/DUROS/DURIN	Research Stage

***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

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and muscle relaxants. While oral analgesics can effectively control post-surgical pain, they commonly cause side effects such as drowsiness, constipation and cognitive impairment. Effective pain management can be compromised if patients fail to adhere to recommended dosing regimens because they are sleeping or disoriented. We believe that the majority of post-surgical pain can be localized to the incision 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 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 this product 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. This product 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 this product candidate.

*Clinical Program.* We are currently conducting Phase II dose escalation trials in Australia and the United Kingdom designed for dose optimization of the product candidate. The Australian trial includes three cohorts, and the United Kingdom trial has two cohorts. Each trial will evaluate safety, pharmacokinetics and efficacy. As of October 2005, we have completed dosing 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 October 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.

The total numbers of doses of supplemental medication (opiate and non-opiate) were 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.

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### ***Chronic Pain (Systemic)***

*Market Opportunity.* Chronic pain, defined as lasting 6 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 \$1.8 billion and \$2.1 billion in sales, respectively.

*Development Strategy.* We are developing three product candidates for the chronic pain market:

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

an ORADUR-based oral oxycodone product candidate (Remoxy) licensed to Pain Therapeutics intended to decrease the potential of oxycodone abuse; and

the CHRONOGESIC (sufentanil) Pain Therapy System, 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 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 additional milestone payments upon the achievement of specified development milestones and royalties based on the sale of TRANSDUR-Sufentanil upon commercialization in the U.S. and Canada. We have also retained limited co-promotion rights to this product candidate in the U.S. and Canada. In the third quarter of 2005, we continued to perform development activities for Endo with respect to this product candidate.

*Clinical Program.* In October 2004, we initiated a Phase I clinical trial for this product candidate, 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 the product candidate as well as to evaluate the pharmacokinetics of sufentanil following transdermal administration. The study evaluated 24 subjects using the product. 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 this product candidate in February 2005. We expect to announce data from this first Phase II trial by the end of 2005.

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*ORADUR-Oxycodone (Remoxy)*

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. 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. We will receive from Pain Therapeutics milestone payments upon the achievement of specified development milestones and royalties on based on sale of Remoxy upon commercialization anywhere in the world.

*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 4-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.

Pain Therapeutics has stated its intention to initiate a second Phase III study by year-end 2005.

*CHRONOGESIC*

Our CHRONOGESIC product candidate, 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. The product candidate 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, the product candidate is designed to deliver sufentanil for period of up to three months from a single application. If approved for marketing and sale, this product 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. Our CHRONOGESIC product candidate is being developed for the U.S. and Canadian markets in collaboration with Endo Pharmaceuticals, 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 upon the achievement of specified development milestones and royalties on based on sale of CHRONOGESIC upon commercialization 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 our CHRONOGESIC product candidate. 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

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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 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.

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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 the CHRONOGESIC product 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 the product candidate 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 our DURIN-Leuprolide (Memryte) product candidate 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. This product candidate 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 upon the achievement of specified development milestones and royalties based on sale of the resulting product upon commercialization anywhere in the world.

*Clinical Program.* In December 2004, the FDA accepted an Investigational New Drug Application and clinical protocol submitted by Voyager for the DURIN-Leuprolide product candidate. 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 product candidate. Voyager completed enrollment of the clinical trial in January 2005. Voyager has completed dosing of one Phase I trial for this product candidate, has performed one Phase II proof of concept trial using the active pharmaceutical agent for this product candidate 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.

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### ***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. The following are some therapeutic opportunities that we are pursuing in this area:

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 also currently have research exploring the feasibility of targeted delivery of drugs directly to the central nervous system. We view our research 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.



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*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 product using such proprietary angiogenic factor or other proprietary agent, we may be required to obtain a license to use such agent in our product. Any required licenses

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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.

### **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.

### **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.

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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 our injectable post-operative pain relief depot product candidate currently under 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 our transdermal sufentanil patch product candidate currently under Phase II testing, which we have licensed to Endo in the U.S. and Canada.

*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

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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.

### *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 DURIN-Leuprolide (Memryte), our product candidate 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 our CHRONOGESIC product candidate 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 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**

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Our objective is to develop and commercialize 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,

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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 products 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 products 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.

*Expand Our Technology Platforms.* Beyond our core technology platforms, we will continue to develop, license and acquire other technologies consistent with our objective of delivering the right drug to the right place in the right amount at the right time. For example, through our April 2001 acquisition of Southern BioSystems, Inc. (SBS), we acquired an experienced team of specialists and patented technologies in the field of controlled release injectables, implants, microspheres and biodegradable polymers. This acquisition, along with our internal development activities, has increased the breadth and depth of our technology platforms. We expect to continue to license or acquire technology that will complement our core capabilities.

*Enable Product Development Through Strategic Partnerships.* We believe that selective partnering of 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 partnering enables us to leverage investment by our partners and reduce our net cash burn, while retaining significant economic rights.

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We have entered into the following collaborations agreements:

*Pain Therapeutics Inc.* In December 2002, we entered into an exclusive agreement with Pain Therapeutics to develop and commercialize on a worldwide basis selected long-acting oral opioid products 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. We are responsible for formulation development, supply of selected raw materials and other specified tasks. We will receive payments upon the achievement of certain development and regulatory milestones, payments for certain research and development expenditures, as well as royalties based on product sales. 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 a sustained release therapy based on Voyager's patented method of treatment of Alzheimer's disease. The agreement also provides Voyager with the right to commercialize the product on a worldwide basis. We are responsible for preclinical development, product manufacture and other specified tasks. We will receive payments upon the achievement of certain development and regulatory milestones, payments for research and development expenditures, as well as 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 our CHRONOGESIC product for the U.S. and Canada. The agreement was amended in January 2004 and again in November 2004 to take into account the increase in the CHRONOGESIC development program timeline due to DURECT's implementation of necessary design and manufacturing enhancements to the product candidate. 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. For the period commencing January 1, 2004 until the earlier of January 1, 2006 or the commencement of a specified clinical trial, Endo will fund 25% of the ongoing development costs for the CHRONOGESIC product in the U.S. and Canada excluding system redesign costs and pharmacokinetic trials necessitated by any system redesign, up to an aggregate amount of \$250,000 for the period. Commencing on January 1, 2006 or, if earlier, the commencement of a specified clinical trial for the CHRONOGESIC product, Endo will fund 50% of the ongoing development costs and will reimburse us for a portion of our prior development costs for the product 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 the CHRONOGESIC product 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 the CHRONOGESIC product. We will share profits from the commercialization of the product in the U.S. and Canada with Endo based on the financial performance of the CHRONOGESIC product. Based on our projected financial performance of the product in the U.S. and Canada, we anticipate that our share of such profits from commercialization of the product 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 January 2006 in the event we have not commenced a specified clinical trial by January 1, 2006. Due to our redesign of the system to address performance issues, we do not anticipate that we will commence the specified trial by January 1, 2006. Therefore, Endo may elect to terminate this agreement.

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*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, with additional payments of up to approximately \$35 million in the aggregate based upon achievement of predetermined regulatory and commercial milestones. 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) 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 product candidate is currently in pre-clinical development. We are responsible for formulation development of product candidates utilizing our drug delivery platforms and manufacture and supply of product components consisting of our drug delivery platforms. We will receive certain milestone payments related to the development and commercialization of products under this agreement, as well as royalties based on product sales. 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.

## **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.



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### *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**

We intend to establish our own sales force when strategically or economically advantageous. Historically, we have established strategic distribution and marketing alliances for our pharmaceutical systems. We recognize that certain pharmaceutical companies have established sales organizations in markets we are targeting. By partnering, we plan to leverage these sales organizations to achieve greater market penetration for some of our products than we could on our own. Because our first products combine drugs for which medical data on efficacy and safety are available with a proven technology platform, we believe we have the flexibility to enter into these alliances under circumstances that allow us to retain greater economic participation.

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.

### **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 strategic partners. For the three months ended September 30, 2005, revenues from our collaborative agreements with Pain Therapeutics (Remoxy), Endo (TRANSDUR-Sufentanil) and Voyager (DURIN-Leuprolide (Memryte)) represented 13%, 20% and 27% of our total revenues, respectively. For the nine months ended September 30, 2005, revenues from our collaborative agreements with Pain Therapeutics, Endo and Voyager represented 15%, 27% and 25% of our total revenues, respectively. At September 30, 2005, three customers accounted for 28%, 24% and 40% of our gross accounts receivable. At December 31, 2004, two customers accounted for 40% and 26% of our gross accounts receivable.

### **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 is a functional multi-discipline site that we have used to manufacture research and clinical supplies of several of our pharmaceutical system product candidates under GMP, including SABER-Bupivacaine, 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

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additional manufacturing space at our current facilities in Cupertino, CA and Pelham, AL. We manufacture our ALZET product in a leased facility located in Vacaville, California.

### **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.

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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 October 25, 2005, we held 25 issued U.S. patents and 18 issued foreign patents. In addition, we have 38 pending U.S. patent applications and have filed 54 patent applications under the Patent Cooperation Treaty, from which 105 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. 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.

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### **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, record keeping, approval, advertising and promotion of our products. We believe that our initial products will be regulated as drugs by the FDA rather than as biologics or devices, whereas later products 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 products 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.

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.

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 product. 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. The 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.

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.



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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, often at 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 product candidates within any specific time period, if at all. Furthermore, the FDA or the Institutional Review Board or

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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.

The results of product development, preclinical studies and clinical studies are submitted to the FDA as part of a new drug application for approval of the marketing and commercial shipment of the product. The FDA may deny a new drug application if the applicable regulatory criteria are not satisfied or may require additional clinical data. Even if such data is submitted, the FDA may ultimately decide that the new drug application does not satisfy the criteria for approval. Once issued, the FDA may withdraw product approval if compliance with regulatory standards is not maintained or if safety problems occur after the product reaches the market. 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.

In addition to the drug approval requirements applicable to our initial product for the treatment of chronic pain through the Center for Drug Evaluation and Research (CDER), the FDA may require an intercenter consultation review by the Center for Devices and Radiological Health (CDRH). This request for consultation may be based on the device-like nature of a number of aspects of the DUROS technology.

Satisfaction of the above 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 products 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. 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. Delays in obtaining, or failures to obtain regulatory approvals would have a material adverse effect on our business. Marketing our products 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 products manufactured or distributed by us pursuant to FDA clearances or 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. Under the FDA Modernization Act of 1997, the FDA will permit the promotion of a drug for an unapproved use in certain circumstances, but subject to very stringent requirements. We and our products are also subject to a variety of state laws and regulations in those states or localities where our products are or will be marketed. Any applicable state or local regulations may hinder our ability to market our products in those states or localities. We are also subject to numerous federal, state and local laws relating to such matters as safe working conditions, manufacturing practices, environmental protection, fire hazard control, and disposal of hazardous or potentially hazardous substances. We may incur significant costs to comply with such laws and regulations now or in the future.

The FDA's policies may change and additional government regulations may be enacted which could prevent or delay regulatory approval of our potential products. Moreover, increased attention to the containment of health



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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 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 our TRANSDUR-sufentanil, Remoxy and CHRONOGESIC product candidates are listed by the DEA as Schedule II under the Controlled Substances Act of 1970. Consequently, their manufacture, research, shipment, storage, sale and use are subject to a high degree of oversight and regulation. For example, all Schedule II drug prescriptions must be signed by a physician, physically presented to a pharmacist and may not be refilled without a new prescription. Furthermore, the amount of Schedule II substances we can obtain for clinical trials and commercial distribution is limited by the DEA and our quota may not be sufficient to complete clinical trials or meet commercial demand. There is a risk that DEA regulations may interfere with the supply of the drugs used in our clinical trials, and, in the future, our ability to produce and distribute our products in the volume needed to meet commercial demand.

## **Competition**

We may face competition from other companies in numerous industries including pharmaceuticals, medical devices and drug delivery. Our SABER-Bupivacaine, TRANSDUR-Sufentanil, Remoxy and CHRONOGESIC product candidates, 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. 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. Although we have exclusivity with respect to our license of the DUROS technology in specific fields of therapy, ALZA is also a potential competitor with technologies other than DUROS. 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.

## **Employees**

As of October 25, 2005 we had 134 employees, including 84 in research and development, 20 in manufacturing and 30 in selling, general and administrative. From time to time, we also employ independent contractors to support our research, development and administrative

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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.

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**Table of Contents****MANAGEMENT**

Our executive officers and their ages as of October 25, 2005 are as follows:

<b>Name</b>	<b>Age</b>	<b>Position</b>
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 and General Counsel
Paula Mendenhall, Ph.D.	62	Senior Vice President, Operations
Su Il Yum, Ph.D.	66	Senior Vice President, Engineering
Tai Wah Chan, Ph.D.	60	Vice President, Pharmaceutical Research and Development
Steven Halladay, Ph.D.	58	Vice President, Clinical and Regulatory
Jian Li	35	Vice President, Finance and Corporate Controller

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, 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. Prior to that, she served as our Vice President of Legal and General Counsel from February 1999 to February 2003. Previously, from October 1998, Ms. Liu served as our Vice President of Legal. Prior to that, Ms. Liu worked as an attorney at Venture Law Group, a law firm, from May 1997 to October 1998. Ms. Liu worked as an attorney at Pillsbury Madison & Sutro LLP, a law firm, from September 1993 to May 1997. Ms. Liu holds a B.S. in Cellular & Molecular Biology from University of Michigan, an M.S. in Biology from Stanford University and a J.D. from Columbia University School of Law.

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, the American Pharmaceutical Association and the Society of Cosmetic Chemists.



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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. He has more than 40 scientific publications and is the holder of more than 60 U.S. and foreign patents. Dr. Yum is a Fellow of the AAPS.

Tai Wah Chan, Ph.D. has served as our Vice President of Pharmaceutical Research and Development since August 2001. Previously, Dr. Chan served as our Executive Director of Pharmaceutical Research from February 2000 to August 2001 and served as our Senior Director of Pharmaceutical Research from November 1999 to February 2000. Prior to that, Dr. Chan was self employed as a pharmaceutical consultant from October 1997 to November 1999 and was a Senior Scientist at Oread, Inc., a pharmaceutical contract research organization, from October 1996 to October 1997. Dr. Chan holds a B.S. in Physics and Chemistry from the University of Hong Kong and a Ph.D. in Chemistry from the University of Chicago.

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.



**Table of Contents****SELLING STOCKHOLDERS**

Below is information with respect to the number of shares of our common stock owned by the selling stockholders as of October 25, 2005. Except as described below, the selling stockholders do not have, or have had, any position, office or other material relationship with us or any of our affiliates beyond their investment in, or receipt of, our securities.

Percentage ownership for each stockholder is based on 53,309,664 shares of common stock outstanding at October 25, 2005, together with options owned by such stockholder. Beneficial ownership is determined in accordance with the rules of the SEC, and includes voting and investment power with respect to the shares. Beneficial ownership also includes shares of stock subject to options exercisable within 60 days of October 25, 2005. Shares of common stock subject to outstanding options are deemed outstanding for computing the percentage of ownership of the person holding such options, but are not deemed outstanding for computing the percentage ownership of any other person.

Except pursuant to applicable community property laws or as indicated in the footnotes to this table, to our knowledge, each stockholder identified in the table possesses sole voting and investment power with respect to all shares of common stock shown as beneficially owned by such stockholder.

Name and address(1)	Ownership Before Offering		Number of Shares Offered	Ownership After Offering	
	Number of Shares Beneficially Owned	Percentage of Shares Beneficially Owned		Number of Shares Beneficially Owned	Percentage of Shares Beneficially Owned
James E. Brown(2)	2,944,700	5.50%	0(3)	2,944,700(3)	4.83%(3)
Tai Wah Chan(4)	210,871	*	10,000	200,871	*
Jonathan Heuer(5)	22,256	*	22,256	0	*

\* Less than one percent.

- Notes: (1) Except as otherwise indicated, the address of the persons above is c/o DURECT Corporation, 10240 Bubb Road, Cupertino, California 95014.
- (2) Includes 248,700 shares issuable upon exercise of options exercisable within 60 days of October 25, 2005. Dr. Brown is our Chief Executive Officer and a member of our Board of Directors.
- (3) If the underwriters exercise their over-allotment option, Dr. Brown will offer 294,470 shares of common stock to be included in the shares purchased by the underwriters to cover over-allotments. After such offering, Dr. Brown will beneficially own 2,650,230 shares of common stock, which will represent 4.35% of outstanding shares of common stock.
- (4) Includes 148,500 shares issuable upon exercise of options exercisable within 60 days of October 25, 2005. Dr. Chan is our Vice President, Pharmaceutical Research and Development.
- (5) Mr. Heuer is the husband of Jean I Liu, our Senior Vice President, General Counsel and Corporate Secretary.

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**UNDERWRITERS**

Under the terms and subject to the conditions contained in an underwriting agreement dated the date of this prospectus, the underwriters named below, for whom Morgan Stanley & Co. Incorporated, J.P. Morgan Securities Incorporated, CIBC World Markets Corp., and WR Hambrecht + Co, LLC are acting as representatives, have severally agreed to purchase, and DURECT Corporation and the selling stockholders have agreed to sell to them, severally, the number of shares indicated below:

<u>Name</u>	<u>Number of Shares</u>
Morgan Stanley & Co. Incorporated	
J.P. Morgan Securities Incorporated	
CIBC World Markets Corp.	
WR Hambrecht + Co, LLC	
<b>Total</b>	<b>7,432,256</b>

The underwriters are offering the shares of common stock subject to their acceptance of the shares from the DURECT Corporation and the selling stockholders and subject to prior sale. The underwriting agreement provides that the obligations of the several underwriters to pay for and accept delivery of the shares of common stock offered by this prospectus are subject to the approval of certain legal matters by their counsel and to certain other conditions. The underwriters are obligated to take and pay for all of the shares of common stock offered by this prospectus if any such shares are taken. However, the underwriters are not required to take or pay for the shares covered by the underwriters' over-allotment option described below.

The underwriters initially propose to offer part of the shares of common stock directly to the public at the public offering price listed on the cover page of this prospectus and part to certain dealers at a price that represents a concession not in excess of \$ \_\_\_\_\_ a share under the public offering price. After the initial offering of the shares of common stock, the offering price and other selling terms may from time to time be varied by the representatives.

We and one of the selling stockholders have granted to the underwriters an option, exercisable for 30 days from the date of this prospectus, to purchase up to 820,368 and 294,470 additional shares of common stock, respectively, at the public offering price set forth on the cover page of this prospectus, less underwriting discounts and commissions. To the extent the option is not exercised in full, the amount sold will be allocated between the selling stockholder and us so that we will each sell approximately the same percentage of the shares we have included in the option. The underwriters may exercise this option solely for the purpose of covering over-allotments, if any, made in connection with the offering of the shares of common stock offered by this prospectus. To the extent the option is exercised, each underwriter will become obligated, subject to certain conditions, to purchase about the same percentage of the additional shares of common stock as the number listed next to the underwriter's name in the preceding table bears to the total number of shares of common stock listed next to the names of all underwriters in the preceding table. If the underwriters' option is exercised in full, the total price to the public would be \$ \_\_\_\_\_, the total underwriters' discounts and commissions would be \$ \_\_\_\_\_, total proceeds to us would be \$ \_\_\_\_\_ and total proceeds to the selling stockholders would be \$ \_\_\_\_\_.

We, our directors, our executive officers and ALZA Corporation have agreed that, without the prior written consent of Morgan Stanley & Co. Incorporated on behalf of the underwriters, it will not, during the period ending 90 days after the date of this prospectus:

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offer, pledge, sell, contract to sell, sell any option or contract to purchase, purchase any option or contract to sell, grant any option, right or warrant to purchase, lend, or otherwise transfer or dispose of directly or indirectly, any shares of common stock or any securities convertible into or exercisable or exchangeable for common stock; or

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enter into any swap or other arrangement that transfers to another, in whole or in part, any of the economic consequences of ownership of the common stock;

whether any such transaction described above is to be settled by delivery of common stock or such other securities, in cash or otherwise. The restrictions described in this paragraph do not apply to:

shares sold to the underwriters;

our issuance of shares of common stock upon the exercise of an option or a warrant or the conversion of a security outstanding on the date of this prospectus;

our grant of options to our directors, employees, consultants or other service providers in the ordinary course of business;

any shares of our common stock or other rights to acquire shares of our capital stock pursuant to equipment financing, lease financing or working capital financing activities entered into in the ordinary course of business;

any shares of our common stock or other rights to acquire shares of our capital stock in connection with the acquisition of complementary businesses or technologies by merger or acquisition or in connection with partnering, license or similar transactions;  
or

our issuance of shares of common stock in exchange transactions with holders of our 6.25% convertible notes due 2008 pursuant to Section 3(a)(9) of the Securities Act.

The 90-day restricted period described above is subject to extension such that, in the event that either (1) during the last 17 days of the 90-day restricted period, we issue an earnings release or material news or a material event relating to us occurs or (2) prior to the expiration of the 90-day restricted period, we announce that we will release earnings results during the 16-day period beginning on the last day of the 90-day period, the lock-up restrictions described above will, subject to limited exceptions, continue to apply until the expiration of the 18-day period beginning on the earnings release or the occurrence of the material news or material event.

The estimated offering expenses payable by us, in addition to the underwriting discounts and commissions, are approximately \$340,000, which includes legal, accounting and printing costs and various other fees associated with registering and listing the common stock.

In order to facilitate the offering of the common stock, the underwriters may engage in transactions that stabilize, maintain or otherwise affect the price of the common stock. Specifically, the underwriters may sell more shares than they are obligated to purchase under the underwriting agreement, creating a short position. A short sale is covered if the short position is no greater than the number of shares available for purchase by the underwriters under the over allotment option. The underwriters can close out a covered short sale by exercising the over allotment option or purchasing shares in the open market. In determining the source of shares to close out a covered short sale, the underwriters will consider, among other things, the open market price of shares compared to the price available under the over allotment option. The underwriters may also sell shares in excess of the over allotment option, creating a naked short position. The underwriters must close out any naked short position by purchasing shares in the open market. A naked short position is more likely to be created if the underwriters are concerned that there may be downward pressure on the price of the common stock in the open market after pricing that could adversely affect investors who purchase in the offering. As an additional means of facilitating the offering, the underwriters may bid for, and purchase, shares of common stock in the open market to stabilize the price of the common stock. The underwriting syndicate may also reclaim selling concessions allowed to an underwriter or

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a dealer for distributing the common stock in the offering, if the syndicate repurchases previously distributed common stock to cover syndicate short positions or to stabilize the price of the common stock. These activities may raise or maintain the market price of the common stock above independent market levels or prevent or retard a decline in the market price of the common stock. The underwriters are not required to engage in these activities, and may end any of these activities at any time.

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A prospectus in electronic format may be made available on the web sites maintained by one or more underwriters. The underwriters may agree to allocate a number of shares to underwriters for sale to their online brokerage account holders. Internet distributions will be allocated by the lead co-managers to underwrites that may make Internet distributions on the same basis as other allocations.

From time to time, the underwriters have provided, and continue to provide, investment banking services to us.

We, the selling stockholders and the underwriters have agreed to indemnify each other against certain liabilities, including liabilities under the Securities Act.

**LEGAL MATTERS**

The validity of the securities being offered by this prospectus will be passed upon by Heller Ehrman LLP of Menlo Park, California. Davis Polk & Wardwell, Menlo Park, California, is representing the underwriters.

**EXPERTS**

Ernst & Young LLP, independent registered public accounting firm, have audited our consolidated financial statements and schedule included in our Annual Report on Form 10-K for the year ended December 31, 2004, and management's assessment of the effectiveness of our internal controls over financial reporting as of December 31, 2004, as set forth in their reports, which are incorporated by reference in this prospectus and elsewhere in the registration statement. Our financial statements and schedule and management's assessment are incorporated by reference in reliance on Ernst & Young LLP's reports, given on their authority as experts in accounting and auditing.

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**PROSPECTUS**

**\$75,000,000**

**Common Stock**

**INVESTING IN OUR SECURITIES INVOLVES RISKS. SEE RISK FACTORS BEGINNING ON PAGE 3.**

We may offer from time to time up to \$75,000,000 in total of shares of our common stock. In addition, selling stockholders may offer from time to time up to 347,256 shares of our common stock. We will not receive any of the proceeds from the sale of the shares being sold by the selling stockholders.

Our common stock trades on the Nasdaq National Market under the symbol `DRRX` . On October 21, 2005, the last reported sale price of the common stock on the Nasdaq National Market was \$6.90 per share.

We will provide specific terms of these securities in supplements to this prospectus. The prospectus supplement will also describe the specific manner in which we will offer the securities and may also supplement, update or amend information contained in this document. You should read this prospectus and any supplement carefully before you purchase any of our securities.

This prospectus may not be used to offer and sell securities unless accompanied by a prospectus supplement.

**Neither the Securities and Exchange Commission nor any state securities commission has approved or disapproved of these securities or determined if this prospectus is truthful or complete. Any representation to the contrary is a criminal offense.**

We may offer the securities in amounts, at prices and on terms determined at the time of offering. We may sell the securities directly to you, through agents we select or through underwriters and dealers we select. If we use agents, underwriters or dealers to sell the securities, we will name them and describe their compensation in a prospectus supplement.

**The date of this prospectus is October 25, 2005**



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No person has been authorized to give any information or make any representations in connection with this offering other than those contained or incorporated by reference in this prospectus and any accompanying prospectus supplement in connection with the offering described in this prospectus and any accompanying prospectus supplement, and, if given or made, such information or representations must not be relied upon as having been authorized by us. Neither this prospectus nor any prospectus supplement shall constitute an offer to sell or a solicitation of an offer to buy offered securities in any jurisdiction in which it is unlawful for such person to make such an offering or solicitation. Neither the delivery of this prospectus or any prospectus supplement nor any sale made hereunder shall under any circumstances imply that the information contained or incorporated by reference in this prospectus or in any prospectus supplement is correct as of any date subsequent to the date of this prospectus supplement or of any prospectus supplement.

SABER, TRANSDUR, DURIN, MICRODUR, ORADUR, CHRONOGESIC®, ALZET® and LACTEL® are trademarks of DURECT Corporation. Remoxy is a trademark of Pain Therapeutics, Inc. DUROS® is a trademark of ALZA Corporation, a Johnson & Johnson Company. Memryte® is a trademark of Voyager Pharmaceutical Corp. Other referenced trademarks belong to their respective owners.

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**ABOUT THIS PROSPECTUS**

This prospectus is part of a registration statement that we filed with the Securities and Exchange Commission, or SEC, using a shelf registration process. Under this shelf registration process, we may, from time to time, issue and sell to the public any part of the securities described in this prospectus in one or more offerings up to a total dollar amount of \$75,000,000. In addition, selling stockholders named in this prospectus may, from time to time in one or more offerings, issue and sell up to an aggregate of 347,256 shares of our common stock.

This prospectus provides you with a general description of the securities we and the selling stockholders may offer. Each time we or the selling stockholders sell the securities, we will provide a prospectus supplement containing specific information about the terms of that offering. The prospectus supplement may also add, update or change information in this prospectus or in documents incorporated by reference in this prospectus. To the extent that any statement that we make in a prospectus supplement is inconsistent with statements made in this prospectus or in documents incorporated by reference in this prospectus, the statements made or incorporated by reference in this prospectus will be deemed modified or superseded by those made in the prospectus supplement. You should carefully read both this prospectus and any prospectus supplement together with the additional information described under the heading *Where You Can Find More Information* before buying any securities offered in this offering. **THIS PROSPECTUS MAY NOT BE USED TO CONSUMMATE A SALE OF SECURITIES UNLESS IT IS ACCOMPANIED BY A PROSPECTUS SUPPLEMENT.**

The registration statement containing this prospectus, including exhibits to the registration statement, provides additional information about us and the securities offered under this prospectus. The registration statement can be read at the Securities and Exchange Commission (the SEC) web site or at the SEC offices mentioned under the heading *Where You Can Find More Information* .

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**ABOUT DURECT**

We are an emerging specialty pharmaceuticals systems company focused on the development of pharmaceutical systems based on the following proprietary drug delivery technology platforms: the SABER Delivery System (a patented and versatile depot injectable useful for protein and small molecule delivery), the TRANSDUR Delivery System (a proprietary transdermal technology), the ORADUR sustained release oral gel-cap technology (an oral sustained release technology with potential abuse deterrent properties), the DURIN Biodegradable Implant (a biodegradable drug-loaded implant), the DUROS<sup>®</sup> System, (an osmotic implant technology licensed to us for specified fields from ALZA Corporation, a Johnson & Johnson Company) and the MICRODUR Biodegradable Microparticulates (a microspheres injectable system).

Our pharmaceutical systems combine engineering innovations and delivery technology with our proprietary pharmaceutical and biotechnology drug formulations. By integrating these technologies, 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.

We were incorporated in Delaware in February 1998. Our principal executive offices are located at 10240 Bubb Road, Cupertino, California 95014 and our telephone number at that address is (408) 777-1417. Our website is [www.durect.com](http://www.durect.com). The information contained or incorporated in our website is not part of this registration statement.

*Securities We Are Offering*

We may offer shares of common stock with a total value of up to \$75,000,000 from time to time under this prospectus at prices and on terms to be determined by market conditions at the time of the offering. In addition, selling stockholders named in this prospectus may from time to time issue and sell up to 347,256 in total of shares of our common stock at prices and on terms to be determined by market conditions at the time of the offering. Our common stock currently is quoted on the Nasdaq National Market under the symbol **DRRX**. Shares of common stock that may be offered in this offering will, when issued and paid for, be fully paid and non-assessable.

We refer to our common stock in this prospectus as **securities**. This prospectus provides you with a general description of the securities we may offer. Each time we or the selling stockholders offer a type or series of securities, we will provide a prospectus supplement that will describe the specific amounts, prices and other important terms of the securities, as described below under **Plan of Distribution**.

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**RISK FACTORS**

*An investment in our securities involves a high degree of risk. You should consider carefully the following risk factors, along with other information contained or incorporated by reference in this prospectus, in deciding whether to invest in our securities. These factors, among others, may cause actual results, events or performances to differ materially from those expressed in any forward-looking statements we made in this prospectus, resulting in a decline in the value of our securities and a loss of all or part of your investment.*

**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 collaborative partners 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 candidate is long and uncertain, and we may not successfully complete these milestones for any of our product candidates in development. We have not yet selected the drug dosages nor finalized the formulation or the system design of any pharmaceutical systems, including our SABER-Bupivacaine and TRANSDUR-Sufentanil product candidates, Remoxy, our DURIN-Leuprolide (Memryte) product candidate and our CHRONOGESIC product candidate, and we have limited experience in developing such products. We may not be able to finalize the design or formulation of any of our product candidates. 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 the product candidate, the product candidate must still complete required clinical trials and additional safety testing in animals before approval for commercialization. See We must conduct and

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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 product candidates 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 product candidates that will be safe and effective and that will have a commercially reasonable treatment and storage period. If we or our collaborative partners are unable to complete development of our SABER-Bupivacaine, TRANSDUR-Sufentanil, Remoxy, DURIN-Leurpolidide (Memryte), CHRONOGESIC or other product candidates, we will not be able to earn revenue from them, which would materially harm our business.

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*We or our collaborative partners 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 collaborative partners 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.

**ORADUR-Oxycodone (Remoxy)** Phase I and Phase III trials completed by Pain Therapeutics. In September 2005, Pain Therapeutics announced positive results from the first Phase III study and that they intend to initiate a second Phase III study by year-end 2005.

**DURIN-Leuprolide (Memryte) for Alzheimer's disease** Dosing completed in one Phase I trial by Voyager Pharmaceuticals. One Phase II proof of concept trial using the drug but not our DURIN-Leuprolide (Memryte) dosage form 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 product candidates 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 product candidates. These studies include laboratory performance studies and safety testing, clinical trials and animal toxicological studies necessary to support regulatory approval of product candidates 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 product candidates. If our trials are permitted, our potential product candidates 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 product candidates which we have not planned or anticipated that could delay commercialization of such product candidates and harm our business and financial conditions.

The length of our clinical trials will depend upon, among other factors, the rate of trial site and patient enrollment and the number of patients required to be enrolled in such studies. We or our third-party collaborators may fail to obtain adequate levels of patient enrollment in our clinical trials. Delays in planned patient enrollment may result in increased costs, delays or termination of clinical trials, which could have a material adverse effect on us. In addition, even if we or our third-party collaborators enroll the number of patients we expect in the time frame we expect, such clinical trials may not provide the data necessary to support regulatory approval for the product candidates 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.

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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,

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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 product candidate under development could delay or prevent regulatory clearance of the potential product candidate, resulting in delays to the commercialization of our product candidates, 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 product candidates, and thus our product candidates may not be approved for marketing.

*We and our third-party collaborators may not be able to manufacture sufficient quantities of our products 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 product candidates 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 product candidates or components including SABER Bupivacaine, TRANSDUR-Sufentanil, Remoxy, DURIN-Leurpolide (Memryte) and CHRONOGESIC. If we and our third-party collaborators, where relevant, fail to timely complete the development of the manufacturing process for our product candidates, we and our third-party collaborators, where relevant, will not be able to timely produce product for clinical trials and commercialization of our product candidates. We have also committed to manufacture and supply product 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 product candidate or component at an acceptable cost, then we and our third-party partners may not be able to commercialize that product candidate or we may be in breach of our supply obligations to our third-party partners.

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 system product candidates 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 system product candidates. 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 product or components in a timely manner or at an acceptable cost, quality or performance level, and attain and maintain compliance with applicable regulations, the clinical trials and the commercial sale of our pharmaceutical systems and those of our third-party partners 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 product candidates 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



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and manufacturing of our product candidates 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 system product candidates to third parties which have not been approved by ALZA.

If we or our third-party collaborators cannot manufacture product or components in time to meet the clinical or commercial requirements of our partners 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 product candidates and result in failure to achieve anticipated revenues***

The manufacture and marketing of our product candidates 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 product candidates 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. 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 product candidates.

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

### ***Failure to comply with ongoing governmental regulations for our product candidates 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



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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 product candidates, 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 product candidates under development; or

identification of serious and unanticipated adverse side effects in our product candidates 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 product candidates. 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 the product candidates 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 product candidates.

***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. In general, our collaboration agreements, including our agreements with Endo with respect to CHRONOGESIC and TRANSDUR-Sufentanil, Pain Therapeutics with respect to Remoxy and Voyager with respect to DURIN-Leuprolide (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.

Our agreement with Endo for the development and commercialization of our CHRONOGESIC product candidate in the United States and Canada can be terminated by Endo starting in January 2006 in the event we have not commenced a specified clinical trial for the CHRONOGESIC product candidate by January 1, 2006, provided that Endo provides us written notice of termination prior to January 31, 2006. Due to our redesign of the system to address performance problems, we do not anticipate commencing the specified trial by January 1, 2006, and therefore Endo may elect to terminate this agreement.

If any of our collaborative agreements are terminated, our revenues will be reduced and our product candidates related to those agreements may not be commercialized.



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***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 product candidates 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 product candidates. We have entered into agreements with Endo related to the development, promotion and distribution of our CHRONOGESIC and TRANSDUR-Sufentanil product candidates 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 DURIN-Leuprolide (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 product candidates, 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 products arising out of our collaborative arrangements or not devote sufficient resources to the development, manufacture, marketing or sale of these products. If any of these events occur, we may not be able to develop our technologies or recognize revenue from the commercialization of our product candidates 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 product candidates. 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 our TRANSDUR-Sufentanil product candidates 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 our SABER-Bupivacaine and to co-promote along with Endo our TRANSDUR-Sufentanil product candidates in the United States, if such product candidates 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 product candidates, if approved, and our failure to do so could materially harm our business.

***We and our third-party collaborators may not effectively sell our product candidates***

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

fail to satisfy financial or contractual obligations to us;

fail to adequately market our products;

cease operations with little or no notice to us;

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offer, design, manufacture or promote competing product lines;

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

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

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

### ***We rely heavily on third parties to support development, clinical testing and manufacturing of our product candidates***

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 product candidates 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 product candidates, 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 our SABER-Bupivacaine, TRANSDUR-Sufentanil, Remoxy, DURIN-Leuprolide (Memryte) and CHRONOGESIC product candidates) 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 product candidate 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 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 product candidates, causing us to lose sales, incur additional costs and delay new product introductions and could harm our reputation.

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*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 September 30, 2005, we had approximately \$57.3 million in long-term convertible subordinated notes which mature in June 2008, \$29,000 in non-current lease obligations, \$875,000 in non-current bonds payable and \$108,000 in other long-term liabilities. Our substantial indebtedness, which totals \$58.3 million, has and will continue to impact us by:

making it more difficult to obtain additional financing; and

constraining our ability to react quickly in an unfavorable economic climate.



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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 September 30, 2005 we had cash and investments valued at approximately \$59.2 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.

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 September 30, 2005, had an accumulated deficit of approximately \$176.0 million. We expect to continue to incur significant operating



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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 product candidates, obtain the required regulatory clearances and manufacture and market our proposed product candidates. 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 products 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 product candidates 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 product candidates. 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 product candidates. 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;

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 product candidates;

costs involved in establishing manufacturing capabilities for clinical and commercial quantities of our product candidates;

competing technological and market developments;

market acceptance of our product candidates; 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 partners 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, product candidates or products that we would otherwise seek to

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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*

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 September 30, 2005, we held 27 issued U.S. patents and 35 issued foreign patents. In addition, we have 41 pending U.S. patent applications and have filed 54 patent applications under the Patent Cooperation Treaty, from which 105 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 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. 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 product candidates 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 product candidates 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



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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 product candidates that incorporate the challenged intellectual property, which would adversely affect our revenue;

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

redesign our product candidates, 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 product candidate 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;

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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 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.



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***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 product candidates, achieve market acceptance of our product candidates 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 product candidates, 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 product candidates and to fund operating losses to be incurred in the next several years.

***Some of our product candidates 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 product candidates 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. Our TRANSDUR-Sufentanil patch, Remoxy and CHRONOGESIC product candidates and other product candidates 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 product candidates containing controlled substances, we and our suppliers, manufacturers, contractors, customers and distributors are required to obtain and maintain applicable registrations from state, federal and foreign law enforcement and regulatory agencies and comply with state, federal and foreign laws and regulations regarding the manufacture, use, sale, importation and distribution of controlled substances. These regulations are extensive and include regulations governing manufacturing, labeling, packaging, testing, dispensing, production and procurement quotas, record keeping, reporting, handling, shipment and disposal. Failure to obtain and maintain required registrations or comply with any applicable regulations could delay or preclude us from developing and commercializing our product candidates containing controlled substances and subject us to enforcement action. In addition, because of their restrictive nature, these regulations could limit our commercialization of our product candidates containing controlled substances.

***Write-offs related to the impairment of long-lived assets and other non-cash charges, as well as future deferred 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. In 2002, Statement of Financial Accounting Standards No. 142, *Goodwill and Other Intangible Assets* (SFAS 142) became effective and as a result, we ceased to amortize approximately \$4.7 million of goodwill and assembled workforce on January 1, 2002.

However, 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 2004 and determined that goodwill was not impaired as of December 31, 2004. 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.



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To date, we have recorded deferred compensation expenses related to stock options grants, including stock options assumed in our acquisition of SBS, which will be amortized through 2006. In addition, deferred compensation expense related to option awards to non-employees will be calculated during the vesting period of the option based on the then-current price of our common stock, which could result in significant charges that 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 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 product candidates, we are subject to federal, state and local laws, rules, regulations and policies governing the use, generation, manufacture, storage, air emission, effluent discharge, handling and disposal of certain materials, biological specimens and wastes. Although we believe that we have complied with the applicable laws, regulations and policies in all material respects and have not been required to correct any material noncompliance, we may be required to incur significant costs to comply with environmental and health and safety regulations in the future. Our research and development involves the use, generation and disposal of hazardous materials, including but not limited to certain hazardous chemicals, solvents, agents and biohazardous materials. The extent of our use, generation and disposal of such substances has increased substantially since we started manufacturing and selling biodegradable polymers. Although we believe that our safety procedures for storing, handling and disposing of such materials comply with the standards prescribed by state and federal regulations, we cannot completely eliminate the risk of accidental contamination or injury from these materials. We currently contract with third parties to dispose of these substances generated by us, and we rely on these third parties to properly dispose of these substances in compliance with applicable laws and regulations. If these third parties do not properly dispose of these substances in compliance with applicable laws and regulations, we may be subject to legal action by governmental agencies or private parties for improper disposal of these substances. The costs of defending such actions and the potential liability resulting from such actions are often very large. In the event we are subject to such legal action or we otherwise fail to comply with applicable laws and regulations governing the use, generation and disposal of hazardous materials and chemicals, we could be held liable for any damages that result, and any such liability could exceed our resources.



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*Our 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 product candidates using DUROS technology in such field. In order to maintain commercialization rights for our products on a worldwide basis, we must diligently develop our product candidates, procure required regulatory approvals and commercialize the product candidates in selected major market countries. If we fail to meet commercialization diligence requirements, we may lose rights for products in 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

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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.

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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 March 2000. If ALZA or its commercialization partner, 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 product candidates. 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 product candidates 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 product candidates 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

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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.



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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 product candidates. Our competitors may develop products that are safer, more effective or less costly than our product candidates 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 product candidates 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 product candidates. 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 product candidates 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 product candidates 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 product candidates, our present product liability insurance may be inadequate and may not fully cover the costs of any claim or any ultimate damages we might be required to pay. Product liability claims or other claims related to our product candidates, 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 product candidates.

***Acceptance of our product candidates 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 our SABER-Bupivacaine, TRANSDUR-Sufentanil, Remoxy, DURIN-Leuprolide (Memryte) and CHRONOGESIC product candidates. Even if approved for marketing, our product candidates 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 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.

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

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

Broad use of our pharmaceutical systems will require extensive training of numerous physicians on the proper and safe use of our products. 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 products 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 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.



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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. In April 2005, the SEC issued a press release that revised the required date of adoption under SFAS 123R. We will be required to adopt SFAS 123R no later than the fiscal year that begins after June 15, 2005. Our adoption will be applied on a modified prospective basis and measured compensation expense will be recognized commencing 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 are evaluating the impact this guidance will have on our consolidated results of operations and financial position.

In May 2005, the FASB issued Statement No. 154, Accounting Changes and Error Corrections a replacement of APB Opinion No. 20 and FASB Statement No. 3 (SFAS 154). SFAS 154 changes the requirements for the accounting for and reporting of a change in accounting principle, and applies to all voluntary changes in accounting principle. It also applies to changes required by an accounting pronouncement in the unusual instance that the pronouncement does not include specific transition provisions. This statement requires retrospective application to prior periods financial statements of changes in accounting principle, unless it is impracticable to determine either the period-specific effects or the cumulative effect of the change. SFAS 154 is effective for accounting changes made in fiscal years beginning after December 15, 2005. We do not expect that adoption of this statement will have a material impact on our consolidated results of operations.

## **Risks Related To Our Common Stock**

### ***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.

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

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

adverse results or delays in our clinical trials of SABER-Bupivacaine, TRANSDUR-Sufentanil, Remoxy, DURIN-Leuprolide (Memryte), CHRONOGESIC or other product candidates;

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

adverse actions taken by regulatory agencies with respect to our product candidates 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 product candidates;

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.

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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 three months ending September 30, 2005, was 373,333 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



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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.

*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;

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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.

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**CAUTIONARY NOTE REGARDING FORWARD LOOKING INFORMATION**

All statements included or incorporated by reference in this prospectus, other than statements of historical facts, that address activities, events or developments that we intend, expect, project, believe or anticipate will or may occur in the future are forward looking statements. Such statements are typically characterized by terminology such as believe, anticipate, should, intend, plan, will, expect, estimate, project, strategy, and similar expressions. These statements are based on assumptions and assessments made by our management in light of its experience and its perception of historical trends, current conditions, expected future developments and other factors our management believes to be appropriate. These forward looking statements are subject to a number of risks and uncertainties, including those risks described or incorporated by reference in this prospectus under Risk Factors above. Any such forward looking statements are not guarantees of future performance and actual results, developments and business decisions may differ from those contemplated by such forward looking statements. We disclaim any duty to update any forward looking statements. You should also carefully consider other information set forth in reports or other documents that we file with the Securities and Exchange Commission.

**USE OF PROCEEDS**

Unless otherwise indicated in a prospectus supplement, the net proceeds from the sale of securities offered by this prospectus will be used for general corporate purposes, including clinical trials, research and development activities, capital expenditures, facilities expansion and to meet working capital needs. We may also use all or a portion of the proceeds from the sale of securities offered by this prospectus to purchase, exchange or induce conversion of some or all of our 6.25% convertible notes due June 2008 in open market or privately negotiated transactions. We expect from time to time to evaluate the acquisition of businesses, products and technologies for which a portion of the net proceeds may be used, although we currently are not planning or negotiating any such transactions. Pending such uses, we may invest the net proceeds in investment-grade interest-bearing securities. We will not receive any proceeds from the sale of the shares of our common stock by the selling stockholders.

The amounts actually expended for each purpose may vary significantly depending upon numerous factors, including the amount and timing of the proceeds from this offering and progress with the commercial development of our products as well as our clinical development programs. Expenditures will also depend upon the establishment of collaborative arrangements with other companies, the availability of additional financing and other factors. Investors will be relying on the judgment of our management regarding the application of the proceeds of any sale of securities.

**DESCRIPTION OF CAPITAL STOCK**

This section describes the general terms and provisions of the shares of our common stock, \$0.0001 par value per share and preferred stock, \$0.0001 par value per share. This description is only a summary. Our certificate of incorporation and our bylaws have been filed as exhibits to our periodic reports filed with the SEC, which are incorporated by reference into this prospectus. You should read our certificate of incorporation and our bylaws for additional information before you buy any of our securities. See [Where You Can Find More Information](#).

**Common Stock**

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*General.* We are authorized to issue up to 110,000,000 shares of common stock. As of October 11, 2005, there were 53,289,445 shares of common stock issued and outstanding.

*Voting Rights.* The holders of our common stock are entitled to one vote for each share held of record on all matters submitted to a vote of the stockholders, including the election of directors, and do not have cumulative voting rights. Accordingly, the holders of a majority of the shares of common stock entitled to vote in any election of directors can elect all of the directors standing for election, if they so choose.

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*Dividends.* Subject to preferences that may be applicable to any then outstanding preferred stock, holders of common stock are entitled to receive ratably dividends, if any, as may be declared by our board of directors out of funds legally available therefor. We have not declared any dividends and have no current plans to do so.

*Other Rights.* Upon our liquidation, dissolution or winding up, the holders of common stock will be entitled to share ratably in the net assets legally available for distribution to stockholders after the payment of all of our debts and other liabilities, subject to the prior rights of any preferred stock then outstanding. Holders of common stock have no preemptive or conversion rights or other subscription rights and there are no redemption or sinking fund provisions applicable to the common stock. All outstanding shares of common stock are, and the common stock offered, when issued, will be, fully paid and nonassessable.

## **Transfer Agent and Registrar for Common Stock**

The transfer agent and registrar for our Common Stock is Computershare. Its offices are located at 250 Royall Street, Canton, MA 02021, and its telephone number is (781) 575-3452.

## **Preferred Stock**

*General.* We are authorized to issue up to 10,000,000 shares of preferred stock. As of October 11, 2005, no shares of preferred stock were issued and outstanding. Our board of directors has the authority, without further action by our stockholders, to issue from time to time the preferred stock in one or more series, and to fix the number of shares, designations, preferences, powers, and other rights and qualifications, limitations or restrictions as our board of directors may authorize, including:

the distinctive designation of each series and the number of shares that will constitute the series;

the purchase price;

the voting rights, if any, of shares of the series and the terms and conditions of the voting rights;

the dividend rate on the shares of the series, the dates on which dividends are payable, any restriction, limitation or condition upon the payment of dividends, whether dividends will be cumulative, and the dates from and after which dividends shall accumulate;

the prices at which, and the terms and conditions on which, the shares of the series may be redeemed, if the shares are redeemable;

the procedures for any auction or remarketing, if any;

the terms and conditions of a sinking or purchase fund for the purchase or redemption of shares of the series, if such a fund is provided;

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any preferential amount payable upon shares of the series in the event of the liquidation, dissolution or winding up of, or upon the distribution of any of our assets; and

any listing of the preferred stock on any securities exchange or market;

preemption rights, if any;

restrictions on transfer, sale or other assignment, if any;

the prices or rates of conversion or exchange at which, and the terms and conditions on which, the shares of the series may be converted or exchanged into other securities, if the shares are convertible or exchangeable; and

any other specific terms, preferences, rights or limitations of, or restrictions on, the preferred stock.

When we issues shares of preferred stock, the shares will be fully paid and nonassessable and will not have, or be subject to, any preemptive or similar rights.

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Delaware General Corporation Law ( DGCL ) provides that the holders of preferred stock will have the right to vote separately as a class on any proposal involving fundamental changes in the rights of holders of that preferred stock. This right is in addition to any voting rights that may be provided for in the applicable certificate of designation.

The issuance of preferred stock could decrease the amount of earnings and assets available for distribution to holders of common stock or adversely affect the rights and powers, including voting rights, of the holders of common stock. The issuance of preferred stock could have the effect of delaying, deferring or preventing a change in control of our company, which could depress the market price of our common stock.

*Series A Participating Preferred Stock.* Of the 10,000,000 shares of preferred stock currently authorized, we have designated 100,000 shares as series A participating preferred stock. As of October 11, 2005, no shares of series A participating preferred stock were issued and outstanding.

*Voting Rights.* The holders of our series A participating preferred stock are entitled to 1,000 votes, subject to certain adjustments, for each share held of record on all matters submitted to a vote of the stockholders. Except as otherwise provided, holders of shares of series A participating preferred stock and the holders of shares of common stock shall vote together as one class on all matters submitted to a vote of the stockholders.

*Dividends.* Subject to preferences that may be applicable to any then outstanding preferred stock, holders of series A participating preferred stock are entitled to receive ratably dividends, if any, as may be declared by our board of directors out of funds legally available therefor, to be paid on a quarterly basis in an amount per share equal to, subject to certain adjustments, 1,000 times the aggregate per share amount of all cash dividends and 1,000 times the aggregate per share amount of all non-cash dividends or other distributions other than a dividend payable in shares of common stock or a subdivision of the outstanding shares of common stock. We will not declare any dividend on, make any distribution on or redeem or purchase or otherwise acquire for consideration any shares of common stock after the first issuance of a share or fraction of a share of series A participating preferred stock unless we concurrently declare a dividend on the series A participating preferred stock. When dividends payable to holders of series A participating preferred stock are in arrears, we will not take certain actions until such all accrued and unpaid dividends and distributions on shares of series A participating preferred stock are paid in full. We have not declared any dividends and have no plans to do so.

*Other Rights.* Upon our liquidation, dissolution or winding up, no distribution shall be made to the holders of shares ranking junior to the series A participating preferred stock unless the holders of series A participating preferred stock have received an amount equal to the accrued and unpaid dividends and distributions, whether or not declared, to the date of such payment plus an amount equal to the greater of (i) \$1,000 per share, or an adjusted amount if we do not have sufficient assets, and (ii) 1,000 times the aggregate per share amount to be distributed to the holders of common stock, subject to certain adjustments. Upon a consolidation, merger, combination or other transaction in which shares of our common stock are exchanged for or changed into other stock or securities, cash and/or any other property, each share of series A participating preferred stock shall be exchanged or changed in an amount equal to 1,000 times the aggregate amount of stock, securities, cash and/or any other property into which or for which each share of common stock is changed or exchanged, subject to certain adjustments. Holders of series A participating preferred stock have no redemption rights. All outstanding shares of series A participating preferred stock, when issued, will be fully paid and nonassessable.

## **Stockholder Rights Plan**

On July 6, 2001, our board of directors adopted a stockholder rights plan. The stockholder rights plan was adopted to give our board of directors increased power to negotiate in our best interests and to discourage appropriation of control of us at a price that is unfair to our stockholders. It is not intended to prevent fair offers for acquisition of control determined by our board of directors to be in the best interest of us and out

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stockholder, nor is it intended to prevent a person or group from obtaining representation on or control of our board of directors through a proxy contest, or to relieve our board of directors of its fiduciary duty to consider any proposal for our acquisition in good faith.



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The material provisions of the rights plan are summarized below. However, since the terms of our rights agreement are complex, this summary may not contain all the information that is important to you. For more information, you should obtain a copy of the agreement, which is filed as an exhibit with the SEC. See [Where You Can Find More Information](#) for information on how to obtain a copy.

Under the rights agreement, we will issue one right with respect to each share of common stock that is issued prior to the distribution date described below. Except as set forth below, each right, when exercisable, entitles the holder to purchase from us one one-thousandth of a share of our series A participating preferred stock at a price of \$120.00, subject to adjustment. The rights trade in tandem with the common stock until, and become exercisable following, a distribution date. Our board of directors retains the right to amend the stockholder rights plan in any respect until 10 days following our announcement of the occurrence of any such triggering event, as defined below, leading to a distribution. Until a right is exercised, the holder of the right, as such, will have no rights as a stockholder of ours and will not have the right to vote or to receive dividends.

In general, the rights separate from the common stock and a distribution date will occur upon the earlier of:

the close of business on the tenth day (or such later date as may be determined by a majority of our board of directors) following a public announcement that a person or group of affiliated or associated persons has acquired, or obtained the right to acquire, beneficial ownership of 17.5% or more of the outstanding common stock; or

the close of business on the tenth day (or such later date as may be determined by a majority of our board of directors) following the commencement of a tender offer or exchange offer, the consummation of which would result in the beneficial ownership by a person or group of 17.5% or more of the outstanding Common Shares.

If a person or group acquires 17.5% or more of our common stock, all rightholders except the buyer will be entitled to acquire our common stock at a discount and, under certain circumstances, to acquire shares of the acquiring company at a discount. Also, in the event our board of directors may authorize the exchange of all or part of the then outstanding and exercisable rights for shares of our common stock at a rate of one share of our common stock per right if the buyer has not acquired 50% or more of our common stock.

Our board of directors may authorize the redemption of the rights, at a price of \$0.01 per right, at any time before a person or group acquires 17.5% or more of our common stock. The rights will expire on July 6, 2011.

## **ADDITIONAL INFORMATION CONCERNING OUR CAPITAL STOCK**

### **Anti-Takeover Effects of Our Certificate of Incorporation and Bylaws**

Our certificate of incorporation and by-laws include a number of provisions that may have the effect of encouraging persons considering unsolicited tender offers or other unilateral takeover proposals to negotiate with our board of directors rather than pursue non-negotiated takeover attempts. These provisions:

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

providing for a classified board of directors with staggered terms;

requiring supermajority stockholder voting to effect certain amendments to our certificate of incorporation and by-laws;

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

prohibiting stockholder action by written consent; and

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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.

These provisions could discourage, delay or prevent certain types of transactions involving an actual or potential change in control of us, including transactions in which stockholders might otherwise receive a premium for their shares over current market prices.

### **Anti-Takeover Effects of Provisions of Delaware Law**

We are subject to the provisions of Section 203 of the DGCL. In general, the statute prohibits a publicly held Delaware corporation from engaging in a business combination with an interested stockholder for a period of three years following the date that person became an interested stockholder, unless the business combination was approved in a prescribed manner. A business combination includes a merger, asset sale or other transaction resulting in a financial benefit to an interested stockholder. An interested stockholder is a person who, together with affiliates and associates, owns, or, within the three years prior to the determination of interested stockholder status, owned, 15% or more of our outstanding voting stock.

Section 203 makes it more difficult for an interested stockholder to effect various business combinations with a corporation for a three-year period. This statute could prohibit or delay mergers or other takeover or change in control attempts not approved in advance by our board of directors, and as a result could discourage attempts to acquire us, which could depress the market price of our common stock.

### **Limitation of Liability and Indemnification**

To the fullest extent permitted by the Delaware law, our certificate of incorporation provides that directors shall not be personally liable to us or any of our stockholders for monetary damages for breach of fiduciary duty as a director. However, this provision does not eliminate the duty of care, and in appropriate circumstances, equitable remedies such as injunctive or other forms of nonmonetary relief that will remain available under Delaware law. In addition, each director will continue to be subject to liability for (i) breach of the directors duty of loyalty to us or our stockholders, (ii) acts or omissions not in good faith or which involve intentional misconduct or a knowing violation of law, (iii) violating Section 174 of the DGCL, or (iv) any transaction from which the director derived an improper personal benefit. The provision also does not affect a director's responsibilities under any other law, such as the federal securities laws or state or federal environmental laws.

Our bylaws provide that we shall, to the maximum extent and in the manner permitted by the Delaware law, indemnify each of our directors and officers against expenses (including attorneys' fees), judgments, fines, settlements and other amounts actually and reasonably incurred in connection with any proceeding, arising by reason of the fact that such person is or was an agent of our company. Our bylaws also provide that we shall have the power to, to the maximum extent and in the manner permitted by the Delaware law, indemnify each of our employees and agents against expenses (including attorneys' fees), judgments, fines, settlements and other amounts actually and reasonably incurred in connection with any proceeding, arising by reason of the fact that such person is or was an agent of our company. Our bylaws provide that expenses incurred in defending any such action or proceeding shall be paid in advance of the final disposition of such action or proceeding upon the receipt of an undertaking by or on behalf of the indemnified party to repay such amount if it shall be ultimately determined that the indemnified party is not entitled to be indemnified as authorized by our bylaws. The indemnification provided by our bylaws shall not be deemed exclusive of any other rights to which those seeking indemnification may have been entitled under any bylaw, agreement, vote of shareholders or disinterested directors or otherwise, to the extent that such additional rights to indemnification are authorized in our certificate of incorporation.

We also maintain liability insurance for our officers and directors and have entered into indemnification agreements with them.

**Table of Contents****SELLING STOCKHOLDERS**

Below is information with respect to the number of shares of our common stock owned by the selling stockholders as of October 11, 2005. Except as described below, the selling stockholders do not have, or have had, any position, office or other material relationship with us or any of our affiliates beyond their investment in, or receipt of, our securities. See Plan of Distribution for additional information about the selling stockholders and the manner in which the selling stockholders may dispose of their shares.

Percentage ownership for each stockholder is based on 53,289,445 shares of common stock outstanding at October 11, 2005, together with options owned by such stockholder. Beneficial ownership is determined in accordance with the rules of the SEC, and includes voting and investment power with respect to the shares. Beneficial ownership also includes shares of stock subject to options exercisable within 60 days of October 11, 2005. Shares of common stock subject to outstanding options are deemed outstanding for computing the percentage of ownership of the person holding such options, but are not deemed outstanding for computing the percentage ownership of any other person.

Except pursuant to applicable community property laws or as indicated in the footnotes to this table, to our knowledge, each stockholder identified in the table possesses sole voting and investment power with respect to all shares of common stock shown as beneficially owned by such stockholder.

We are registering 347,256 shares of our common stock for resale by the selling stockholders identified in this prospectus. Our registration of these shares does not necessarily mean that the selling stockholders will sell any or all of the shares covered by this prospectus.

The number of shares of common stock that may actually be sold by the selling stockholders will be determined by the selling stockholders. Because each selling stockholder may sell all, some or none of the shares of common stock which it holds, and because the offering contemplated by this prospectus is not currently being underwritten, no estimate can be given as to the number of shares of common stock that will be held by each selling stockholder upon termination of the offering. The information set forth in the following table regarding the beneficial ownership after resale of shares is based on the premise that the selling stockholder will sell all of the shares of common stock owned by that selling stockholder and covered by this prospectus.

Name and address(1)	Ownership Before Offering		Ownership After Offering	
	Number of Shares Beneficially Owned	Percentage of Shares Beneficially Owned	Number of Shares Offered	Percentage of Shares Beneficially Owned
James E. Brown(2)	2,913,450	5.44%	300,000	4.88%
Tai Wah Chan(3)	194,121	*	25,000(4)	*
Jonathan Heuer(5)	22,256	*	22,256	*

\* Less than one percent.

(1) Except as otherwise indicated, the address of the persons above is our address appearing on page 2 of this prospectus.

(2) Includes 217,450 shares issuable upon exercise of options exercisable within 60 days of October 11, 2005. Dr. Brown is our Chief Executive Officer and a member of our Board of Directors.

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- (3) Includes 131,750 shares issuable upon exercise of options exercisable within 60 days of October 11, 2005. Dr. Chan is our Vice President, Pharmaceutical Research and Development.
- (4) Includes shares of common stock to be sold by such holder pursuant to a prospectus supplement, which shares will be issued immediately prior to the sale as a result of the exercise of options.
- (5) Mr. Heuer is the husband of Jean I Liu, our Senior Vice President, General Counsel and Corporate Secretary.

Generally, only selling stockholders identified in the foregoing table who beneficially own the securities set forth opposite their respective names may sell offered securities under the registration statement of which this prospectus forms a part. We may from time to time include additional selling stockholders in an amendment to this registration statement or a supplement to this prospectus.

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**PLAN OF DISTRIBUTION**

We may sell the securities being offered by this prospectus separately or together through any of the following methods:

to or through one or more underwriters or dealers in a public offering and sale by them;

directly to investors;

through agents;

to holders of our 6.25% convertible promissory notes due June 2008 in transactions to repurchase, exchange or induce conversion of such notes; or

through block trades in which the broker or dealer engaged to handle the block trade will attempt to sell the securities as agent, but may position and resell a portion of the block as principal to facilitate the transaction.

We may sell the securities from time to time in one or more transactions at a fixed price or prices, which may be changed from time to time:

at market prices prevailing at the times of sale;

at prices related to such prevailing market prices; or

at negotiated prices.

We will describe the method of distribution of the securities in the applicable prospectus supplement. We may also determine the price or other terms of the securities offered under this prospectus by use of an electronic auction. We will describe how any auction will determine the price or any other terms, how potential investors may participate in the auction and the nature of the obligations of the underwriter, dealer or agent in the applicable prospectus supplement.

Underwriters, dealers or agents may receive compensation in the form of discounts, concessions or commissions from us or our purchasers (as their agents in connection with the sale of the securities). In addition, underwriters may sell the securities to or through dealers, and those dealers may receive compensation in the form of discounts, concessions or commissions from the underwriters and/or commissions from the purchasers for whom they act as agent. These underwriters, dealers or agents may be considered to be underwriters under the Securities Act. As a result, discounts, commissions, or profits on resale received by the underwriters, dealers or agents may be treated as underwriting discounts and commissions. The prospectus supplement will identify any such underwriter, dealer or agent, and describe any compensation received by them from us. Only underwriters named in the prospectus supplement are underwriters of the securities offered by the prospectus supplement. Any initial public offering price and any discounts or concessions allowed or reallocated or paid to dealers may be changed from time to time.

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We may sell the securities directly or through agents we designate from time to time. We will name any agent involved in the offering and sale of securities and we will describe any commissions we will pay the agent in the prospectus supplement. Unless the prospectus supplement states otherwise, our agent will act on a best-efforts basis for the period of its appointment.

We may authorize agents or underwriters to solicit offers by certain types of institutional investors to purchase securities from us at the public offering price set forth in the prospectus supplement pursuant to delayed delivery contracts providing for payment and delivery on a specified date in the future. We will describe the conditions to these contracts and the commissions we must pay for solicitation of these contracts in the prospectus supplement.



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Underwriters, dealers and agents may be entitled to indemnification by us against certain civil liabilities, including liabilities under the Securities Act, or to contribution with respect to payments made by the underwriters, dealers or agents, under agreements between us and the underwriters, dealers and agents.

We may grant underwriters who participate in the distribution of the securities an option to purchase additional securities to cover over-allotments, if any, in connection with the distribution. Any underwriter may engage in over-allotment, stabilizing transactions, short covering transactions and penalty bids in accordance with Regulation M under the Securities Exchange Act of 1934, as amended, or the Exchange Act. Over-allotment involves sales in excess of the offering size, which create a short position. Stabilizing transactions permit bids to purchase the underlying security so long as the stabilizing bids do not exceed a specified maximum. Short covering transactions involve purchases of the common stock in the open market after the distribution is completed to cover short positions. Penalty bids permit the underwriters to reclaim a selling concession from a dealer when the common stock originally sold by the dealer is purchased in a covering transaction to cover short positions. Those activities may cause the price of the common stock to be higher than it would otherwise be. If commenced, the underwriters may discontinue any of the activities at any time.

Any underwriters who are qualified market makers on the Nasdaq National Market may engage in passive market making transactions in the common stock on the Nasdaq National Market in accordance with Rule 103 of Regulation M, during the business day prior to the pricing of the offering, before the commencement of offers or sales of the common stock. Passive market makers must comply with applicable volume and price limitations and must be identified as passive market makers. In general, a passive market maker must display its bid at a price not in excess of the highest independent bid for such security; if all independent bids are lowered below the passive market maker's bid, however, the passive market maker's bid must then be lowered when certain purchase limits are exceeded.

Underwriters or agents and their associates may be customers of, engage in transactions with or perform services for us in the ordinary course of business and any such relationships will be described in the applicable prospectus supplement.

### *Selling Stockholders*

The selling stockholders, or their pledgees, donees, transferees, or any of their successors in interest selling shares received from a named selling stockholder as a gift, partnership distribution or other non-sale-related transfer after the date of this prospectus (all of whom may be selling stockholders) may sell the common stock offered by this prospectus from time to time on any stock exchange or automated interdealer quotation system on which the common stock is listed or quoted at the time of sale, in the over-the-counter market, in privately negotiated transactions or otherwise, at fixed prices that may be changed, at market prices prevailing at the time of sale, at prices related to prevailing market prices or at prices otherwise negotiated. The selling stockholders may sell the common stock by one or more of the following methods, without limitation:

Block trades in which the broker or dealer so engaged will attempt to sell the common stock as agent but may position and resell a portion of the block as principal to facilitate the transaction;

An exchange distribution in accordance with the rules of any stock exchange on which the common stock is listed;

Ordinary brokerage transactions and transactions in which the broker solicits purchases;

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Privately negotiated transactions;

In connection with short sales of company shares;

In connection with an underwritten offering by the company;

By pledge to secure debts of other obligations;

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In connection with the writing of non-traded and exchange-traded call options, in hedge transactions and in settlement of other transactions in standardized or over-the-counter options;

Purchases by a broker-dealer as principal and resale by the broker-dealer for its account; or

In a combination of any of the above.

These transactions may include crosses, which are transactions in which the same broker acts as an agent on both sides of the trade. The selling stockholders may also transfer the common stock by gift. We do not know of any arrangements by the selling stockholders for the sale of any of the common stock.

The selling stockholders may engage brokers and dealers, and any brokers or dealers may arrange for other brokers or dealers to participate in effecting sales of the common stock. These brokers or dealers may act as principals, or as an agent of a selling stockholder. Broker-dealers may agree with a selling stockholder to sell a specified number of the stocks at a stipulated price per share. If the broker-dealer is unable to sell common stock acting as agent for a selling stockholder, it may purchase as principal any unsold shares at the stipulated price. Broker-dealers who acquire common stock as principals may thereafter resell the shares from time to time in transactions in any stock exchange or automated interdealer quotation system on which the common stock is then listed, at prices and on terms then prevailing at the time of sale, at prices related to the then-current market price or in negotiated transactions. Broker-dealers may use block transactions and sales to and through broker-dealers, including transactions of the nature described above. The selling stockholders may also sell the common stock in accordance with Rule 144 or Rule 144A under the Securities Act, rather than pursuant to this prospectus. In order to comply with the securities laws of some states, if applicable, the shares of common stock may be sold in these jurisdictions only through registered or licensed brokers or dealers.

From time to time, the selling stockholders may pledge, hypothecate or grant a security interest in some or all of the shares owned by them. The pledgees, secured parties or person to whom the shares have been hypothecated will, upon foreclosure in the event of default, be deemed to be selling stockholders. The number of a selling stockholder's shares offered under this prospectus will decrease as and when it takes such actions. The plan of distribution for that selling stockholder's shares will otherwise remain unchanged. In addition, a selling stockholder may, from time to time, sell the shares short, and, in those instances, this prospectus may be delivered in connection with the short sales and the shares offered under this prospectus may be used to cover short sales.

To the extent required under the Securities Act, the aggregate amount of selling stockholder's shares being offered and the terms of the offering, the names of any agents, brokers, dealers or underwriters, any applicable commission and other material facts with respect to a particular offer will be set forth in an accompanying prospectus supplement or a post-effective amendment to the registration statement of which this prospectus is a part, as appropriate. Any underwriters, dealers, brokers or agents participating in the distribution of the common stock may receive compensation in the form of underwriting discounts, concessions, commissions or fees from a selling stockholder and/or purchasers of selling stockholder's shares, for whom they may act (which compensation as to a particular broker-dealer might be less than or in excess of customary commissions). Neither we nor the selling stockholders can presently estimate the amount of any such compensation.

The selling stockholders and any underwriters, brokers, dealers or agents that participate in the distribution of the common stock may be deemed to be underwriters within the meaning of the Securities Act, and any discounts, concessions, commissions or fees received by them and any profit on the resale of the securities sold by them may be deemed to be underwriting discounts and commissions. If a selling stockholder is deemed to be an underwriter, the selling stockholder may be subject to certain statutory liabilities including, but not limited to Sections 11, 12 and 17 of the Securities Act and Rule 10b-5 under the Exchange Act. Selling stockholders who are deemed underwriters within the meaning of the Securities Act will be subject to the prospectus delivery requirements of the Securities Act. The SEC staff is of a view that selling stockholders who are registered broker-dealers or affiliates of registered broker-dealers may be underwriters under the Securities Act. We will not pay any compensation or give any discounts or commissions to any underwriter in connection with the securities being offered by this

prospectus.

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A selling stockholder may enter into hedging transactions with broker-dealers and the broker-dealers may engage in short sales of the common stock in the course of hedging the positions they assume with that selling stockholder, including, without limitation, in connection with distributions of the common stock by those broker-dealers. A selling stockholder may enter into option or other transactions with broker-dealers, who may then resell or otherwise transfer those common stock. A selling stockholder may also loan or pledge the common stock offered hereby to a broker-dealer and the broker-dealer may sell the common stock offered by this prospectus so loaned or upon a default may sell or otherwise transfer the pledged common stock offered by this prospectus.

The selling stockholders and other persons participating in the sale or distribution of the common stock will be subject to applicable provisions of the Exchange Act, and the rules and regulations under the Exchange Act, including Regulation M. This regulation may limit the timing of purchases and sales of any of the common stock by the selling stockholders and any other person. The anti-manipulation rules under the Exchange Act may apply to sales of common stock in the market and to the activities of the selling stockholders and their respective affiliates. Regulation M may restrict the ability of any person engaged in the distribution of the common stock to engage in market-making activities with respect to the particular common stock being distributed for a period of up to five business days before the distribution. These restrictions may affect the marketability of the common stock and the ability of any person or entity to engage in market-making activities with respect to the common stock.

We have agreed to indemnify the selling stockholders and any brokers, dealers and agents who may be deemed to be underwriters, if any, of the common stock offered by this prospectus, against specified liabilities, including liabilities under the Securities Act. The selling stockholders have agreed to indemnify us against specified liabilities.

We cannot assure you that the selling stockholders will sell all or any portion of the common stock offered by this prospectus. In addition, we cannot assure you that the selling stockholders will not transfer the shares of our common stock by other means not described in this prospectus.

## **LEGAL MATTERS**

The validity of the securities being offered by this prospectus will be passed upon by Heller Ehrman LLP of Menlo Park, California.

## **EXPERTS**

Ernst & Young LLP, independent registered public accounting firm, has audited our consolidated financial statements and schedule included in our Annual Report on Form 10-K for the year ended December 31, 2004, and management's assessment of the effectiveness of our internal controls over financial reporting as of December 31, 2004, as set forth in their reports, which are incorporated by reference in this prospectus and elsewhere in the registration statement. Our financial statements and schedule and management's assessment are incorporated by reference in reliance on Ernst & Young LLP's reports, given on their authority as experts in accounting and auditing.

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**WHERE YOU CAN FIND MORE INFORMATION**

We are a reporting company and file annual, quarterly and current reports, proxy statements and other information with the Securities and Exchange Commission, or the SEC. You may read and copy these reports, proxy statements and other information at the SEC's public reference rooms at 450 Fifth Street, N.W., Washington, D.C., 20549. You can request copies of these documents by writing to the SEC and paying a fee for the copying cost. Please call the SEC at 1-800-SEC-0330 for more information about the operation of the public reference rooms. Our SEC filings are also available at the SEC's web site at [www.sec.gov](http://www.sec.gov) and our website at [www.durect.com](http://www.durect.com). We have not incorporated by reference into this prospectus the information contained on our website and you should not consider it to be part of this prospectus. In addition, you can read and copy our SEC filings at the office of the National Association of Securities Dealers, Inc. at 1735 K Street, Washington, D.C. 20006.

The SEC allows us to incorporate by reference information that we file with them, which means that we can disclose important information to you by referring you to those documents. The information incorporated by reference is an important part of this prospectus, and information that we file later with the SEC will automatically update and supersede this information. We incorporate by reference the documents listed below and any future filings we will make with the SEC under Section 13(a), 13(c), 14 or 15(d) of the Securities Exchange Act of 1934:

our annual report on Form 10-K for the fiscal year ended December 31, 2004, filed with the SEC on March 14, 2005;

our quarterly report on Form 10-Q for the quarter ended March 31, 2005, filed with the SEC on May 6, 2005;

our quarterly report on Form 10-Q for the quarter ended June 30, 2005, filed with the SEC on August 4, 2005, as amended by Amendment No. 1 to Form 10-Q filed with the SEC on August 9, 2005;

our quarterly report on Form 10-Q for the quarter ended September 30, 2005, filed with the SEC on October 13, 2005;

our definitive proxy statement dated April 28, 2005 for our annual stockholders' meeting on June 22, 2005; and

our current reports on Form 8-K, filed with the SEC on January 13, 2005, January 25, 2005, January 28, 2005, February 10, 2005, February 16, 2005; March 14, 2005, April 11, 2005, April 18, 2005, June 20, 2005, July 11, 2005, July 22, 2005, August 10, 2005, September 9, 2005, September 19, 2005, September 21, 2005, October 13, 2005, October 14, 2005 and October 18, 2005 (except for information concerning financial results contained in such current reports on Form 8-K);

the description of our common stock in our Registration Statements on Form 8-A filed with the SEC on July 10, 2001, as amended by Amendment No. 1 to Form 8-A filed with the SEC on June 24, 2003.

All documents subsequently filed by us pursuant to Sections 13(a), 13(c), 14 or 15(d) of the Securities Exchange Act of 1934, as amended after the date of this registration statement and prior to the effectiveness of this registration statement, shall be deemed to be incorporated by reference.

We will provide to you at no cost a copy of any and all of the information incorporated by reference into the registration statement of which this prospectus is a part. You may make a request for copies of this information in writing or by telephone. Requests should be directed to:

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DURECT Corporation

Attention: Schond L. Greenway, Executive Director, Investor Relations and Strategic Planning

10240 Bubb Road

Cupertino, CA 95014

(408) 777-1417

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