NEKTAR THERAPEUTICS
Form 10-K
March 06, 2009

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UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
WASHINGTON, DC 20549

FORM 10-K

FOR ANNUAL AND TRANSITION REPORTS PURSUANT TO SECTIONS 13 OR 15(d)
OF THE SECURITIES EXCHANGE ACT OF 1934

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

For the fiscal year ended December 31, 2008

or

o **TRANSITION REPORTS PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934.**

Commission File Number: 0-24006

NEKTAR THERAPEUTICS
(Exact name of registrant as specified in its charter)

Delaware	**94-3134940**
(State or other jurisdiction of incorporation or organization)	**(IRS Employer Identification No.)**

201 Industrial Road
San Carlos, California 94070
(Address of principal executive offices and zip code)
650-631-3100
(Registrant s telephone number, including area code)

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

Title of Each Class	**Name of Each Exchange on Which Registered**
Common Stock, $0.0001 par value	**NASDAQ Global Select Market**

Securities registered pursuant to Section 12(g) of the Act: **None**
Indicate by check mark if the registrant is a well-known seasoned issuer, as defined in Rule 405 of the Securities Act. Yes o No þ
Indicate by check mark if the registrant is not required to file reports pursuant to Section 13 or Section 15(d) of the Act. Yes o No þ
Indicate by check mark whether the registrant (1) has filed all reports required to be filed by Section 13 or 15(d) of the Securities Exchange Act of 1934 during the preceding 12 months (or for such shorter period that the registrant was required to file such reports), and (2) has been subject to such filing requirements for the past 90 days) Yes þ No o
Indicate by check mark if disclosure of delinquent filers pursuant to Item 405 of Regulation S-K (§ 229.405) is not contained herein, and will not be contained, to the best of registrant s knowledge, in definitive proxy or information

statements incorporated by reference in Part III of this Form 10-K or any amendment to this Form 10-K. þ

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

Large accelerated filer o	Accelerated filer þ	Non-accelerated filer o	Smaller reporting company o
		(Do not check if a smaller reporting company)	

Indicate by check mark whether the registrant is a shell company (as defined in Exchange Act Rule 12b-2) Yes o No þ

The approximate aggregate market value of voting stock held by non-affiliates of the registrant, based upon the last sale price of the registrant s common stock on the last business day of the registrant s most recently completed second fiscal quarter, June 30, 2008 (based upon the closing sale price of the registrant s common stock listed as reported on the NASDAQ Global Select Market), was approximately $300,233,348. This calculation excludes approximately 2,792,787 shares held by directors and executive officers of the registrant. Exclusion of these shares does not constitute a determination that each such person is an affiliate of the registrant.

As of February 27, 2009, the number of outstanding shares of the registrant s common stock was 92,506,054.

DOCUMENTS INCORPORATED BY REFERENCE

Portions of registrant s definitive Proxy Statement to be filed for its 2009 Annual Meeting of Stockholders are incorporated by reference into Part III hereof. Such Proxy Statement will be filed with the Securities and Exchange Commission within 120 days of the end of the fiscal year covered by this Annual Report on Form 10-K.

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2008 ANNUAL REPORT ON FORM 10-K
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PART IV

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Forward-Looking Statements

This report includes forward-looking statements within the meaning of Section 27A of the Securities Act of 1933, as amended (the Securities Act), and Section 21E of the Securities Exchange Act of 1934, as amended (the Exchange Act). All statements other than statements of historical fact are forward-looking statements for purposes of this annual report on Form 10-K, including any projections of earnings, revenue or other financial items, any statements of the plans and objectives of management for future operations (including, but not limited to, pre-clinical development, clinical trials and manufacturing), any statements concerning proposed drug candidates or other new products or services, any statements regarding future economic conditions or performance and any statements of assumptions underlying any of the foregoing. In some cases, forward-looking statements can be identified by the use of terminology such as may, will, expects, plans, anticipates, estimates, potential or continue, or the negat other comparable terminology. Although we believe that the expectations reflected in the forward-looking statements contained herein are reasonable, such expectations or any of the forward-looking statements may prove to be incorrect and actual results could differ materially from those projected or assumed in the forward-looking statements. Our future financial condition and results of operations, as well as any forward-looking statements, are subject to inherent risks and uncertainties, including, but not limited to, the risk factors set forth in Part I, Item 1A Risk Factors below and for the reasons described elsewhere in this annual report on Form 10-K. All forward-looking statements and reasons why results may differ included in this report are made as of the date hereof and we do not intend to update any forward-looking statements except as required by law or applicable regulations. Except where the context otherwise requires, in this annual report of Form 10-K, the Company, Nektar, we, us, and our refer to Nektar Therapeutics, a Delaware corporation, and, where appropriate, its subsidiaries.

Trademarks

The Nektar brand and product names, including but not limited to Nektar®, contained in this document are trademarks, registered trademarks or service marks of Nektar Therapeutics in the United States (U.S.) and certain other countries. This document also contains references to trademarks and service marks of other companies that are the property of their respective owners.

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PART I

Item 1. Business

We are a clinical-stage biopharmaceutical company developing a pipeline of drug candidates that utilize our PEGylation and advanced polymer conjugate technology platforms, which are designed to improve the benefits of drugs for patients. Our current proprietary product pipeline is comprised of drug candidates across a number of therapeutic areas including oncology, pain, anti-infectives, anti-viral and immunology. Our research and development activities involve small molecule drugs, peptides and other potential biologic drug candidates. We create our innovative drug candidates by using our proprietary chemistry platform to modify the chemical structure of drugs using unique polymer conjugates. Polymer chemistry is a science focused on the synthesis or bonding of polymer architectures with drug molecules to alter the properties of the molecule when it is bonded with our proprietary polymers. Additionally, we may utilize established pharmacologic targets to engineer a new drug candidate relying on a combination of the known properties of these targets and our polymer chemistry technology and expertise. Our drug candidates are designed to improve the pharmacokinetics, pharmacodynamics, half-life, bioavailability, metabolism or distribution of drugs and improve the overall benefits and use of a drug for the patient. Our objective is to apply our advanced polymer conjugate technology platform to create new drugs in multiple therapeutic areas.

Each of our drug candidates which we are currently developing internally is a proprietary new chemical or biological entity that addresses large potential markets. We are developing drug candidates that can be delivered by oral or subcutaneous administration. Our most advanced proprietary product candidate, Oral NKTR-118, is a peripheral opioid antagonist that is currently being evaluated for the treatment of opioid-induced constipation (OIC) and we recently announced that we were terminating our Phase 2 clinical trial for this program due to positive preliminary results. Our other lead product candidate, NKTR-102, is a cytotoxic topoisomerase I inhibitor that is being evaluated or will be evaluated in four separate Phase 2 clinical trials for the treatment of multiple cancers, including ovarian, breast, cervical and colorectal.

In addition to our internal pipeline, we have a number of collaborations and license agreements for our technology with leading biotechnology and pharmaceutical companies, including Amgen, Schering-Plough, Baxter, UCB and Roche. A total of nine products using our PEGylation technology platform have received regulatory approval in the U.S. or Europe, and are currently marketed by our partners. There are also a number of other products in clinical development that use our technology platform. These licensing collaborations will represent the majority of our revenue stream in 2009 which will be comprised of a combination of upfront and contract research fees, milestones, manufacturing product sales and product royalties.

We also have a significant collaboration with Bayer Healthcare LLC to develop BAY41-6551 (NKTR-061, Amikacin Inhale), which is an inhaled solution of amikacin, an aminoglycoside antibiotic. We originally developed the liquid aerosol inhalation platform and product and entered into a collaboration with Bayer Healthcare LLC in 2007 for its development. We have another proprietary product candidate, NKTR-063 (Inhaled Vancomycin), which uses the same aerosol platform as BAY41-6551. A Phase 1 clinical trial has been completed for NKTR-063 to treat patients with Gram-positive pneumonias.

On December 31, 2008, we completed the sale and transfer of certain pulmonary technology rights, certain pulmonary collaboration agreements and approximately 140 of our dedicated pulmonary personnel and operations to Novartis Pharma AG. We retained all of our rights to BAY41-6551 and NKTR-063, certain rights to receive royalties on net sales of the Cipro Inhale (also known as Ciprofloxacin Inhaled Powder or CIP) program with Bayer Schering Pharma AG that we transferred to Novartis as part of the transaction, and we also retained certain intellectual property rights to patents specific to inhaled insulin. In connection with the closing of the transaction, we also terminated the Tobramycin Inhalation Powder (TIP) collaboration agreement with Novartis.

We were incorporated in California in 1990 and reincorporated in Delaware in 1998. We maintain our executive offices at 201 Industrial Road, San Carlos, California 94070, and our main telephone number is (650) 631-3100.

Our Technology Platform

With our expertise as a leader in the field of PEGylation, we have advanced our technology platform to include first-generation PEGylation and new advanced polymer conjugate chemistries that can be tailored in very specific and customized ways to optimize and significantly improve the profile of a wide range of molecules and many classes of

drugs and disease areas.

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PEGylation has been a highly effective technology platform for the development of therapeutics with significant commercial success, such as Roche s PEGASYS® (PEG-interferon alfa-2a) and Amgen s Neulasta® (pegfilgrastim). All of the PEGylated drugs approved over the last fourteen years were enabled with our PEGylation technology through our collaborations and licensing partnerships with pharmaceutical companies. PEG (polyethylene glycol) is a versatile technology and is a water soluble, amphiphilic, non-toxic, non-immunogenic compound that is safely cleared from the body. Its primary use to date has been in currently approved biologic drugs to favorably alter their pharmacokinetic or pharmacodynamic properties. However, in spite of its widespread success in commercial drugs, there are limitations with the first-generation PEGylation approaches used with biologics. These limitations include the inability of the earlier approaches of PEGylation technology to be used successfully with small molecule drugs, antibody fragments and peptides, all of which could potentially benefit from the application of the technology. Other limitations of the early approaches of PEGylation technology include resulting sub-optimal bioavailability and bioactivity, and its limited ability to be used to fine-tune properties of the drug, as well as its inability to be used to create oral drugs. With our expertise and proprietary technology in PEGylation, we have created the next-generation of PEGylation technology. Our advanced polymer conjugate technology platform is designed to overcome the limitations of the first generation of the technology platform and allow the platform to be utilized with a broader range of molecules across many therapeutic areas.

Both our PEGylation and advanced polymer conjugate technology platforms have the potential to offer one or more of the following benefits:

- improve efficacy or safety in certain instances as a result of better pharmacokinetics, pharmacodynamics, longer half-life and sustained exposure of the drug;
- improve targeting or binding affinity of a drug to its target receptors with the potential to improve efficacy and reduce toxicity or drug resistance;
- enable oral administration of parenterally-administered drugs, or drugs that must be administered intravenously or subcutaneously, and increase oral bioavailability of small molecules;
- prevent drugs from crossing the blood-brain barrier and limiting undesirable central nervous system effects;
- reduce first-pass metabolism effects of certain drug classes with the potential to improve efficacy, which could reduce the need for other medicines and reduce toxicity;
- reduce rate of drug absorption and of elimination or metabolism by improving stability of the drug in the body and providing it with more sufficient time to act on its target; and
- reduce immune response to certain macromolecules with the potential to prolong their effectiveness with repeated doses.

We have a broad range of approaches that we may use when designing our own drug candidates, some of which are outlined below:

Small Molecule Polymer Conjugates

Our customized approaches with small molecule polymer conjugates allows for the fine-tuning of the physicochemical and pharmacological properties of small molecule oral drugs to potentially increase their therapeutic benefit. In addition, this approach can enable oral administration of subcutaneously-delivered small molecule drugs that have shown low bioavailability when delivered orally. Benefits of this approach can also include: improved potency, increased oral bioavailability, modified biodistribution with enhanced pharmacodynamics, and reduced transport across specific membrane barriers in the body, such as the blood-brain barrier. A primary example of the application of membrane transport inhibition, specifically reducing transport across the blood-brain barrier is Oral NKTR-118, a novel peripheral opioid antagonist that is in the final stages of Phase 2 clinical development. An example of a drug candidate that uses this approach to avoid first-pass metabolism is NKTR-140, a novel protease inhibitor in preclinical development.

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Small Molecule Pro-Drug Conjugates

The pro-drug polymer conjugation approach can be used to optimize the pharmacokinetics and pharmacodynamics of a small molecule drug to substantially increase both its efficacy and side effect profile. We are currently using this platform with oncolytics, which typically have sub-optimal half-lives that can limit their therapeutic efficacy. With our technology platform, we believe that these drugs can be modulated for programmed release within the body, optimized bioactivity and increased sustained exposure of active drug to tumor cells in the body. We are using this approach with the two oncolytic candidates in our pipeline, NKTR-102, a novel PEGylated form of irinotecan in Phase 2 clinical development, and NKTR-105, a novel PEGylated form of docetaxel in Phase 1 clinical development.

Peptide Large Molecule Polymer Conjugates

Our customized approaches with large molecule polymer conjugates have enabled numerous successful PEGylated biologics on the market today. We are using our advanced polymer conjugation technology-based approach to enable peptides, which are much smaller in size than other biologics, such as proteins and antibody fragments. We are in the early stages of research with a number of peptides that utilize this proprietary approach. Peptides are important in modulating many physiological processes in the body. Some of the benefits of working with peptides are: they are small, more easily optimized, and can be rapidly investigated for therapeutic potential. However, peptide drug discovery has been slowed by the extremely short half-life and limited bioavailability of these molecules.

Based on our knowledge of the technology and biologics, our scientists have designed a novel hydrolyzable linker that can be used to optimize the bioactivity of a peptide. Through rational drug design and the use of our approach, a peptide s pharmacokinetics and pharmacodynamics can be substantially improved and its half-life can be significantly extended. The approach can also be used with proteins and larger molecules, as well.

Antibody Fragment Conjugates

This approach uses a large molecular weight polyethylene glycol (PEG) conjugated to antibody fragments in order to potentially improve their toxicity profile, extend their half-life and allow for ease of synthesis with the antibody. The specially designed PEG then becomes part of the antibody fragment Fc. Since the antibody fragment is more like a biologic, this conjugation has a branched architecture with either stable or degradable linkage. This approach can be used to reduce antigenicity, reduce glomerular filtration rate, and retain antigen-binding affinity and recognition.

There is currently one approved product on the market that utilizes our technology with an antibody fragment, CIMZIA (certoluzimab pegol), which was developed by our partner UCB Pharma and is approved for the treatment of Crohn s Disease in the U.S.

Our Strategy

The key elements of our business strategy are outlined below:

Advance Our Internal Clinical Pipeline of Drug Candidates that Leverage Our PEGylation and Advanced Polymer Conjugate Chemistry Platform

Our objective is to create value by advancing our lead drug candidates through early to mid-stage clinical development. To support this strategy, in 2008, we significantly expanded our strong internal expertise in our clinical development and regulatory departments. We intend to decide on a product-by-product basis whether we wish to continue development into Phase 3 pivotal clinical trials and commercialize products on our own, or seek a partner, or pursue a combination of these approaches.

A key component of our development strategy is to potentially reduce the risks and time associated with drug development by capitalizing on the known safety and efficacy of approved drugs as well as established pharmacologic targets and drugs directed to those targets. For many of our novel drug candidates, we may seek approval in indications for which the parent drugs have not been studied or approved. We believe that the improved characteristics of our drug candidates will provide meaningful benefit to patients compared to the existing therapies, and allow for approval to provide new treatments for patients for which the parent drugs are not currently approved.

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Ensure Future Growth of our Pipeline through Internal Research Efforts and Advancement of our Preclinical Drug Candidates into Clinical Trials

We believe it is important to maintain a diverse pipeline of new drug candidates to continue to build on the value of our business. Our early research organization is identifying new drug candidates by applying our technology platform to a wide range of molecule classes, including small molecules and large proteins, peptides and antibodies, across multiple therapeutic areas. We continue to advance our most promising early research drug candidates into preclinical development with the objective to advance these early stage research programs to human clinical studies over the next several years.

Enter into Strategic and High-Value Partnerships to Bring Our Drugs to Market

Our partnering strategy is to enter into collaborations with larger pharmaceutical and biotechnology companies at appropriate stages in our drug development process to fund further clinical development, manage the global regulatory filing process, and market and sell the approved drugs. The options for future collaboration arrangements range from comprehensive licensing arrangements to co-promotion and co-development agreements with the structure of the collaboration depending on factors such as the cost and complexity of development, marketing and commercialization needs and therapeutic area focus.

Continue to Build a Leading Intellectual Property Estate in the Field of PEGylation and Polymer Conjugate Chemistry across Therapeutic Modalities

We are committed to continuing to build on our intellectual property position in the field of PEGylation and polymer conjugate chemistry. To that end, we have a comprehensive patent strategy providing us with ownership of patents and patent applications covering a wide range of approaches, including, among others, polymer materials, conjugates, formulations, synthesis, therapeutic areas and methods of treatment.

Approved Drugs and Drug Candidates Enabled By Our Technology through Licensing Collaborations

The following table outlines our collaborations with a number of pharmaceutical companies that license our technology, including Amgen, Schering-Plough, Baxter, UCB and F. Hoffmann-La Roche. A total of nine products using our PEGylation technology have received regulatory approval in the U.S. or Europe. There are also a number of other candidates that have been filed for approval or are in various stages of clinical development. These collaborations generally contain several elements including license rights to our proprietary technology, manufacturing and supply agreements under which we may receive manufacturing revenue, milestone payments, and/or product royalties on commercial sales.

Drug	Primary or Target Indications	Licensing Partner and Drug Marketer	Status(1)
Neulasta® (pegfilgrastim)	Neutropenia	Amgen Inc.	Approved
PEGASYS® (peginterferon alfa-2a)	Hepatitis-C	F. Hoffmann-La Roche Ltd	Approved
Somavert® (pegvisomant)	Acromegaly	Pfizer Inc.	Approved
PEG-INTRON® (peginterferon alfa-2b)	Hepatitis-C	Schering-Plough Corporation	Approved
Macugen® (pegaptanib sodium injection)	Age-related macular degeneration	OSI Pharmaceuticals (formerly Eyetech)	Approved
CIMZIA (certolizumab pegol)	Crohn s disease	UCB Pharma	Approved in U.S. and Switzerland
MIRCERA® (C.E.R.A.) (Continuous Erythropoietin Receptor Activator)	Anemia associated with chronic kidney disease in patients on dialysis and patients not on dialysis	F. Hoffmann-La Roche Ltd	Approved in U.S. and EU (Launched only in the EU)*

CIMZIA (certolizumab pegol)	Rheumatoid arthritis	UCB Pharma	Filed in the U.S. and EU
Hematide (synthetic peptide-based, erythropoiesis-stimulating agent)	Anemia	Affymax, Inc.	Phase 3
MAP0004	Migraine	MAP Pharmaceuticals	Phase 3
Cipro Inhale	Cystic fibrosis lung infections	Bayer Schering Pharma AG	Phase 2**
CIMZIA (certoluzimab pegol)	Psoriasis	UCB Pharma	Phase 2
CDP-791 (PEG-antibody fragment angiogenesis inhibitor)	Non-small cell lung cancer	UCB Pharma	Phase 2
Longer-acting Factor VIII and other blood clotting proteins	Hemophilia	Baxter	Preclinical

(1) Status definitions are:

Approved regulatory approval to market and sell product obtained in the U.S., EU and other countries.

Filed Products for which a New Drug Application (NDA) or Biologics License Application (BLA) has been filed

Phase 3 or Pivotal product in large-scale clinical trials conducted to obtain regulatory approval to market and sell the drug (these trials are typically initiated following encouraging Phase 2 trial results).

Phase 2 product in clinical trials to establish dosing and efficacy in patients.

Phase 1 product in clinical trials, typically in healthy subjects, to test safety. In the case of oncology drug candidates, Phase 1 clinical trials are typically conducted in cancer patients.

Research/preclinical product is being studied in research by way of vitro studies and/or animal studies

* Amgen Inc. prevailed in a patent lawsuit against F. Hoffmann-La Roche Ltd and as a result of this legal ruling Roche is currently prevented from marketing MIRCERA® in the U.S.

** This product candidate was developed using our proprietary pulmonary delivery technology that

was transferred to Novartis in an asset sale transaction that closed on December 31, 2008. As part of the transaction, Novartis assumed our rights and obligations for our Cipro Inhale agreements with Bayer Schering PharmaAG; however, we maintained the rights to receive certain royalties on commercial sales of Cipro Inhale if the product candidate is approved.

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Nektar Proprietary Internal Drug Candidates in Clinical Development

The following table summarizes our proprietary product development pipeline and significant partnerships. The table includes the type of molecule or drug, the primary indication for the product or product candidate, and the clinical trial status of the program.

Drug Candidate	Target Indications	Status (1)
BAY41-6551 (NKTR-061, Amikacin Inhale)	Gram-negative pneumonias	Phase 2 (Partnered with Bayer Healthcare LLC)*
NKTR-102 (PEGylated irinotecan)	Second-line colorectal cancer in patients with the KRAS gene mutation	Phase 2
NKTR-102 (PEGylated irinotecan)	Metastatic breast cancer	Phase 2
NKTR-102 (PEGylated irinotecan)	Metastatic ovarian cancer	Phase 2
NKTR-102 (PEGylated irinotecan)	Metastatic cervical cancer	Phase 2
Oral NKTR-118 (PEGylated naloxol)	Opioid-induced constipation (OIC)	Phase 2
NKTR-105 (PEGylated docetaxel)	Solid tumors	Phase 1
NKTR-063 (Inhaled Vancomycin)	Gram-positive pneumonias	Phase 1*
NKTR-140 (protease inhibitor candidate)	HIV	Research/Preclinical
NKTR-171 (undisclosed pain candidate)	Neuropathic pain	Research/Preclinical
NKTR-125 (PEGylated antihistamine candidate)	Allergic rhinitis	Research/Preclinical

(1) Status definitions are:

Phase 3 or Pivotal product in large-scale clinical trials conducted to obtain regulatory approval to market and sell the drug (these trials are typically initiated following encouraging Phase 2 trial results).

Phase 2 product in clinical trials to establish dosing and efficacy in patients.

Phase 1 product in clinical trials, typically in healthy subjects, to test safety. In the case of oncology drug candidates, Phase 1 clinical trials are typically conducted in cancer patients.

Research/preclinical product is being studied in research by way of vitro studies and/or animal studies

* This product candidate uses a liquid aerosol technology platform that was transferred to Novartis in the pulmonary asset sale transaction that was completed on December 31, 2008. As part of that transaction, we retained an exclusive license to this technology

for the development and commercialization of this drug candidate originally developed by Nektar.

Overview of Selected Proprietary Product Development Programs

NKTR-102 (PEGylated irinotecan)

We are developing NKTR-102, a novel PEGylated form of irinotecan that was designed using our advanced polymer conjugate technology platform. The product candidate is currently in Phase 2 clinical development. Irinotecan, also known as Camptosar®, is a topoisomerase I inhibitor used for the treatment of solid tumors, including colorectal and lung cancers. By applying our proprietary pro-drug conjugate technology to irinotecan, NKTR-102 has the potential to be a more effective and tolerable anti-tumor agent. Using a proprietary approach that directly conjugates the drug to a multi-arm polymer architecture, we are the first company to have created a PEGylated small molecule with a unique pharmacokinetic profile that has demonstrated therapeutic activity in patients.

NKTR-102 is currently in Phase 2 clinical development for the treatment of multiple cancers, including colorectal, ovarian, and breast. In addition, we also plan to commence a Phase 2 trial for NKTR-102 in patients with cervical cancer. A Phase 2 randomized trial of NKTR-102 was initiated in early 2009 that will evaluate the efficacy and safety of NKTR-102 monotherapy versus irinotecan in second-line colorectal cancer patients with the KRAS mutant gene. According to the National Comprehensive Clinical Network, colorectal cancer is the most frequently diagnosed cancer in men and women in the United States. In 2008, it is estimated that over 108,000 new cases of colon cancer and approximately 40,780 cases of rectal cancer occurred. During the same year, it is estimated that 49,960 people died from colon and rectal cancer. The primary endpoint of the Phase 2 placebo-controlled trial of NKTR-102 in colorectal cancer will be a clinically meaningful improvement in progression-free survival as compared to standard irinotecan monotherapy. According to recent data presented at the American Society of Clinical Oncology in 2008, it is estimated that up to 45% of colorectal cancer cases have this mutation in the KRAS gene and do not respond to EGFR-inhibitors, such as cetuximab. A Phase 2a study of NKTR-102 is also ongoing to evaluate NKTR-102 in combination with cetuximab in 18 patients with refractory solid tumors, primarily gastrointestinal-related cancers.

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Two separate NKTR-102 Phase 2 studies are also ongoing in ovarian and breast cancers. These studies are open label, single arm studies encompassing two treatment regimens (every 14 days or every 21 days). Patients include those with metastatic breast cancer with prior taxane treatment, those with metastatic and platinum-resistant ovarian cancer. The Phase 2 study for cervical cancer that we plan to initiate in 2009 is for patients with metastatic cervical cancer. The trials will evaluate the overall response rate (ORR) of NKTR-102 monotherapy in each tumor setting, with secondary endpoints including progression-free survival, safety and six and 12-month overall survival.

Ovarian, breast, and cervical cancers remain significant health problems for women worldwide. In 2008, there were an estimated 21,650 new diagnoses and an estimated 15,520 deaths from ovarian cancer in the United States and, historically, less than 40% of women with ovarian cancer are cured. The American Cancer Society estimated that over 184,000 new cases of invasive breast cancer were diagnosed and nearly 41,000 women died of breast cancer in the United States in 2008. Cervical cancer is a major world health problem for women. The global annual incidence of cervical cancer in 2002 was over 490,000 with an annual death rate of over 270,000. It is currently the third most common cancer in women worldwide.

Oral NKTR-118 (PEGylated naloxol)

Oral NKTR-118 is a novel oral drug candidate that is in the final stages of Phase 2 clinical development, combines our stable conjugate polymer technology with naloxol, a derivative of the opioid-antagonist drug naloxone. On March 2, 2009, we announced that we were terminating the Phase 2 trial for Oral NKTR-118 as a result of positive preliminary results. The peripheral opioid antagonist Oral NKTR-118 targets opioid receptors within the enteric nervous system, which mediate opioid-induced bowel dysfunction (OBD), a symptom resulting from opioid use that encompasses constipation, bloating, abdominal cramping and gastroesophageal reflux. Opioid-induced constipation (OIC) is the hallmark of this syndrome and is generally its most prominent component. According to the American Pain Society, over 200 million opioid prescriptions are filled in the U.S. annually with worldwide sales of opioids reaching $7.5 billion in 2007. Depending on the population studied and the definitions used, constipation occurs in up to 90% of patients taking opioids. Currently, there are no specific oral drugs approved or specifically indicated to treat OBD or OIC.

We are also conducting early discovery research on a new drug candidate, NKTR-119, which we intend to develop as a co-formulation of NKTR-118 and a long-acting opioid analgesic. Our research plan for NKTR-119 program is to create a long-acting opioid without the related gastrointestinal side effects, such as OBD including OIC.

NKTR-105 (PEGylated docetaxel)

NKTR-105 is a novel PEGylated conjugate form of docetaxel, an anti-neoplastic agent belonging to the taxoid family that acts by disrupting the microtubular network in cells. Docetaxel is a major chemotherapy agent approved for use in five different cancer indications: breast, non-small cell lung, prostate, gastric, and head and neck. Annual sales of docetaxel in 2007 exceeded $2 billion. Oncolytics, such as docetaxel, typically have sub-optimal half-lives which can limit their therapeutic efficacy. Our advanced polymer conjugation technology can be used to optimize the bioactivity of these drugs and increase the sustained exposure of active drug to tumor cells in the body.

NKTR-105 is currently being evaluated in a Phase 1 clinical trial in cancer patients that began in February 2009. The study will assess the safety, pharmacokinetics, and anti-tumor activity of NKTR-105 in approximately 30 patients with refractory solid tumors who have failed all prior available therapies.

NKTR-140 (protease inhibitor)

NKTR-140 is a novel protease inhibitor product candidate to treat human immunodeficiency virus (HIV), which can lead to acquired immunodeficiency syndrome or AIDS. The product was developed using Nektar s advanced small molecule polymer conjugate technology. The drug candidate is designed to have improved potency as compared to leading protease inhibitors used in clinical practice today, and also to eliminate the need for a co-administered protease inhibitor booster, such as ritonavir. NKTR-140 is currently being studied in a number of preclinical trials.

Overview of Select Licensing Partnerships for Approved Products

All of the approved products today that use our technology platforms are a result of licensing collaborations with partners. We also have a number of product candidates in clinical development by our partners that use our technology or involve rights over which we have patents or other proprietary intellectual property. In a typical collaboration involving our PEGylation technology, we license our proprietary intellectual property related to our PEGylation

technology or proprietary conjugated drug molecules in consideration for upfront payments, development milestone payments and royalties from sales of the resulting commercial product as well as sales milestones. We also manufacture and supply our proprietary PEGylation materials to our partners.

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Neulasta®, Agreement with Amgen, Inc.

In July 1995, we entered into a non-exclusive supply and license agreement with Amgen, Inc. (Amgen), pursuant to which we license our proprietary PEGylation technology to be used in the development and manufacture of Neulasta. Neulasta selectively stimulates the production of neutrophils that are depleted by cytotoxic chemotherapy, a condition called neutropenia that makes it more difficult for the body to fight infections. We manufacture and supply our proprietary PEGylation materials for Amgen on a fixed price basis. The term of the agreement is for a fixed duration with a limited number of renewal options. This agreement is scheduled to expire in 2010.

PEGASYS®, Agreement with F. Hoffmann-La Roche Ltd

In February 1997, we entered into a license, manufacturing and supply agreement with F. Hoffmann-La Roche Ltd and Hoffmann-La Roche Inc. (Roche), under which we granted Roche a worldwide, exclusive license to use certain PEGylation materials to manufacture and commercialize a certain class of products, of which PEGASYS is the only product currently commercialized. PEGASYS is approved in the U.S., E.U. and other countries for the treatment of Hepatitis C and is designed to help the patient s immune system fight the Hepatitis C virus. We currently manufacture our proprietary PEGylation materials for Roche on a price per gram basis. Roche has an option for a license extension related to the agreement. The agreement expires on the later of January 10, 2015 or the expiration of our last relevant patent containing a valid claim.

Somavert®, Agreement with Pfizer, Inc.

In January 2000, we entered into a license, manufacturing and supply agreement with Sensus Drug Development Corporation (subsequently acquired by Pharmacia Corp. in 2001 and then acquired by Pfizer, Inc. in 2003), for the PEGylation of Somavert (pegvisomant), a human growth hormone receptor antagonist for the treatment of acromegaly. We currently manufacture our proprietary PEGylation reagent for Pfizer on a price per gram basis. The agreement expires on the later of ten years from the grant of first marketing authorization in the designated territory, which occurred in March 2003, or the expiration of our last relevant patent containing a valid claim. In addition, Pfizer may terminate the agreement if marketing authorization is withdrawn or marketing is no longer feasible due to certain circumstances, and either party may terminate for cause if certain conditions are met.

PEG-Intron®, Agreement with Schering-Plough Corporation

In February 2000, we entered into a manufacturing and supply agreement with Schering-Plough Corporation (Schering) for the manufacture and supply of our proprietary PEGylation materials to be used by Schering in production of a pegylated recombinant human interferon-alpha (PEG-Intron). PEG-Intron is a treatment for patients with Hepatitis C. We currently manufacture our proprietary PEGylation materials for Schering on a price per gram basis. The agreement is for a fixed duration with renewal terms conditioned upon mutual agreement.

Macugen®, Agreement with OSI Pharmaceuticals (formerly Eyetech)

In 2002, we entered into a license, manufacturing and supply agreement with Eyetech Pharmaceuticals, Inc., subsequently acquired by OSI Pharmaceuticals, Inc. (OSI) in 2005, pursuant to which we license our proprietary PEGylation technology for the development and commercialization of Macugen®, a PEGylated anti-vascular endothelial growth factor aptamer currently approved in the U.S. and E.U. for use in treating age-related macular degeneration. We currently manufacture our proprietary PEGylation materials for OSI on a price per gram basis. Under the terms of the agreement, we will receive royalties on net product sales in any particular country covered by a valid patent claim for the longer of ten years from the date of the first commercial sale of the product in that country or the manufacture, use or sale of such product in that country. The agreement expires upon the expiration of our last relevant patent containing a valid claim. In addition, OSI may terminate the agreement if marketing authorization is withdrawn or marketing is no longer feasible due to certain circumstances, and either party may terminate for cause if certain conditions are met.

CIMZIA , Agreement with UCB Pharma

In December 2000, we entered into a license, manufacturing and supply agreement for CIMZIA (certolizumab pegol, CDP870) with Celltech Chiroscience Ltd., which was acquired by UCB Pharma (UCB) in 2004. Under the terms of the agreement, UCB is responsible for all clinical development, regulatory, and commercialization expenses. We have the right to receive manufacturing revenue on a cost-plus basis and royalties on net product sales. We are entitled to receive royalties on net sales of the CIMZIA product in any particular country for the longer of ten years from the first

commercial sale of the product in that country or the expiration of patent rights in that particular country. CIMZIA is currently approved in the treatment of Crohn s Disease in the U.S. The agreement expires upon the expiration of all of UCB s royalty obligations, provided that the agreement can be extended for successive two year renewal periods upon mutual agreement of the parties. In addition, UCB may terminate the agreement should it cease the development and marketing of CIMZIA and either party may terminate for cause under certain conditions.

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In April 2008, UCB received FDA approval for CIMZIA in the U.S. in the treatment of moderate to severe Crohn s disease. Crohn s disease is a chronic digestive disorder of the intestines commonly referred to as inflammatory bowel disease that affects an estimated 400,000 to 600,000 individuals in the U.S. In March 2008, the European Medicines Agency (EMEA) rejected the appeal following CHMP refusal of the MAA for CIMZIA in the treatment of patients with Crohn s disease, a chronic and debilitating inflammatory disease.

In December 2007, UCB submitted a Biologics License Application (BLA) to the FDA for CIMZIA for the treatment of rheumatoid arthritis. Rheumatoid arthritis is an autoimmune disease that causes chronic inflammation of the joints. The submission was accepted in February of 2008. In January 2009, UCB announced that the FDA issued a Complete Response Letter (CRL) relating to the BLA of CIMZIA , the first PEGylated anti-TNF, for the treatment of rheumatoid arthritis. In July 2008, UCB announced that a Marketing Authorisation Application (MAA) has been submitted to and accepted for review by the EMEA requesting the approval of CIMZIA (certolizumab pegol) as a subcutaneous treatment for adults with moderate to severe active rheumatoid arthritis.

UCB is also conducting clinical trials on CIMZIA for psoriasis and other indications. The product is in Phase 2 trials for the treatment of psoriasis.

MIRCERA® (C.E.R.A.) (Continuous Erythropoietin Receptor Activator), Agreement with F. Hoffmann-La Roche Ltd

In December 2000, we entered into a license, manufacturing and supply agreement with F. Hoffmann-La Roche Ltd and Hoffmann-La Roche Inc. (Roche), which was amended and restated in its entirety in December 2005. Pursuant to the agreement, we license our proprietary PEGylation materials for use in the development and manufacture of Roche s MIRCERA product. MIRCERA is a novel continuous erythropoietin receptor activator indicated for the treatment of anemia associated with chronic kidney disease in patients on dialysis and patients not on dialysis. We are entitled to receive royalties on net sales of the MIRCERA product in any particular country for the longer of ten years from the first commercial sale of the product in that country or the expiration of patent rights in that particular country. The agreement expires upon the expiration of all of Roche s royalty obligations, unless earlier terminated by Roche for convenience or by either party for cause under certain conditions.

In April 2006, Roche filed a BLA for MIRCERA with the FDA for the treatment of anemia associated with chronic kidney disease, including patients on dialysis or not on dialysis, and an MAA with the EMEA to treat patients with chronic kidney disease. In May 2007, MIRCERA was approved in the EU and the product was subsequently launched by Roche in the EU in August of 2007. In November 2007, the FDA approved Roche s BLA application for MIRCERA but the product has not been launched in the U.S. as a result of patent-related issues.

In October 2008, a federal district court ruled in favor of Amgen Inc. in a patent infringement lawsuit involving MIRCERA and issued a permanent injunction which prevents Roche from marketing or selling MIRCERA in the U.S. even though the FDA approved MIRCERA. This federal district court decision is currently on appeal to the U.S. Court of Appeals for the Federal Circuit. Given the uncertain and lengthy nature of the legal appeal process, it is not possible for us to estimate the timing of a decision on Roche s appeal or potential remand of this case for additional proceedings. If Roche is not successful in getting relief from the current permanent injunction, we estimate that Roche would not be able to market or sell MIRCERA in the U.S. until 2013 at the earliest.

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Overview of Select Partnered Drug Development Programs

BAY41-6551 (NKTR-061, Amikacin Inhale), Agreement with Bayer Healthcare LLC

In August 2007, we entered into a co-development, license and co-promotion agreement with Bayer Healthcare LLC (Bayer) to develop a specially-formulated Amikacin (BAY41-6551, NKTR-061, Amikacin Inhale). Under the terms of the agreement, Bayer is responsible for most future clinical development and commercialization costs, all activities to support worldwide regulatory filings, approvals and related activities, further development of formulated Amikacin and final product packaging for BAY41-6551. We are responsible for any future development of the nebulizer device used in BAY41-6551through the completion of Phase 3 clinical trials and scale-up for commercialization. Under the terms of the agreement, we are entitled to development milestones and sales milestones upon achievement of certain annual sales targets. We are also entitled to royalties based on annual worldwide net sales of BAY41-6551. Our right to receive these royalties in any particular country will expire upon the later of ten years after the first commercial sale of the product in that country or the expiration of certain patent rights in that particular country, subject to certain exceptions. The agreement expires in relation to a particular country upon the expiration of all royalty and payment obligations between the parties related to such country. Subject to termination fee payment obligations, Bayer also has the right to terminate the agreement for convenience. In addition, the agreement may also be terminated by either party for certain product safety concerns, the product s failure to meet certain minimum commercial profile requirements or uncured material breaches by the other party. For certain Bayer terminations, we may have reimbursement obligations to Bayer.

BAY41-6551 is under development to treat Gram-negative pneumonias, including Hospital-Acquired (HAP), Healthcare-Associated, and Ventilator-Associated pneumonias. Gram-negative pneumonias are often the result of complications of other patient conditions or surgeries. BAY41-6551 will be adjunctive therapy to the current antibiotic therapies administered intravenously as standard of care. The targeted aerosol delivery platform in BAY41-6551 delivers antimicrobial agent directly to the site of infection in the lungs. The product can be integrated with conventional mechanical ventilators or used as a hand-held off-vent device for patients no longer requiring breathing assistance.

Gram-negative pneumonia carries a mortality risk of over 50% in mechanically-ventilated patients and accounts for a substantial proportion of the pneumonias in intensive care units (ICUs) today.

Hematide , Agreement with Affymax, Inc.

In April 2004, we entered into a license, manufacturing and supply agreement with Affymax, Inc. (Affymax), under which we granted Affymax a worldwide, non-exclusive license under certain of our proprietary PEGylation technology to develop, manufacture and commercialize Hematide. We currently manufacture our proprietary PEGylation materials for Affymax on a fixed price basis subject to annual adjustments. Affymax has an option to convert this manufacturing pricing arrangement to cost plus at any time prior to the date the NDA for Hematide is submitted to the FDA. In addition, Affymax is responsible for all clinical development, regulatory and commercialization expenses and we are entitled to development milestones and royalties on net sales of Hematide. Our right to receive royalties in any particular country will expire upon the later of ten years after the first commercial sale of the product in that country or the expiration of patent rights in that particular country. The agreement expires on a country-by-country basis upon the expiration of Affymax s royalty obligations. The agreement may also be terminated by either party for the other party s continued material breach after a cure period or by us in the event that Affymax challenges the validity or enforceability of any patent licensed to them under the agreement.

CDP-791, Agreement with UCB Pharma

In December 2000, we entered into a licensing, manufacturing and supply agreement with Celltech Chiroscience Ltd. (subsequently acquired by UCB Pharma or UCB) for several PEGylated antibody fragment products, one of which was a PEG-antibody fragment angiogenesis inhibitor for non-small cell lung cancer. In August 2002, the agreement was superseded by an agreement that relates only to CDP-791. Under the terms of the 2002 agreement, we provide development and manufacturing services for the CDP-791 product. UCB is responsible for all clinical development, regulatory and commercialization expenses. We have the right to receive development milestone payments, manufacturing revenue on a cost-plus basis and royalties on net product sales following commercial launch. Our right to receive royalties in any particular country will expire upon the later of between ten or twelve years (which period

depends on certain factors) after the first commercial sale of the product in that country or the expiration of patent rights in that particular country. The agreement expires upon the expiration of all of UCB s royalty obligations, provided that the agreement can be extended for successive two year renewal periods upon mutual agreement of the parties. In addition, UCB may terminate the agreement should it cease the development and marketing of the product and either party may terminate for cause under certain conditions.

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Hemophilia Programs, Agreement with Subsidiaries of Baxter International

In September 2005, we entered into an exclusive research, development, license and manufacturing and supply agreement with Baxter Healthcare SA and Baxter Healthcare Corporation (Baxter) to develop products with an extended half-life for the treatment and prophylaxis of Hemophilia A patients using our PEGylation technology. In December 2007, we expanded our agreement with Baxter to include the license of our PEGylation technology and proprietary PEGylation methods with the potential to improve the half-life of any future products Baxter may develop for the treatment and prophylaxis of Hemophilia B patients. Under the terms of the agreement, we are entitled to research and development funding, and we manufacture our proprietary PEGylation materials for Baxter on a cost plus basis. Baxter is responsible for all clinical development, regulatory, and commercialization expenses. In relation to Hemophilia A, we are entitled to development milestones and royalties on net sales varying by product and country of sale. Our right to receive these royalties in any particular country will expire upon the later of ten years after the first commercial sale of the product in that country or the expiration of patent rights in certain designated countries or in that particular country. In relation to Hemophilia B, we are entitled to development and sales milestones and royalties on net sales varying by product and country of sale. Our right to receive these royalties in any particular country will expire upon the later of twelve years after the first commercial sale of the product in that country or the expiration of patent rights in certain designated countries or in that particular country. The agreement expires in relation to a particular product and country upon the expiration of all of Baxter s royalty obligations related to such product and country. The agreement may also be terminated by either party for the other party s material breach or insolvency, provided that such other party has been given a chance to cure or remedy such breach or insolvency. Subject to certain limitations as to time, and possible termination fee payment obligations, Baxter also has the right to terminate the agreement for convenience. We have the right to terminate the agreement or convert Baxter s license from exclusive to non-exclusive in the event Baxter fails to comply with certain diligence obligations.

Cipro Inhale, Assigned to Novartis as of December 31, 2008

We were a party to a collaborative research, development and commercialization agreement with Bayer Schering Pharma AG related to the development of an inhaled powder formulation of Ciprofloxacin for the treatment of chronic lung infections caused by *Pseudomonas aeruginosa* in cystic fibrosis patients. As of December 31, 2008, we assigned the collaborative research, development and commercialization agreement to Novartis Pharma AG in connection with the closing of the asset sale transaction. Pursuant to the terms of the transaction, we maintain the right to receive certain potential royalties in the future based on net product sales if Cipro Inhale receives regulatory approval and is successfully commercialized.

2008 Developments in Our Business

Exit from the Inhaled Insulin Programs

In 1995, we entered into a collaborative development and licensing agreement with Pfizer to develop and market Exubera® and, in 2006 and 2007, we entered into a series of interim letter agreements with Pfizer to develop a next generation form of dry powder inhaled insulin and proprietary inhaler device, also known as NGI. In January 2006, Exubera received marketing approval in the U.S. and EU for the treatment of adults with Type 1 and Type 2 diabetes. Under the collaborative development and licensing agreement, Pfizer had sole responsibility for marketing and selling Exubera. We performed all of the manufacturing of the Exubera dry powder insulin, and through third party contract manufacturers (Bespak Europe Ltd. and Tech Group, Inc.), we supplied Pfizer with the Exubera inhalers. Our total revenue from Pfizer was nil, $189.1 million, and $139.9 million, representing 0%, 69% and 64% of total revenue, for the years ended December 31, 2008, 2007, and 2006, respectively.

On October 18, 2007, Pfizer announced that it was exiting the Exubera business and gave notice of termination under our collaborative development and licensing agreement. On November 9, 2007, we entered into a termination agreement and mutual release with Pfizer. Under this agreement we received a one-time payment of $135.0 million in November 2007 from Pfizer in satisfaction of all outstanding contractual obligations under our then-existing agreements relating to Exubera and NGI. All agreements between Pfizer and us related to Exubera and NGI, other than the termination agreement and mutual release and a related interim Exubera manufacturing maintenance letter, terminated on November 9, 2007. In February 2008, we entered into a termination agreement with Bespak and Tech Group pursuant to which we paid an aggregate of $39.9 million in satisfaction of outstanding accounts payable and

termination costs and expenses that were due under the Exubera inhaler contract manufacturing agreement. We also entered into a maintenance agreement with both Pfizer and Tech Group to preserve key personnel and manufacturing capacity to support potential future Exubera inhaler manufacturing if we found a new partner for the inhaled insulin program.

On April 9, 2008, we announced that we had ceased all negotiations with potential partners for Exubera and NGI as a result of new data analysis from ongoing clinical trials conducted by Pfizer which indicated an increase in the number of new cases of lung cancer in Exubera patients who were former smokers as compared to patients in the control group who were former smokers. In April 2008, we ceased all spending associated with maintaining Exubera manufacturing capacity and any further NGI development, including, but not limited to, terminating the Exubera manufacturing capacity maintenance arrangements with Pfizer and Tech Group.

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Asset Sale to Novartis

On December 31, 2008, we completed the sale of certain assets related to our pulmonary business, associated technology and intellectual property to Novartis Pharma AG and Novartis Pharmaceuticals Corporation (together referred to as Novartis) for a purchase price of $115.0 million in cash (Novartis Pulmonary Asset Sale). Under the terms of the transaction, we transferred to Novartis certain assets and obligations related to our pulmonary technology, development and manufacturing operations including:

- dry powder and liquid pulmonary technology platform including but not limited to our pulmonary inhalation devices, formulation technology, manufacturing technology and related intellectual property;
- capital equipment, information systems and facility lease obligations for our pulmonary development and manufacturing facility in San Carlos, California;
- manufacturing and associated development services payments for the Cipro Inhale program;
- manufacturing and royalty rights to the Tobramycin Inhalation Powder (TIP) program through the termination of our collaboration agreement with Novartis;
- certain other interests that we had in two private companies; and
- approximately 140 of our personnel primarily dedicated to our pulmonary technology, development programs, and manufacturing operations.

In consideration for the transfer of the above described pulmonary assets, we received $115.0 million in cash on December 31, 2008. In addition, we retained all of our rights to BAY41-6551, partnered with Bayer Healthcare LLC, certain royalty rights for the Cipro Inhale development program partnered with Bayer Schering Pharma AG, all rights to the ongoing development program for NKTR-063, and certain intellectual property rights specific to inhaled insulin.

In connection with Novartis Pulmonary Asset Sale, we also entered into an Exclusive License Agreement with Novartis Pharma. Pursuant to the Exclusive License Agreement, Novartis Pharma granted back to us an exclusive, irrevocable, perpetual, non-transferable, royalty-free and worldwide license under certain specific patent rights and other related intellectual property rights acquired by Novartis Pharma from Nektar in the transaction, as well as certain improvements or modifications thereto that are made by Novartis Pharma after the closing. Certain of such patent rights and other related intellectual property rights relate to our development program for NKTR-063 or are necessary for us to satisfy certain of our continuing contractual obligations to third parties, including in connection with development, manufacture, sale, and commercialization activities related to BAY41-6551. We also entered into a service agreement pursuant to which we have subcontracted to Novartis certain services to be performed related to our partnered program for BAY41-6551 and a transition services agreement pursuant to which Novartis and we will provide each other with specified services for limited time periods following the closing of the Novartis Pulmonary Asset Sale to facilitate the transition of the acquired assets and business from us to Novartis.

Research and Development

Our total Research and development expenditures can be disaggregated into the following significant types of expenses (in millions):

	Years ended December 31,		
	2008	**2007**	**2006**
Salaries and employee benefits	$ 58.4	$ 70.7	$ 69.9
Stock compensation expense	4.6	6.3	9.7
Facility and equipment	25.9	33.9	31.0
Outside services, including Contract Research Organizations	40.2	26.8	24.1
Supplies, including clinical trial materials	19.0	10.8	8.9
Travel, lodging, and meals	3.3	2.2	2.4
Other	3.0	2.9	3.4
Research and development	$ 154.4	$ 153.6	$ 149.4

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Manufacturing and Supply

We have a manufacturing facility located in Huntsville, Alabama related to our PEGylation and advanced polymer conjugate technologies. This facility is capable of manufacturing PEGylation derivatives and starting materials for active pharmaceutical ingredients (APIs). The facility is also used to produce APIs for clinical development for our proprietary product candidates that utilize our PEGylation and advanced polymer conjugate technology. The facility and associated equipment is designed and operated to be in compliance with the guidelines of the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) applicable to APIs (ICH Q7A guidelines).

We source drug starting materials for our manufacturing activities from one or more suppliers. If we are responsible for manufacturing activities under a collaboration arrangement, we typically source drug starting materials from the collaboration partner. For the drug starting materials necessary for our proprietary drug candidate development, we have agreements for the supply of such drug components with drug suppliers that we believe have sufficient capacity to meet our demands. However, from time to time, we source critical raw materials from one or a limited number of suppliers and there is a risk that if such supply were interrupted, it would materially harm our business. In addition, we typically order raw materials on a purchase order basis and do not enter into long-term dedicated capacity or minimum supply arrangements.

Prior to the closing of the Novartis Pulmonary Asset Sale on December 31, 2008, we operated a drug powder manufacturing and packaging facility in San Carlos, California capable of producing drug powders in quantities sufficient for clinical trials of product candidates utilizing our pulmonary technology. As part of the Novartis Pulmonary Asset Sale, we transferred this manufacturing facility and the related operations, and Novartis hired approximately 140 of the related supporting personnel, as of December 31, 2008.

Government Regulation

The research and development, clinical testing, manufacture and marketing of products using our technologies are subject to regulation by the Food and Drug Administration (FDA) and by comparable regulatory agencies in other countries. These national agencies and other federal, state and local entities regulate, among other things, research and development activities and the testing (in vitro, in animals, and in human clinical trials), manufacture, labeling, storage, recordkeeping, approval, marketing, advertising and promotion of our products.

The approval process required by the FDA before a product using any of our technologies may be marketed in the U.S. depends on whether the chemical composition of the product has previously been approved for use in other dosage forms. If the product is a new chemical entity that has not been previously approved, the process includes the following:

- extensive preclinical laboratory and animal testing;
- submission of an Investigational New Drug application (IND) prior to commencing clinical trials;
- adequate and well-controlled human clinical trials to establish the safety and efficacy of the drug for the intended indication; and
- submission to the FDA of a New Drug Application (NDA) for approval of a drug, a Biologic License Application (BLA) for approval of a biological product or a Premarket Approval Application (PMA) or Premarket Notification 510(k) for a medical device product (a 510(k)).

If the active chemical ingredient has been previously approved by the FDA, the approval process is similar, except that certain preclinical tests relating to systemic toxicity normally required for the IND and NDA or BLA may not be necessary if the company has a right of reference to such data or is eligible for approval under Section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act.

Preclinical tests include laboratory evaluation of product chemistry and animal studies to assess the safety and efficacy of the product and its chosen formulation. Preclinical safety tests must be conducted by laboratories that comply with FDA good laboratory practices (GLP) regulations. The results of the preclinical tests for drugs, biological products and combination products subject to the primary jurisdiction of the FDA s Center for Drug Evaluation and Research (CDER) or Center for Biologics Evaluation and Research (CBER) are submitted to the FDA as part of the IND and are reviewed by the FDA before clinical trials can begin. Clinical trials may begin 30 days after receipt of the IND by the FDA, unless the FDA raises objections or requires clarification within that period.

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Clinical trials involve the administration of the drug to healthy volunteers or patients under the supervision of a qualified, identified medical investigator according to a protocol submitted in the IND for FDA review. Drug products to be used in clinical trials must be manufactured according to current good manufacturing practices (cGMP). Clinical trials are conducted in accordance with protocols that detail the objectives of the study and the parameters to be used to monitor participant safety and product efficacy as well as other criteria to be evaluated in the study. Each protocol is submitted to the FDA in the IND.

Apart from the IND process described above, each clinical study must be reviewed by an independent Institutional Review Board (IRB) and the IRB must be kept current with respect to the status of the clinical study. The IRB considers, among other things, ethical factors, the potential risks to subjects participating in the trial and the possible liability to the institution where the trial is conducted. The IRB also reviews and approves the informed consent form to be signed by the trial participants and any significant changes in the clinical study.

Clinical trials are typically conducted in three sequential phases. Phase 1 involves the initial introduction of the drug into healthy human subjects (in most cases) and the pr