2008 Annual Report

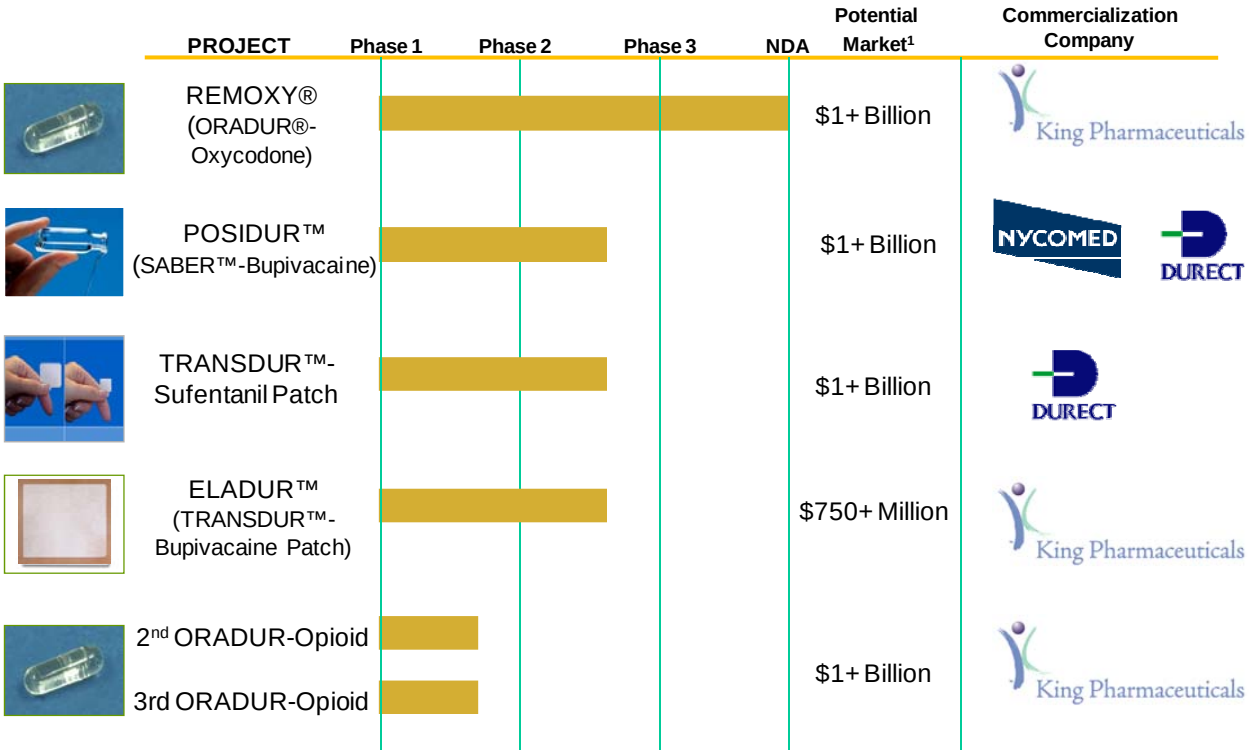
Letter to the Shareholders

Dear Fellow Shareholders:

One of the hallmarks of our Company has been operating the business in a fiscally conservative manner. Over the last four years, while investing in building a pipeline of late stage product candidates, our average cash burn rate has been approximately $12 million per year. In that spirit, given the economic environment and the costs of design/printing, we've decided this year to forego our traditional annual report and instead communicate via this shareholders letter. For additional information on DURECT, please refer to our SEC filings including our 10-K, our website (www.durect.com), or call us at anytime.

DURECT continued to advance our late stage pipeline in 2008, licensed ELADUR™ on attractive terms including a $20 million upfront payment, and strengthened our balance sheet through the elimination of our convertible debt. Another important development in early 2009 occurred with the completion of a successful end-of-Phase II meeting with the FDA for TRANSDUR™-Sufentanil and the restoration of worldwide rights to that program.

Product Pipeline



1) Estimates for potential market opportunities are based on publicly available information, research reports and company reports.

Highlights for DURECT in Fiscal Year 2008, early Fiscal 2009 and Next Steps:

- **REMOXY®.** In June 2008, an NDA for REMOXY (ORADUR®-based oxycodone) was submitted to the U.S. Food and Drug Administration (FDA). In August, this NDA filing was accepted and granted Priority Review by the FDA. The FDA typically grants Priority Review to drug candidates that have the potential to demonstrate significant improvements compared to marketed products. Pain Therapeutics received a Complete Response Letter from the FDA in December 2008 indicating that the NDA is not approved in its present form. According to Pain Therapeutics, the FDA indicated that additional non-clinical data will be required to support the approval of REMOXY but the FDA has not requested or recommended additional clinical efficacy studies prior to approval. Our understanding is that Pain Therapeutics, King Pharmaceuticals and their outside technical advisors have been evaluating the FDA Complete Response Letter and there are plans to meet with the FDA in mid-2009, which should provide our collaborators with a more reliable context with which to make projections about REMOXY.

  REMOXY, an investigational drug, is a long acting oral formulation of oxycodone intended to treat moderate to severe pain. Based on DURECT's ORADUR® technology, which is covered by issued patents and pending patent applications owned by us, REMOXY is designed to resist common methods of prescription drug misuse and abuse.

- **POSIDUR™ (SABER™-Bupivacaine).** We have recently received detailed feedback from the FDA on our proposed Phase III program. We are pursuing a target label for POSIDUR that would allow POSIDUR to be used for a broad range of surgeries**.** Based on FDA feedback, in contrast to the two pivotal efficacy studies that we had previously planned, we now anticipate conducting one pivotal efficacy study and several other supportive clinical studies in additional surgical models to provide greater definition for the settings in which the product should be used and to support our target label. We currently expect that the total number of patient exposures that we will submit to the FDA in an NDA will be approximately 700-800. Under our current development program, approximately 300 human subjects have been exposed to POSIDUR. Assuming the program progresses as we expect, we anticipate that the Phase III program should take approximately two years from initiation to NDA filing. To review the major planned activities for POSIDUR in 2009:

  - We expect to have data from our approximately 60 patient Phase IIb clinical study in shoulder surgery this year.

  - We plan to conduct a thorough QTc (tQTc) study in 2009. A tQTc study is a cardiac safety test increasingly recommended by the FDA. To date, we have not observed any differences in cardiovascular or central nervous system side effects between the roughly 300 patients dosed to date with POSIDUR versus approximately 150 placebo patients.

  - Nycomed is conducting a Phase IIb study in hysterectomy patients and a Phase IIb study in shoulder surgery patients beginning in 2009. Those studies will be conducted in a different manner than U.S. studies as they are designed for European regulatory approval purposes. We anticipate that these studies will provide data from an additional surgical model (hysterectomy) and will add considerably to our safety database.

  - Lastly, we are in discussions with various parties about licensing development and commercialization rights to POSIDUR in the U.S., Canada and Asia.

POSIDUR is our investigational post-operative pain relief depot that utilizes our patented SABER technology to deliver bupivacaine to provide up to three days of pain relief after surgery. POSIDUR is licensed to Nycomed for commercialization in Europe and select other countries, and we have retained commercialization rights in the U.S., Canada and Asia.

- **ELADUR™ (TRANSDUR™-Bupivacaine).** During 2008, DURECT presented data showing improved pain control with ELADUR versus placebo over the three day treatment period in a Phase IIa study. We also received Orphan Drug Designation, such that if ELADUR is the first bupivacaine product approved for Post-Herpetic Neuralgia (PHN), ELADUR will receive seven years of market exclusivity for PHN following its approval by the FDA.

  Effective October 2008, we licensed the worldwide development and commercialization rights for ELADUR to Alpharma Ireland, Ltd. (which was acquired by King Pharmaceuticals in December 2008). Under this agreement, Alpharma paid us an upfront license fee of $20 million in the fourth quarter of 2008, with possible additional payments of up to $93 million upon the achievement of predefined development and regulatory milestones spread over multiple clinical indications and geographical territories as well as possible additional payments of up to $150 million in sales-based milestones. If ELADUR is commercialized, DURECT would also receive royalties on product sales. Our main activities since that time have involved interacting with the King team on the program such that specific decisions can be made with respect to the clinical program.

  ELADUR is our proprietary transdermal patch intended to deliver bupivacaine for a period of up to three days from a single application.

- **TRANSDUR™-Sufentanil.** A 74 patient Phase IIb clinical trial of chronic pain patients using TRANSDUR-Sufentanil was completed during 2008. In this trial, all of the primary and secondary objectives were met by showing patients could be successfully converted from oral opioids such as OxyContin® and from fentanyl patches such as Duragesic® to TRANSDUR-Sufentanil, while also showing a reduction in pain scores on our therapy. A successful end-of-Phase II meeting was held with the FDA in February 2009. As a result of that meeting, we believe we understand the anticipated regulatory pathway for the Phase III program and approval, which we expect will follow a 505(b)2 pathway as discussed with FDA. We are in active discussions with several potential partners regarding licensing of this program.

  TRANSDUR-Sufentanil is our proprietary transdermal patch intended to deliver sufentanil to chronic pain sufferers for a period of up to seven days from a single application.

- **Reduction in Convertible Notes.** Our balance sheet was strengthened during 2008 by the elimination of all of our $23.6 million of convertible debt, which was converted into common stock in June 2008 per the original terms of our indenture.

A major priority for DURECT is on the business development front where we have multiple late stage programs that are the subject of partnering discussions. These include TRANSDUR-Sufentanil (worldwide), POSIDUR (U.S., Canada and Asia), as well as various internal programs which we have not described publicly in detail.

Investment Highlights

- **Multiple drug candidates in late stage development.** The value of most pharmaceutical companies ultimately comes down to the products they can produce. We are fortunate to have multiple drug candidates in late stage development, including one NDA submitted to the FDA, 3 product candidates in Phase II and 2 programs in Phase I. Each of these product candidates address large market opportunities in the underserved pain management field and have product features that represent what we believe constitute meaningful advancements over current therapies.
- **Productive R&D team.** The R&D team at DURECT is led by senior scientists that have successfully developed products in the past and that are committed to doing so in the future. In addition to the later stage programs described above, we have other pre-clinical programs underway that we believe will yield additional drug candidates in the future.
- **Balanced business model.** Our business model complements the diversification we possess in product candidates and technologies. Certain programs have already been licensed to strong partners on attractive terms, providing financial, development and commercialization resources beyond the means of an emerging company. Strategically, we've retained worldwide or territorial rights to other programs, which provide the basis for future partnering and financing of product development.

On behalf of everyone at DURECT, we thank you for your continued support and look forward to reporting on our continued progress in 2009 and beyond.

Felix Theeuwes, D.Sc.
Chairman and
Chief Scientific Officer

James E. Brown, D.V.M.
President and
Chief Executive Officer

Forward Looking Statement: The statements in this shareholders letter regarding our possible licensing of development and commercialization rights to POSIDUR, TRANSDUR-Sufentanil and other programs to third parties, our collaborators' anticipated meeting with the FDA regarding REMOXY, our intended dose, target label and anticipated total patient exposures, our and Nycomed's clinical development plans including tQTc and other clinical studies, potential timing of completion of our Phase IIb clinical trial and Phase III program for POSIDUR are forward-looking statements involving risks and uncertainties that can cause actual results to differ materially from those in such forward-looking statements. Potential risks and uncertainties include, but are not limited to, failure of our clinical trials to produce intended results, possible adverse events associated with the use of our drug candidates, delays and costs due to additional work or other requirements imposed by regulatory agencies for continued development, approval or sale of our drug candidates, DURECT's (and that of its third party collaborators where applicable) difficulty or failure to obtain approvals from regulatory agencies with respect to its development activities and products, design, enroll, conduct and complete clinical trials, complete the design, development, and manufacturing process development of the referenced product candidates, consummate collaborative agreements relating to our product candidates and technologies, manufacture and commercialize the referenced product candidates, obtain marketplace acceptance of the referenced product candidates, avoid infringing patents held by other parties and secure and defend patents of our own, and manage and obtain capital to fund its growth, operations and expenses. Further information regarding these and other risks is included in DURECT's Form 10-Q under the heading "Risk Factors."