SECURITIES AND EXCHANGE COMMISSION
Washington, D.C. 20549

FORM 10-K

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

For the fiscal year ended December 31, 1999

Commission File Number: 0-23736

GUILFORD PHARMACEUTICALS INC.

(Exact name of registrant as specified in its charter)

Delaware	**52-1841960**
(State or other jurisdiction of incorporation or organization)	(IRS Employer Identification No.)

6611 Tributary Street
Baltimore, Maryland 21224
(410) 631-6300
(Address and telephone number of principal executive offices)

Securities registered pursuant to Section 12(b) of the Act:
None

Securities registered pursuant to Section 12(g) of the Act:
Common Stock, $.01 par value
Title of Class

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 and (2) has been subject to such filing requirements for the past 90 days. Yes ☒ No ☐

Indicate by check mark if disclosure of delinquent filers pursuant to Item 405 of Regulation S-K is not contained herein, and will not be contained, to the best of Registrant's knowledge, in definitive proxy or information statements incorporated by reference in Part III of this Form 10-K or any amendment to this Form 10-K. ☐

As of March 13, 2000, the aggregate value of the approximately 23,562,733 shares of common stock of the Registrant issued and outstanding on such date, excluding approximately 1,772,958 shares held by all affiliates of the Registrant, was approximately $799,423,265. This figure is based on the closing sales price of $36.688 per share of the Registrant's common stock as reported on the Nasdaq® National Market on March 10, 2000.

DOCUMENTS INCORPORATED BY REFERENCE

List hereunder the following documents incorporated by reference and the Part of the Form 10-K into which the document is incorporated:

Portions of the 1999 Annual Report to Stockholders are incorporated by reference into Part II. Portions of the Notice of Annual Meeting and Proxy Statement to be filed no later than 120 days following December 31, 1999 are incorporated by reference into Part III.

PART I

In this annual report, we may make forward-looking statements. You should note that we are making these forward-looking statements under the safe harbor provisions of the Private Securities Litigation Reform Act of 1995. Generally the forward-looking statements in this annual report relate to our current expectations regarding future results of operations, economic performance, and financial condition of our business. In general, we have introduced these forward-looking statements by words such as "anticipates", "believes", "estimates", "expects", "hopes" and similar expressions. Although these statements reflect our current plans and expectations, we may nevertheless not be able to successfully implement these plans and we may not realize our expectations in whole or in part in the future.

The forward-looking statements in this annual report may cover, but are not necessarily limited to, the following topics: (1) our efforts in conjunction with Aventis to obtain international regulatory clearances to market and sell GLIADEL® Wafer and to increase end-user sales of the product; (2) our efforts in conjunction with Aventis S.A., or "Aventis", to expand the labeled uses for GLIADEL® Wafer; (3) our efforts to develop polymer drug delivery product line extensions and new polymer drug delivery products; (4) the conduct and completion of research and development programs related to our FKBP neuroimmunophilin ligand technology and other technologies; (5) clinical development activities, including commencing, conducting and completing clinical trials related to our polymer-based drug delivery candidates and pharmaceutical product candidates; (6) our efforts to scale-up product candidates from laboratory bench quantities to commercial quantities; (7) our efforts to secure a supply of the active pharmaceutical ingredients for the clinical development and commercialization of our polymer-based and other drug candidates; (8) our efforts to manufacture drug candidates for clinical development and eventual commercial supply; (9) our strategic plans; and (10) anticipated expenditures and the potential need for additional funds, all of which involve significant risks and uncertainties. We caution you that our actual results may differ significantly from the results that we discuss in the forward-looking statements. We discuss some important factors that could cause or contribute to this difference in the "Risk Factors" section of this annual report. In addition, we intend any forward-looking statement that we make to speak only as of the date on which we make it. We are not undertaking any obligation to update any forward-looking statement to reflect events or circumstances that occur after the date on which we made the statement.

Item 1. Business

Guilford Pharmaceuticals Inc. is a biopharmaceutical company engaged in the development and commercialization of novel products in two principal areas: (1) targeted and controlled drug delivery systems using proprietary biodegradable polymers for the treatment of cancer and other diseases; and (2) therapeutic and diagnostic products for neurological diseases and conditions. Throughout this discussion, "we", "us", "our" and "Guilford" refer to Guilford Pharmaceuticals Inc. and its subsidiaries.

GLIADEL® Wafer and DOPASCAN® Injection are registered trademarks of Guilford. TAXOL® is a registered trademark of Bristol-Myers Squibb Company.

Product and Development Programs

The following table summarizes the current status of Guilford's product, product candidates and research programs:

Program/Product Candidates Drug Delivery Business	Disease Indications/Conditions	Status (1)	Corporate Partner
GLIADEL® Wafer (3.85% BCNU)	Recurrent glioblastoma Multiforme	Market	Aventis (2); Orion Corporation Pharma (3)
	Malignant glioma at time of Initial surgery	Phase III	Aventis (2); Orion Corporation Pharma (3)
GLIADEL® Wafer High-Dose (up to 28% BCNU)	Malignant glioma	Phase I/II	Aventis (2); Orion Corporation Pharma (3)(4)
PACLIMER™ Microspheres (paclitaxel in PPE microspheres)	Ovarian cancer	Phase I	—
PACLIMER™ Microspheres (paclitaxel in PPE microspheres)	Prostate, head & neck and lungs	Pre-clinical	—
LIDOMER™ Microspheres (lidocaine in PPE microspheres)	Post-surgical pain management	Pre-clinical	—
Neurological Products Program			
Neurotrophic Drugs			
Neuroimmunophilin ligands	Parkinson's disease	Phase I	Amgen
	Other nerve growth and repair indications (Alzheimer's disease, traumatic brain injury, traumatic spinal cord injury, multiple sclerosis, neuropathy, stroke and others)	Pre-clinical	Amgen
Neuroprotective Drugs			
NAALADase inhibitors	Glutamate neurotoxity (such as stroke and head trauma)	Pre-clinical	—
PARP inhibitors	Stroke, cardiac ischemia, septic shock, inflammation	Research	—
D-Serine Racemase	Stroke, head trauma, Amyotrophic Lateral Sclerosis, Parkinson's disease, and peripheral neuropathics	Research	—
Propofol Pro-Drug	Surgical anesthesia/sedation	Pre-clinical	—
Diagnostic Imaging Agent			
DOPASCAN® Injection	Imaging agent to diagnose and monitor Parkinson's disease	Phase II	Daiichi Radioisotope Laboratories, Ltd. (5)
Addiction Therapeutics			
Dopamine transporter ligand	Cocaine addiction	Research	—

(1) "Research" includes initial research related to specific molecular targets, synthesis of new chemical entities, and assay development for the identification of lead compounds. "Pre-clinical" includes testing of lead compounds in vitro and in animal models, pharmacology and toxicology testing, product formulation and process development prior to the commencement of clinical trials.

(2) Aventis is our corporate partner for GLIADEL® Wafer throughout the world, excluding Scandinavia and Japan.

(3) Orion Corporation Pharma, which was formerly Orion Corporation Farmos, is our corporate partner for GLIADEL® Wafer in Scandinavia.

(4) Orion Corporation Pharma has certain rights of first refusal for a high-dose GLIADEL® Wafer product in Scandinavia.

(5) Daiichi Radioisotope Laboratories, Ltd. is our corporate partner for DOPASCAN® Injection in Japan, Korea and Taiwan.

Our efforts to develop and commercialize GLIADEL® Wafer and our product candidates are subject to numerous risks and uncertainties. We describe some of these risks under the section captioned "Risk Factors" and elsewhere in this annual report.

Drug Delivery Business

Our drug delivery business involves the use of biodegradable polymers for targeted and controlled delivery of drugs to treat cancer and other uses. Delivering high drug concentrations locally for a sustained period of time may increase the efficacy of chemotherapy in slowing tumor growth and/or reducing tumor mass and may decrease the side effects associated with systemic drug administration. Additionally, site-specific, controlled-release delivery of other agents may enhance the utility of those agents. Guilford has developed expertise in the discovery, clinical development and manufacturing of polymer-based drug delivery products.

GLIADEL® Wafer

Our first product in our drug delivery business is GLIADEL® Wafer, a novel treatment for glioblastoma multiforme, and the most common and rapidly fatal form of primary brain cancer. GLIADEL® Wafer is a proprietary biodegradable polymer that contains the cancer chemotherapeutic drug BCNU (carmustine). Up to eight GLIADEL® Wafer wafers are implanted in the cavity created when a neurosurgeon removes a brain tumor. The wafers gradually erode from the surface and deliver BCNU directly to the tumor site in high concentrations for an extended period of time without exposing the rest of the body to the toxic side effects of BCNU. GLIADEL® Wafer is used to complement surgery, radiation therapy and systemic intravenous chemotherapy in patients with recurrent glioblastoma multiforme. The availability of GLIADEL® Wafer gives physicians an additional treatment option for this rapidly fatal disease.

The FDA cleared GLIADEL® Wafer for marketing in September 1996 for use as an adjunct to surgery to prolong survival in patients with recurrent glioblastoma multiforme for whom surgical resection is indicated. Glioblastoma multiforme is one of the most common and rapidly fatal forms of brain cancer. Our worldwide marketing partner, except in Scandinavia and Japan, Aventis, commercially launched GLIADEL® Wafer in the United States in February 1997.

Through December 31, 1999, GLIADEL® Wafer has received health authority approval in approximately 21 countries for use in patients with recurrent glioblastoma multiforme, including:

Argentina	Greece	Portugal
Austria	Ireland	Singapore
Brazil	Israel	South Korea
Canada	Luxembourg	Spain
France	Netherlands	United States
Germany	Peru	Uruguay

In the case of Canada, GLIADEL® Wafer has also received health authority approval for use upon the initial diagnosis of glioblastoma multiforme.

Applications for health authority approval are pending in other countries, including:

Australia	Italy	Taiwan
Ecuador	Philippines	Thailand
Indonesia	South Africa	United Kingdom

In a number of countries, including Canada, additional governmental approvals, e.g., relating to pricing and/or reimbursement, are necessary before a medicinal product may be marketed. As of December 31, 1999, almost all sales of GLIADEL® Wafer were in the United States and France, and in Scandinavia on a named hospital basis.

Guilford entered into a series of agreements with Aventis in June 1996, under which Aventis agreed to pay signing, milestone, transfer and royalty payments for the right to market, sell and distribute GLIADEL® Wafer worldwide, currently excluding Scandinavia and Japan, and agreed to seek international regulatory approvals for the product. During 1996, Aventis paid Guilford $27.5 million in milestone payments, purchased $7.5 million of our common stock, and extended to us a line of credit for up to $7.5 million to support future expansion of our GLIADEL® Wafer and other polymer manufacturing capacity. Under these agreements, Aventis pays to Guilford a combined transfer price and royalty of between 35% and 40% on Aventis' net sales of GLIADEL® Wafer to hospitals.

Guilford and Aventis are working together to expand the label for GLIADEL® Wafer in the United States and other countries so that it may be marketed for use in malignant glioma at the time of initial surgery. Malignant glioma is a broader category of brain cancer including but not limited to glioblastoma multiforme. In the summer of 1999, patient enrollment was completed in a 240-person, placebo-controlled, Phase III clinical trial for GLIADEL® Wafer in patients undergoing initial surgery for malignant glioma at 42 clinical sites in Europe, the United States and Israel. We expect the results to be available in the second half of 2000, following a minimum of one year follow-up period for each study participant. If the results are favorable, Guilford and Aventis intend to file in the United States and other countries for use of GLIADEL® Wafer in first surgery for malignant glioma.

Pursuant to the terms of our marketing, sales and distribution rights agreement with Aventis, we are eligible to receive the following non-recurring milestone payments if and when Aventis obtains all the required approvals needed to sell GLIADEL® Wafer in the following countries for the following indications:

Country	Milestone for recurrent indication	Milestone for First Surgery Indication
United States	$20.0 million*	$15.0 million**
France	$ 2.5 million*	$ 2.5 million
Germany	$ 2.0 million*	$ 2.0 million
Canada	$ 2.0 million	—
Italy	$ 1.5 million	$ 1.5 million
Spain	$ 1.0 million	$ 1.0 million
United Kingdom	$ 1.0 million	$ 1.0 million
Australia	$ 1.0 million	$ 1.0 million

* already earned

** $7.5 million cash and $7.5 million in equity investment

Thus, if GLIADEL® Wafer is approved for first surgery patients in all of the countries listed above, we are eligible to receive up to an aggregate of $30.5 million in milestone and equity payments from Aventis.

Our collaboration with Aventis also encompasses development of a high-dose formulation of GLIADEL® Wafer. The current formulation contains a 3.85% concentration of BCNU, the anti-cancer agent in the product. Based on promising preclinical data, Guilford and Aventis have been conducting a Phase I dose-escalation clinical trial of GLIADEL® Wafer using concentrations of BCNU ranging from 6.5% up to 28%. Final results of this trial are expected this summer.

We entered into our agreement with Orion Corporation Pharma, a major Scandinavian health care company, for the sales, marketing and distribution of GLIADEL® Wafer in Scandinavia in October 1995. Under this agreement, Orion Corporation Pharma purchases GLIADEL® Wafer from Guilford on an exclusive basis for sale in Scandinavia. Orion Corporation Pharma commenced sales of GLIADEL® Wafer in Scandinavia in 1997 on a named hospital basis.

For 1999, our revenues related to the sales and distribution of GLIADEL® Wafer were $6.8 million. Of this amount, we received $4.4 million as a transfer price on units sold to Aventis and to Orion Corporation Pharma and $2.4 million as royalties on sales by Aventis to hospitals and other end-users. In addition, under our agreements with Aventis, we are eligible for additional milestone payments totaling up to $30.5 million, including $7.5 million in the form of an equity investment, if Guilford and Aventis achieve certain regulatory objectives. These objectives include expanding the labeling in the United States to include the use of GLIADEL® Wafer at the time of initial surgery as well as obtaining specified international regulatory approvals to market and sell GLIADEL® Wafer. Guilford does not control the timing and extent of any future regulatory approvals for GLIADEL® Wafer, and thus we may not receive any or all of these payments. Whether we and Aventis will attain any or all of such regulatory objectives remains uncertain. We pay a royalty to Massachusetts Institute of Technology on sales of GLIADEL® Wafer pursuant to the license agreement under which we acquired the underlying technology for this product.

Future sales of GLIADEL® Wafer are subject to certain risks and uncertainties. We discuss a number of these risks in detail in the section of this annual report entitled "Risks Factors" below.

PACLIMER™ Microspheres

We are also working to broaden our line of polymer-based oncology products through the use of other chemotherapeutic agents, different polymer systems and various formulations. In November 1999, we filed an application for an Investigational New Drug, or an "IND," for the intraperitoneal administration of our second generation polymer oncology product, PACLIMER™ Microspheres, in women with ovarian cancer. PACLIMER™ Microspheres is a site-specific, controlled release formulation of paclitaxel (TAXOL®) in a PPE polymer developed in collaboration with scientists at Johns Hopkins. We are conducting a Phase I clinical trial in association with the Gynecologic Oncology Group, a consortium of leading academic clinical investigators in the field. We are additionally engaged in research on the suitability of this site-specific, controlled release formulation of paclitaxel for other local cancers, such as tumors of the lung, prostate, and head and neck.

We are the exclusive licensee from MIT and Johns Hopkins of several issued U.S. patents relating to the use of polymers to deliver paclitaxel and certain other chemotherapeutics to solid tumors. In addition, we have applied for a number of patent applications in the U.S. and abroad relating to the composition of matter of PPE polymers and their use for various kinds of cancer, including ovarian cancer.

Other Polymer-Based Drug Delivery Products

We are also exploring the use of our proprietary biodegradable polymer platform to deliver other agents which may have therapeutic utility. Guilford scientists have demonstrated that PPEs can deliver agents ranging from DNA to proteins to peptides to small molecules in therapeutically effective doses in animal models. In the first quarter of 2000, we announced a new development

program for LIDOMER™ Microspheres, a site-specific, controlled release formulation of the widely used local anesthetic, lidocaine.

Neurological Programs

Guilford is extensively engaged in the research and development of small molecules that *regenerate* damaged nerves, our neurotrophic program, or *protect* nerves from damage, our neuroprotectant program, for potential treatment of a range of neurodegenerative diseases and conditions, such as Parkinson's disease, Alzheimer's disease, stroke, Amyotrophic Lateral Sclerosis (ALS), multiple sclerosis, spinal cord injury and peripheral neuropathies. We also announced in the first quarter of 2000 that we have licensed exclusive worldwide rights to a pro-drug of the widely used anesthetic, propofol, at a late pre-clinical stage of development. We have also been developing an imaging agent for the diagnosis and monitoring of Parkinson's disease, DOPASCAN® Injection, which is expected to enter Phase III in Japan in the second half of 2000. In addition, we are researching small molecule therapeutics for cocaine abuse and possibly other addictive behaviors.

Neurotrophic Program

Guilford is a pioneer in the effort to develop small molecule, orally-bioavailable compounds to promote nerve growth and repair, called neurotrophic agents, for the treatment of neurological disorders. The degeneration or damage of nerve cells in the brain and peripheral neurons resulting from certain diseases and conditions causes a loss of either central nervous system function, such as Alzheimer's disease, Parkinson's disease, multiple sclerosis, spinal cord injury and stroke, or peripheral nerve function, such as diabetic neuropathy and other peripheral neuropathies. Under normal circumstances, damaged nerves have limited ability to regrow or otherwise recover, which poses a major obstacle for the treatment of these conditions.

Our neurotrophic program originated from observations first made in the laboratory of Dr. Solomon Snyder, Director of the Department of Neuroscience at Johns Hopkins and Chairman of our Scientific Advisory Board. These observations revealed that certain intracellular proteins, known as "immunophilins", which are targets of immunosuppressant drugs such as FK 506, are enriched 10-40 fold in certain areas of the central nervous system. Johns Hopkins scientists went on to discover that commonly used immunosuppressive drugs, and other immunophilin ligands, can promote nerve growth. Guilford exclusively licensed rights to these inventions from Johns Hopkins. Subsequently, Guilford scientists and their academic collaborators demonstrated that the pathway leading to nerve regeneration could be separated from the immunosuppressant pathway. Guilford scientists have synthesized a large number of proprietary small molecules, called "neuroimmunophilin ligands," a number of which have been shown in cell culture and animal models to be neurotrophic without being immunosuppressive, orally-bioavailable and able to cross the blood-brain barrier. In contrast, many naturally occurring nerve growth factors, proteins and peptides are not orally-bioavailable and do not normally cross the blood-brain barrier.

Some of our neuroimmunophilin ligands have induced functional and histological recovery of damaged dopamine nerve cells, which are the nerve cells that degenerate in Parkinson's disease, in rodent and primate models. Neuroimmunophilin ligands have also shown similar neurotrophic effects in a range of different neurons, including dopaminergic, cholinergic, serotonergic and sensory neurons, which means they may be useful in a range of disorders characterized by degeneration of these types of neurons, and in animal models of a range of neurodegenerative diseases and conditions, such as Alzheimer's disease, stroke, traumatic brain and spinal cord injury and peripheral neuropathy. Moreover, our scientists are researching the potential of these compounds in certain non-neurological diseases and conditions.

In August 1997, we entered into a collaboration with Amgen to research, develop and commercialize a broad class of neuroimmunophilin ligands, referred to as FKBP neuroimmunophilin ligands, as well as any other compounds that may result from the collaboration, for all human therapeutic and diagnostic applications. Amgen initially paid us a one time, non-refundable signing

fee of $15 million in 1997 and also invested an additional $20 million in Guilford in exchange for 640,095 shares of our common stock and five-year warrants to purchase up to an additional 700,000 shares of Guilford common stock at an exercise price of $35.15 per share. In connection with the sale of these securities, we granted Amgen certain demand and "piggyback" registration rights under applicable securities laws.

As part of this collaboration, Amgen agreed to fund up to a total of $13.5 million to support research at Guilford relating to the FKBP neuroimmunophilin ligand technology. This research funding began on October 1, 1997 and is payable quarterly over three years. Amgen also has the option to fund a fourth year of research.

If Amgen achieves certain specified development objectives in each of ten different clinical indications, Amgen has agreed to pay to Guilford up to a total of $392 million in milestone payments. Of these ten clinical indications, seven are neurological, consisting of Parkinson's disease, Alzheimer's disease, traumatic brain injury, traumatic spinal cord injury, multiple sclerosis, neuropathy and stroke, and three are non-neurological.

In 1998, Amgen nominated a second-generation lead FKBP neuroimmunophilin compound, called "NIL-A", initially targeted for the treatment of Parkinson's disease. Amgen completed a one-month Good Laboratory Practice study of NIL-A, the initiation of which triggered a one-time, non-refundable milestone payment to Guilford of $1 million under the collaboration agreement. In the summer of 1999, Amgen initiated a Phase I safety, tolerability and pharmacokinetics study in healthy human volunteers in Europe of a second-generation lead FKBP neuroimmunophilin compound, NIL-A. In the fourth quarter of 1999, Amgen filed an IND for human testing in the United States of NIL-A, initially targeting Parkinson's disease. This milestone earned Guilford a $5 million payment under the collaboration agreement with Amgen. Amgen has conducted, and is preparing to conduct, additional clinical trials pursuant to its clinical development plan.

Under a license agreement pursuant to which we acquired rights to certain patent applications relating to the FKBP neuroimmunophilin ligand technology, we are obligated to pay to Johns Hopkins a portion of all milestone payments paid by Amgen as well as a royalty on any and all net sales of any FKBP neuroimmunophilin ligand product Amgen markets and sells in the future.

We have filed a number of patent applications in the United States and internationally relating to both novel compositions and methods of treating neurological disorders utilizing these compounds. These compounds induce nerve growth directly, as well as potentiate nerve growth in the presence of nerve growth factors. As of December 31, 1999, we have rights to approximately 20 issued U.S. patents in the field, including those claiming multiple proprietary chemical series of neuroimmunophilin ligands and their neurotrophic uses.

As noted in the section herein captioned "Risk Factors" and elsewhere in this annual report, there is no guarantee that Guilford or Amgen will be able to successfully develop any FKBP neuroimmunophilin compounds or other product candidates into safe and effective drug(s) for neurological or other uses. Consequently, Guilford may not earn additional milestone payments related to Amgen's development activities or revenues related to product sales.

In particular, the research, development and commercialization of early-stage technology like the FKBP neuroimmunophilin ligand technology is subject to significant risks and uncertainty. For discussion of these and other risks, see the section herein captioned "Risk Factors".

Neuroprotectant Program

In Guilford's neuroprotectant program, Guilford scientists are developing novel compounds to protect brain and other cells from ischemia, which is the lack of oxygen delivery from reduced blood flow, and other disorders caused by massive release of excitatory amino acid neurotransmitters such as glutamate. We are exploring distinct intervention points in a biochemical pathway that can lead to neuronal damage, including the pre-synaptic inhibition of glutamate release by inhibiting the enzyme,

N-acetylated alpha-linked acidic dipeptidase ("NAALADase"), and the post-synaptic inhibition of the enzyme, poly(ADP-ribose) polymerase ("PARP").

It has been hypothesized that the release of the neurotransmitter glutamate may be mediated in part by the enzyme NAALADase, which cleaves glutamate from the abundant neuro-peptide, N-acetyl-aspartyl-glutamate (NAAG), and results in stimulation of post-synaptic glutamate receptors (including n-methyl-D-aspartate (NMDA) receptors). This release plays a critical role in many central neuronal functions. However, in conditions such as ischemia and epilepsy, there is a massive increase in synaptic glutamate concentrations, which results in excessive activation of glutamate receptors. Dr. Solomon Snyder and his colleagues at Johns Hopkins have shown that this activation, in turn, causes excess production of the neurotransmitter nitric oxide, mediated by the enzyme NOS, which results in damage to cellular DNA. DNA damage activates PARP, a nuclear repair enzyme, which can deplete cellular energy stores and lead to cell death. In 1999, Dr. Snyder's laboratory announced the discovery of an enzyme, D-Serine Racemase, which plays a key role in the activation of an important post-synaptic glutamate receptor, the N-Methyl D-Aspartate (NMDA) receptor. Guilford is working on the selective inhibition of NAALADase, PARP, D-Serine Racemase and other enzymes in the biochemical pathway to neuronal damage and death as possible mechanisms for inhibiting the toxic effects of excess glutamate in neurological diseases and conditions.

NAALADase Inhibitors

Glutamate is a neurotransmitter which is required for normal brain functioning. However, excess amounts of glutamate can be toxic and can kill brain cells. Excess glutamate neurotransmission has been implicated in a number of neurological disorders, such as diabetic peripheral neuropathy, pain, head trauma, stroke, ALS, Alzheimer's disease, schizophrenia, Huntington's disease and Parkinson's disease. Because of the large range of potential applications, blocking excess glutamate has been an intense area of research in the pharmaceutical industry. However, to date much of the research and development activity has focused on blocking post-synaptic glutamate receptors, with compounds such as NMDA antagonists, glycine antagonists, and other post-synaptic excitatory amino acid (EAA) receptor blockers. Unfortunately, these agents have generally been associated with severe toxicities, both in pre-clinical and clinical studies, which have greatly limited their clinical potential.

In contrast, scientists at Guilford have been pioneers in investigating a novel means of blocking excess glutamate release mediated by inhibition of NAALADase. Guilford chemists have identified a number of chemical series of novel NAALADase inhibitors, some of which have nanomolar potency in inhibiting NAALADase activity and robustly protect against neurodegeneration both in cell and animal models. Since Guilford's NAALADase inhibitors do not appear to interact with post-synaptic glutamate receptors, they seem to be devoid of the behavioral toxicities associated with post-synaptic glutamate antagonists. For example, neuropathology studies in rats dosed with a NAALADase inhibitor have shown no evidence of the neuronal degeneration seen with post-synaptic glutamate inhibitors.

We are closely investigating a novel, orally-bioavailable lead compound, which may advance into clinical development later this year. The initial therapeutic target is expected to be diabetic peripheral neuropathy. Diabetic peripheral neuropathy is a debilitating and progressive disorder involving severe pain sensitivity, tingling, weakness and numbness in a patient's extremities. It may affect close to one million Americans, yet there is currently no therapy that is approved to treat this disorder in the United States. Guilford researchers have demonstrated in animal models that treatment with a NAALADase inhibitor can normalize pain sensitivity, improve nerve conduction velocity, which is the speed at which a nerve impulse travels, and promote re-myelination of peripheral nerves. Additional potential target indications for NAALADase inhibitors may include chronic pain, schizophrenia, head trauma, stroke, ALS, Alzheimer's disease and Parkinson's disease.

We have filed numerous patent applications in the U.S. and abroad relating to novel compositions of matter and methods of use. As of December 31, 1999, we have rights to

approximately 13 issued U.S. patents in the field, relating to novel compositions of matter and methods of use of NAALADase inhibitors, including those claiming multiple proprietary chemical series of NAALADase inhibitors for uses ranging from stroke to prostate cancer.

PARP Inhibitors

During conditions of nerve degeneration, the cascade of events that is believed to result in cell death is initiated by an increase in synaptic glutamate levels, which results in an over-stimulation of post-synaptic glutamate receptors. This stimulation results in a dramatic increase in intracellular calcium, which leads to the formation of free radicals, such as nitric oxide, a neurotransmitter involved in normal brain functioning. However, too much nitric oxide, which can arise under conditions of neurological disease or damage, can be toxic and can cause DNA damage. This damage in turn leads to over-activation of the enzyme, poly(ADP-ribose) polymerase (PARP), which is involved in the repair of damaged DNA. This repair process is very energy intensive, and excessive activation of PARP rapidly leads to a drop in the cellular energy level, resulting in cell death.

The inhibition of PARP may represent a common intervention point for neurodegeneration resulting from several different pathways of damage, including the generation of nitric oxide and other oxygen species, all of which trigger PARP activation. Thus the inhibition of PARP may offer a unique approach to the development of neuroprotective agents for a range of neurological conditions. In addition, the over-stimulation of PARP has been implicated in a broad spectrum of other diseases, including myocardial ischemia, which occurs in heart attacks, traumatic head and spinal cord injuries, neurodegenerative disorders such as Alzheimer's disease, Parkinson's, disease, Huntington's disease, septic or hemorrhagic shock, arthritis, type I diabetes and inflammatory bowel disease.

Guilford scientists and their academic collaborators were among the first to investigate the use of PARP inhibitors for the prevention of glutamate neurotoxicity. Recent studies by several academic laboratories using mice that have been genetically altered to possess no or greatly diminished PARP activity suggest that absence of PARP activity may reduce the area of neuronal damage from stroke by up to 85%-90%, and the area of heart muscle damage during a heart attack by about 40%. Strikingly, some of our prototype PARP inhibitors have achieved similar results in preclinical models of stroke and heart attack in animals whose PARP genes had not been knocked out. In addition, our scientists have achieved neuroprotective results not only in transient ischemia models of stroke, but also in the more rigorous global ischemia models of stroke.

Guilford chemists have identified a number of distinct chemical series of novel PARP inhibitors with pre-clinical efficacy. In addition, our biologists have obtained results in animal experiments suggesting that PARP inhibitors may have potential utility in a range of therapeutic areas, including traumatic head and spinal cord injuries, Alzheimer's disease, septic shock and arthritis.

We have filed numerous patent applications in the U.S. and abroad relating to novel compositions of matter and methods of use. As of December 31, 1999, we had rights to two issued U.S. patents in the field, including one generally claiming the use of PARP inhibitors for the prevention of glutamate neurotoxicity.

As used in this annual report, a "prototype" compound is one which Guilford uses to establish scientific proof-of-principle respecting the relevant biomedical mechanism of action. In general, we do not intend to develop prototype compounds into products because of sub-optimal drug metabolism or pharmacokinetic characteristics, our proprietary position with respect to the compound, or for other reasons. Once we have *in vitro* and *in vivo* proof of principal of intervention in what we believe to be a medically relevant biochemical mechanism of action, we seek to develop proprietary lead compounds through medicinal chemistry. We seek to develop these proprietary lead compounds both around the prototype compounds and other promising chemical structures generated by molecular modeling, combinatorial or computational chemistry, and/or high throughput screening.

D-Serine Racemase and Other Inhibitors

In the first quarter of 2000, we announced that we had licensed from Johns Hopkins rights relating to another potential intervention point in the biochemical cascade of glutamate neurotoxicity. Dr. Snyder's laboratory demonstrated that an enzyme, D-Serine Racemase, plays a key role in the activation of an important post-synaptic glutamate receptor, the NMDA receptor. Guilford is engaged in research on the selective inhibition of this and several other enzymes, which may result in neuroprotection during neurodegenerative diseases and conditions.

Propofol Pro-Drug

Also in the first quarter of 2000, we announced that we had licensed from ProQuest Pharmaceuticals Inc. rights relating to a novel pro-drug of a widely used anesthetic, propofol. A pro-drug is a compound that is metabolized in the body into a drug. The compound, GPI-15715, is water soluble and rapidly converts to propofol once administered intravenously in animals. In contrast, propofol is administered in a lipid emulsion, which can cause complications, such as short shelf-life, clogged IV routes of administration, elevated blood lipids and a potentially higher incidence of bacterial contamination. GPI-15715 may offer a clinical benefit to patients both as an ICU sedating agent and an anesthesia-induction drug. GPI-15715, is at a late pre-clinical stage of development, and we hope to commence human trials later in 2000 or in early 2001.

Imaging Agent Program — DOPASCAN® Injection

Our product candidate for the diagnosis and monitoring of Parkinson's disease, DOPASCAN® Injection, is administered intravenously in trace quantities. It allows physicians to obtain images and measure the degeneration of dopamine neurons in the brain. Dopamine neurons are highly concentrated in a specialized area of the brain that degenerates in Parkinson's disease. Parkinson's disease is a common neurodegenerative disorder affecting more than 900,000 patients in the United States. In Parkinson's disease, there is a decrease in the dopaminergic nerve terminals and thus dopamine release.

In its early stages, Parkinson's disease can be very difficult to distinguish clinically from other diseases with similar symptoms but which do not respond well or at all to specific therapy for Parkinson's disease. Unfortunately, there are no diagnostic tests currently marketed or commercially available that can reliably detect the neuronal degeneration in Parkinson's disease, and the typical delay between the onset of symptoms and clinical diagnosis is more than two years. The primary way to establish the diagnosis at present is through repeated physician visits and the use of therapeutic trials of drugs such as L-Dopa, which carry with them the risk of unnecessary, sometimes severe side effects.

Following intravenous injections with DOPASCAN® Injection, images of a subject's brain are obtained with a SPECT camera and can identify the loss of dopamine neurons in the brain. To date, over 2,000 patients have been imaged in the United States and Europe using DOPASCAN® Injection. In a multi-center Phase IIb clinical trial conducted by the Parkinson's Study Group in the United States and completed in 1997, DOPASCAN® Injection accurately differentiated patients clinically diagnosed with a Parkinsonian disorder, i.e., Parkinson's disease and progressive supranuclear palsy, from subjects without a Parkinsonian disorder, e.g., essential tremor and healthy controls, with a sensitivity of 98% and specificity of 97%. In addition, no serious adverse events were attributed to DOPASCAN® Injection in this study. In addition, in late 1998 we completed a multi-center Phase IIb trial in Europe.

We have entered into an agreement with Daiichi Radioisotope Laboratories, Ltd., a leading Japanese radiopharmaceutical company, to develop and commercialize DOPASCAN® Injection in Japan, Korea and Taiwan. Daiichi Radioisotope Laboratories, Ltd. has informed us that it plans to commence Phase III clinical trials in the second half of 2000. We have sought partners for the manufacture and/or distribution of this product in other territories, including the United States and

Europe. However, to date, we have not been able to enter into an arrangement with a third-party manufacturer for the supply of DOPASCAN® Injection for commercial supply on acceptable terms. Unless and until Guilford comes to agreement with a suitable manufacturer or corporate partner, the development of DOPASCAN®Injection will be limited to the activities of our Japanese partner.

Addiction Therapeutics

We are also researching therapeutics for cocaine addiction and other addictive behaviors. Researchers have shown that cocaine binds to structures in the brain known as dopamine transporters. Our cocaine addiction therapeutics program focuses on the research and development of drugs which will prevent cocaine from binding to dopamine transporters, thus potentially limiting the effects of cocaine, and at the same time will minimally affect normal dopamine transporter function.

Based on reported findings about the cocaine binding site, Guilford scientists have used rational drug design techniques to identify and synthesize novel compounds with recognition site in the brain. In addition, we have generated further lead chemical series from screening our own library of compounds. We are in the process of chemical optimization and testing in animal models. We have filed patent applications covering several novel classes of compounds for use in cocaine addiction. Guilford also intends to test its optimized lead compounds on other forms of addiction, including alcohol and heroin addiction, which may result from facilitation of dopaminergic neurotransmission in certain areas of the brain.

Manufacturing and Raw Materials

We currently manufacture GLIADEL® Wafer using a proprietary process at our 18,000 square foot manufacturing facility in Baltimore, Maryland. This facility, which includes areas designated for packaging, quality control, laboratory, and warehousing, has been in operation since April 1995. The FDA initially inspected it in October 1995 and recently re-inspected it in February 1999. Our current facilities are designed to enable us to produce up to 8,000 GLIADEL® Wafer treatments annually, with each treatment consisting of eight GLIADEL® Wafers.

In January 1998, we completed construction of an expansion of our manufacturing facilities to allow for the additional synthesis of the polyanhydride co-polymer used in the manufacture of GLIADEL® Wafer. We will also be able to use this facility to produce our newest proprietary biodegradable polymers, the PPEs, in connection with the development of other polymer-based products. In addition, we completed construction of a second clean room facility in 1998, which we expect could increase our GLIADEL® Wafer manufacturing capacity to 20,000-30,000 treatments annually. Furthermore, we expect that this second clean room facility will also provide sufficient capacity to produce any clinical supply of PPE polymer-based product candidates needed in the future, including its paclitaxel/PPE polymer product candidate currently under development for ovarian cancer.

We believe that the various materials used in GLIADEL® Wafer are readily available and will continue to be available at reasonable prices. Nevertheless, while we believe that we have an adequate supply of BCNU, the active chemotherapeutic ingredient in GLIADEL® Wafer, to meet current demand, any interruption in the ability of the two current suppliers to deliver this ingredient could prevent us from delivering the product on a timely basis. We depend upon the availability of certain single-source raw materials in our formulations, but are seeking alternate suppliers for most of these raw materials. We cannot be sure that we will be able to secure alternate sources successfully on terms acceptable to us or at all. Failure of any supplier to provide sufficient quantities of raw material in accordance with the FDA's current Good Manufacturing Practice regulations could cause delays in clinical trials and commercialization of products, including GLIADEL® Wafer.

Government Regulation and Product Testing

All domestic prescription pharmaceutical manufacturers are subject to extensive regulation by the federal government, principally the FDA and, to a lesser extent, by state and local governments as well as foreign governments if products are marketed abroad. Biologics and controlled drug products, such as vaccines and narcotics, and radiolabeled drugs, are often regulated more stringently than are other drugs. The Federal Food, Drug, and Cosmetic Act and other federal statutes and regulations govern or influence the development, testing, manufacture, labeling, storage, approval, advertising, promotion, sale and distribution of prescription pharmaceutical products. Pharmaceutical manufacturers are also subject to certain recordkeeping and reporting requirements. Noncompliance with applicable requirements can result in warning letters, fines, recall or seizure of products, total or partial suspension of production and/or distribution, refusal of the government to enter into supply contracts or to approve marketing applications and criminal prosecution.

Upon FDA approval, a drug may only be marketed in the United States for the approved indications in the approved dosage forms and at the approved dosage levels. The FDA also may require post-marketing testing and surveillance to monitor a drug in larger and more diverse patient populations. Manufacturers of approved drug products are subject to ongoing compliance with FDA regulations. For example, the FDA mandates that drugs be manufactured in conformity with the FDA's applicable current Good Manufacturing Practice regulations. In complying with the current Good Manufacturing Practice regulations, manufacturers must continue to expend time, money and effort in production, recordkeeping and quality control to ensure that the product meets applicable specifications and other requirements. The FDA periodically inspects drug manufacturing facilities to ensure compliance with its current Good Manufacturing Practice regulations. Failure to comply subjects the manufacturer to possible FDA action, such as suspension of manufacturing, seizure of the product or voluntary recall of a product. Adverse experiences with the commercialized product must be reported to the FDA. The FDA also may require the submission of any lot of the product for inspection and may restrict the release of any lot that does not comply with FDA regulations, or may otherwise order the suspension of manufacture, voluntary recall or seizure. Product approvals may be withdrawn if compliance with regulatory requirements is not maintained or if problems concerning safety or efficacy of the product occur following approval.

Full Clinical Testing Requirements

The steps required before a newly marketed drug may be commercially distributed in the United States include:

(1) conducting appropriate preclinical laboratory and animal tests;

(2) submitting to the FDA an application for an IND, which must become effective before clinical trials may commence;

(3) conducting well-controlled human clinical trials that establish the safety and efficacy of the drug product;

(4) filing with the FDA a New Drug Application, or "NDA", for non-biological drugs; and

(5) obtaining FDA approval of the NDA prior to any commercial sale or shipment of the non-biological drug.

In addition to obtaining FDA approval for each indication to be treated with each product, each domestic drug manufacturing establishment must register with the FDA, list its drug products with the FDA, comply with the FDA's current Good Manufacturing Practice requirements and be subject to inspection by the FDA. Foreign manufacturing establishments distributing drugs in the United States also must comply with current Good Manufacturing Practice requirements, register and list their products, and are subject to periodic inspection by FDA or by local authorities under agreement with the FDA. The FDA also regulates drug advertising and promotion as well as the distribution physician samples. Individual states also often impose licensing requirements on drug manufacturers

and distributors. NDA's also must include a description of the manufacturing processes, including quality control procedures and validation requirements.

With respect to a drug product with an active ingredient not previously approved by the FDA, the manufacturer must usually submit a full NDA to prove that the product is safe and effective. The NDA must include complete reports of pre-clinical, clinical and laboratory studies. A full NDA may also need to be submitted for a drug product with a previously approved active ingredient if studies are required to demonstrate safety and efficacy. This could occur when the drug will be used to treat an indication for which the drug was not previously approved or where the dose or method of drug delivery is changed. In addition, the manufacturer of an approved drug may be required to submit for the FDA's review and approval a supplemental NDA, including reports of appropriate clinical testing, prior to marketing the drug with additional indications or making other significant changes to the product or its manufacture. A manufacturer intending to conduct clinical trials ordinarily will be required first to submit an IND to the FDA containing information relating to previously conducted pre-clinical studies.

Pre-clinical testing includes formulation development, laboratory evaluation of product chemistry and animal studies to assess the potential safety and efficacy of the product formulation. Pre-clinical tests to support an FDA application must be conducted in accordance with the FDA regulations concerning Good Laboratory Practices. The results of the pre-clinical tests are submitted to the FDA as part of the IND and are reviewed by the FDA prior to authorizing the sponsor to conduct clinical trials in human subjects. Unless the FDA issues a clinical hold on an IND, the IND will become effective 30 days following its receipt by the FDA. There is no certainty that submission of an IND will result in the commencement of clinical trials or that the commencement of one phase of a clinical trial will result in commencement of other phases or that the performance of any clinical trials will result in FDA approval.

Clinical trials for new drugs typically are conducted in three phases, are subject to detailed protocols and must be conducted in accordance with the FDA's regulations concerning good clinical practices. Clinical trials involve the administration of the investigational drug product to human subjects. Each protocol indicating how the clinical trial will be conducted in the United States must be submitted for review to the FDA as part of the IND. The FDA's review of a study protocol does not necessarily mean that, if the study is successful, it will constitute proof of efficacy or safety. Further, each clinical study must be conducted under the auspices of an independent institutional review board, or "IRB", established pursuant to FDA regulations. The IRB considers, among other factors, ethical concerns and informed consent requirements. The FDA or the IRB may require changes in a protocol both prior to and after the commencement of a trial. There is no assurance that the IRB or the FDA will permit a study to go forward or, once started, to be completed. Clinical trials may be placed on hold at any time for a variety of reasons, particularly if safety concerns arise, or regulatory requirements are not met.

The three phases of clinical trials are generally conducted sequentially, but they may overlap. In Phase I, the initial introduction of the drug into humans, the drug is tested for safety, side effects, dosage tolerance, metabolism and clinical pharmacology. Phase II involves controlled tests in a larger but still limited patient population to determine the efficacy of the drug for specific indications, to determine optimal dosage and to identify possible side effects and safety risks. Phase II testing for an indication typically takes at least from one and one-half to two and one-half years to complete. If preliminary evidence suggesting effectiveness has been obtained during Phase II evaluations, expanded Phase III trials are undertaken to gather additional information about effectiveness and safety that is needed to evaluate the overall benefit-risk relationship of the drug and to provide an adequate basis for physician labeling. Phase III studies for a specific indication generally take at least from two and one-half to five years to complete. We cannot be sure that we will successfully complete Phase I, Phase II or Phase III testing within any specified time period, if at all, with respect to any of our product candidates.

Reports of results of the preclinical studies and clinical trials for non-biological drugs are submitted to the FDA in the form of an NDA for approval of marketing and commercial shipment. User fee legislation now requires the submission in fiscal year 2000 of $285,740 to cover the costs of FDA review of a full NDA. Annual fees also exist for certain approved prescription drugs and the establishments that make them. The NDA typically includes information pertaining to the preparation of drug substances, analytical methods, drug product formulation, details on the manufacture of finished product as well as proposed product packaging and labeling. Submission of an NDA does not assure FDA approval for marketing. In May 1999, the FDA published final regulations describing criteria that the FDA will use to evaluate the safety and efficacy of diagnostic radiopharmaceuticals like DOPASCAN® Injection. It is unclear how these provisions may affect the potential for approval of DOPASCAN® Injection.

The median FDA approval time is currently about 12 months, although clinical development, reviews, or approvals of treatments for cancer and other serious or life-threatening diseases may be accelerated, expedited or fast-tracked. In addition, approval times can vary widely among the various reviewing branches of the FDA. The approval process may take substantially longer if, among other things, the FDA has questions or concerns about the safety and/or efficacy of a product. In general, the FDA requires at least two properly conducted, adequate and well-controlled clinical studies demonstrating safety and efficacy with sufficient levels of statistical assurance. In certain limited cases, the FDA may consider one clinical study sufficient. The FDA also may request long-term toxicity studies or other studies relating to product safety or efficacy. For example, the FDA may require additional clinical tests following NDA approval to confirm product safety and efficacy, known as Phase IV clinical tests, or require other conditions for approval. Notwithstanding the submission of such data, the FDA ultimately may decide that the application does not satisfy its regulatory criteria for approval.

Confirmatory studies similar to Phase III clinical studies may be conducted after, rather than before, FDA approval under certain circumstances. The FDA may determine under its expedited, accelerated, or fast-track provisions that previous limited studies establish an adequate basis for drug product approval, provided that the sponsor agrees to conduct additional studies after approval to verify safety and effectiveness. Treatment of patients not in clinical trials with an experimental drug may also be allowed under a Treatment IND before general marketing begins. Charging for an investigational drug also may be allowed under a Treatment IND to recover certain costs of development if various requirements are met. These cost-recovery, Treatment IND, and expedited, accelerated or fast-track approval provisions are limited, for example, to drug products (1) intended to treat AIDS or other serious severely debilitating or life-threatening diseases especially and that provide meaningful therapeutic benefit to patients over existing treatments, (2) that are for diseases for which no satisfactory alternative therapy exists, or (3) that address an unmet medical need. We cannot assure you that any of our product candidates will qualify for cost-recovery, expedited, accelerated, or fast-track approvals or for treatment use under the FDA's regulations or the current statutory provisions.

The full NDA process for newly marketed non-biological drugs, such as those being developed by Guilford, including FKBP neuroimmunophilin ligand products and inhibitors of NAALADase and PARP, can take a number of years and involves the expenditure of substantial resources. We cannot be sure that any approval will be granted on a timely basis, or at all, or that we will have sufficient resources to carry potential products through the regulatory approval process.

Abbreviated Testing Requirements

The Drug Price Competition and Patent Term Restoration Act of 1984 established abbreviated procedures for obtaining FDA approval for many non-biological drugs which are off-patent and whose marketing exclusivity has expired. Applicability of the Drug and Patent Act of 1984 means that a full NDA is not required for approval of a competitive product. Abbreviated requirements are applicable to drugs which are, for example, either bioequivalent to brand-name drugs, or otherwise similar to

brand-name drugs, such that all the safety and efficacy studies previously done on the innovator product need not be repeated for approval. Changes in approved drug products, such as in the delivery system, dosage form, or strength, can be the subject of abbreviated application requirements. We cannot assure you that abbreviated applications will be available or suitable for our non-biological drug products, including our efforts to develop a controlled-release formulation of the chemotherapeutic agent, paclitaxel (TAXOL®) using our PPE polymers, or that we will be able to obtain FDA approval of such applications.

Newly marketed active ingredients of drug products not previously approved have a five-year period of market exclusivity and certain changes in approved drug products for which reports of new clinical investigations are essential for approval, other than bioequivalence studies, have a three-year period of market exclusivity. A period of three years is available for changes in approved products, such as in delivery systems of previously approved products. Both periods of marketing exclusivity mean that abbreviated applications, which generally rely to some degree on approvals or on some data submitted by previous applicants for comparable innovator drug products, cannot be marketed during the period of exclusivity. The market exclusivity provisions of the Drug and Patent Act of 1984 bar only the marketing of competitive products that are the subject of abbreviated applications, not products that are the subject of full NDAs. The Drug and Patent Act of 1984 also may provide a maximum time of five years to be restored to the life of any one patent for the period it takes to obtain FDA approval of a drug product, including biological drugs. We cannot offer any assurance that the exclusivity or patent restoration benefits of the Drug and Patent Act of 1984 will apply to any of our product candidates.

Other Regulation

Products marketed outside the United States which are manufactured in the United States are subject to certain FDA export regulations, as well as regulation by the country in which the products are to be sold. U.S. law can prohibit the export of unapproved drugs to certain countries abroad. Guilford also would be subject to foreign regulatory requirements governing clinical trials and pharmaceutical sales, if products are marketed abroad. Whether or not a company has obtained FDA approval, it must usually obtain approval of a product by the comparable regulatory authorities of foreign countries before beginning to market the product in those countries. The approval process varies from country to country and the time required may be longer or shorter than that required for FDA approval.

In addition to the requirements for product approval, before a pharmaceutical product may be marketed and sold in certain foreign countries the proposed pricing for the product must be approved as well. Products may be subject to price controls and/or limits on reimbursement. The requirements governing product pricing and reimbursement vary widely from country to country and can be implemented disparately at the national level. As to reimbursement, the European Union generally provides options for its fifteen Member States to restrict the range of medicinal products that are covered by their national health insurance systems. Member States in the European Union can opt to have a "positive" or a "negative" list. A positive list is a listing of all medicinal products covered under the national health insurance system, whereas a negative list designates which medicinal products are excluded from coverage. In the European Union, the United Kingdom and Spain use a negative list approach, while France uses a positive list approach. In Canada, each province decides on reimbursement measures.

The European Union also generally provides options for its Member States to control the prices of medicinal products for human use. A Member State may approve a specific price for the medicinal product or it may instead adopt a system of direct or indirect controls on the profitability of the company placing the medicinal product on the market. For example, the regulation of prices of pharmaceuticals in the United Kingdom is generally designed to provide controls on the overall profits pharmaceutical companies may derive from their sales to the U.K. National Health Service. The U.K. system is generally based on profitability targets or limits for individual companies which are

normally assessed as a return on capital employed by the company in servicing the National Health Service market, comparing capital employed and profits.

In comparison, Italy generally establishes prices for pharmaceuticals based on a price monitoring system. The reference price is the European average price calculated on the basis of the prices in four reference markets: France, Spain, Germany and the United Kingdom. Italy typically levels the price of medicines belonging to the same therapeutic class on the lowest price for a medicine belonging to that category. Medicines are in the same therapeutic class if, for example, they have the same active principle, same pharmaceutical form or same route of administration. Spain generally establishes the selling price for new pharmaceuticals based on the prime cost, plus a profit margin within a range established each year by the Spanish Commission for Economic Affairs. Promotional and advertising costs are limited.

In Canada, prices for most new drugs are generally limited such that the cost of therapy for the new drug is in the range of the cost of therapy for existing drugs used to treat the same disease in Canada. Prices of breakthrough drugs and those which bring a substantial improvement are generally limited to the median of the prices charged for those drugs in other industrialized countries, such as France, Germany, Italy, Sweden, Switzerland, the United Kingdom and the United States.

We cannot be sure that any country which has price controls or reimbursement limitations for pharmaceuticals will allow favorable reimbursement and pricing arrangements with respect to us or our corporate partners, including Aventis and its applications for GLIADEL in Canada and elsewhere outside of the United States.

Guilford also is governed by other federal, state and local laws of general applicability. These laws include, but are not limited to, those regulating working conditions enforced by the Occupational Safety and Health Administration and regulating environmental hazards under such statutes as the Toxic Substances Control Act, the Resource Conservation and Recovery Act and other environmental laws enforced by the United States Environmental Protection Agency. The DEA regulates controlled substances, such as narcotics. A precursor compound to DOPASCAN® Injection is a tropane-derivative similar to cocaine and thus is subject to DEA regulations. Establishments handling controlled substances must, for example, be licensed and inspected by the DEA, and may be subject to export, import, security and production quota requirements. Radiolabeled products, including drugs, are also subject to regulation by the Department of Transportation and to state and federal licensing requirements. Various states often have comparable health and environmental laws, such as those governing the use and disposal of controlled and radiolabeled products.

While we are currently focused on polymer drug delivery and small molecule therapies, we are not actively involved in product areas involving biotechnology and have no current plans to develop products utilizing modern biotechnology. If we were to move in that direction, we would potentially be subject to extensive regulation. The EPA, the FDA and other federal and state regulatory bodies have developed or are in the process of developing specific requirements concerning products of biotechnology that may affect research and development programs and product lines. We are unable to predict whether any governmental agency will adopt requirements, including regulations, which would have a material and adverse effect on any future product applications involving biotechnology.

Patents and Proprietary Technology

Guilford believes that intellectual property protection is crucial to its business and that its future will depend in large part on its ability to obtain intellectual property protection and operate without infringing the proprietary rights of others. As of December 31, 1999, we owned or had licensed rights to more than 160 U.S. patents and patent applications protecting our key technologies and to corresponding foreign patents and patent applications.

The role, validity and value of Guilford's intellectual property are subject to various uncertainties and contingencies. Guilford's success will depend in part on its ability to obtain, maintain and enforce intellectual property protection for its products and processes and operate without infringing upon the

proprietary rights of others. The degree of intellectual property protection afforded to pharmaceutical and biotechnological inventions is uncertain, and a number of Guilford's product candidates are subject to this uncertainty.

We are aware that other companies have been issued patents, and have filed or may be engaged in filing patent applications, that claim matter relating to polymer drug delivery technology, including polymer-based oncology products, and neurological therapeutics and diagnostics, including small molecule neuroimmunophilin ligands and neuroprotectants. While we do not believe that we are infringing valid third-party patents of which we are aware, we cannot give you any assurance as to the ability of our patents and patent applications to adequately protect our products or product candidates. In addition, our products or product candidates may infringe or be dominated by patents that have issued or may issue in the future to third parties.

We cannot be sure that any patent applications filed by, or assigned or licensed to, us will be granted, that we will develop additional products or processes that are patentable, or that any patents issued to, or licensed by, us will provide us with any competitive advantages or adequate protection for our products. In addition, existing or future patents or intellectual property issued to, or licensed by, us may subsequently be challenged, invalidated or circumvented by others.

It is Guilford's policy to control the disclosure and use of Guilford's proprietary information under confidentiality agreements with employees, consultants and other parties. We cannot be sure, however, that our confidentiality agreements will be honored, that others will not independently develop equivalent or competing technology, that disputes will not arise concerning the ownership of intellectual property or the applicability of confidentiality obligations, or that disclosure of Guilford's proprietary information will not occur. To the extent that consultants or other research collaborators use intellectual property owned by others in their work with us, disputes may also arise as to the rights to related or resulting intellectual property.

Guilford supports and collaborates in research conducted by other companies, universities and governmental research organizations. We cannot be sure that we will have or be able to acquire exclusive rights to the inventions or technical information derived from such collaborations. Also, disputes may arise as to rights in derivative or related research programs conducted by us. In addition, in the event of a contractual breach by Guilford, certain of Guilford's collaborative research contracts provide for transfer of technology, including any patents or patent applications, to the relevant organization. In addition, this type of breach may cause us to lose our rights to use technology, including any patents or patent applications, licensed from the relevant company or organization.

If we are required to defend against charges of infringement of patent or proprietary rights of third parties or to protect our own patent or proprietary rights against third parties, we may incur substantial costs. We could also lose rights to develop or market certain products or be required to pay monetary damages or royalties to license proprietary rights from third parties. In response to actual or threatened litigation, we may seek licenses from third parties or attempt to redesign our products or processes to avoid infringement. However, we cannot be sure that we will be able to obtain licenses on acceptable terms or at all or redesign our products or processes. In addition to being a party to patent infringement litigation, we could be required to participate in U.S. or foreign opposition patent interference proceedings. We may also be forced to initiate legal proceedings to protect its intellectual property position. Even if we were to prevail, those types of proceedings are usually costly and extremely lengthy.

In order to protect its intellectual property position with respect to its neuroimmunophilin ligands, Guilford filed an opposition in 1998 in an effort to prevent the final issuance of a European patent to a competing company. While Guilford does not believe the claims of this European patent would be valid, any final issuance could result in future litigation if this company were to allege that Guilford or Amgen infringed the claims of this patent in Europe.

Technology Licensing Agreements

In March 1994, we entered into an agreement called the "GLIADEL® Wafer Agreement" with Scios Inc. Under the GLIADEL® Wafer Agreement, we licensed from Scios exclusive worldwide rights to numerous U.S. patents and patent applications and corresponding international patents and patent applications for polyanhydride biodegradable polymer technology for use in the field of tumors of the central nervous system and cerebral edema. GLIADEL® Wafer is covered by two of the U.S. patents under this license which expire in 2005 and certain related international patents and patent applications. In April 1994, Scios assigned all of its rights and obligations under the GLIADEL® Wafer Agreement to the Massachusetts Institute of Technology.

Under this agreement, Guilford is obligated to pay a royalty on all net sales of products incorporating such technology as well as a percentage of all royalties received by Guilford from sublicensees and certain advance and minimum annual royalty payments. Guilford has exclusive worldwide rights to the technology for brain cancer therapeutics, subject to certain conditions, including a requirement to perform appropriate pre-clinical tests and file an IND with the FDA within 24 months of the identification of a drug-polymer product having greater efficacy than GLIADEL® Wafer. In addition, Guilford is obligated to meet certain development milestones. Although we believe that we can comply with these obligations, our failure to perform these obligations could result in the loss of our right to new polymer-based product(s).

In June 1996, we entered into a license agreement with the Massachusetts Institute of Technology and Johns Hopkins respecting a patent application covering certain biodegradable polymers for use in connection with the controlled local delivery of certain chemotherapeutic agents (including paclitaxel (TAXOL®) and camptothecin) for treating solid tumors. Under this agreement, we are obligated to make certain annual and milestone payments to the Massachusetts Institute of Technology and to pay royalties based on any sales of products incorporating the technology licensed to Guilford. Furthermore, under the terms of the agreement, we have committed to spend minimum amounts to develop the technology and to meet certain development milestones. Although we believe that we can comply with such obligations, our failure to perform these obligations could result in the loss of our rights to that technology.

In July 1996, we entered into a license agreement with Johns Hopkins relating to U.S. patents respecting certain PPE polymers developed at Johns Hopkins and additional PPE patent applications. This agreement, among other things, requires Guilford to pay certain processing, maintenance and/or up-front fees, milestone payments and royalties, a portion of proceeds from sublicenses, and fees and costs related to patent prosecution and maintenance and to spend minimum amounts for, and meet deadlines regarding, development of this technology. Although we believe that we can comply with such obligations, our failure to perform these obligations could result in the loss of our rights to that technology.

Guilford and Johns Hopkins are parties to exclusive license agreements covering certain patents and patent applications relating to neuroimmunophilin ligands and their neurotrophic and other uses, and inhibition of PARP for neuroprotective uses and certain other technologies. These agreements, among other things, require Guilford to pay certain processing, maintenance, and/or up-front fees, milestone payments and royalties, a portion of proceeds from sublicenses, and fees and costs related to patent prosecution and maintenance and to spend minimum amounts for, and meet deadlines regarding, development of the technologies. Although we believe that we can comply with these obligations, our failure to perform these obligations could result in the loss of our rights to that technology or in the case of joint inventions, exclusive use of the technology. In the case of Guilford's license with Johns Hopkins relating to neuroimmunophilin ligands, Johns Hopkins is entitled to a portion of all milestone payments paid to Guilford, including payments under Guilford's collaboration

with Amgen, and a royalty on net sales of neuroimmunophilin ligand products, including sale of products under Guilford's collaboration with Amgen.

We obtained exclusive worldwide rights to DOPASCAN® Injection pursuant to a March 1994 license agreement with Research Triangle Institute, which grants Guilford rights to various U.S. and international patents and patent applications relating to binding ligands for certain receptors in the brain which are or may be useful as dopamine neuron imaging agents. DOPASCAN® Injection and certain related precursors and analogues are covered by U.S. patents which start expiring in 2009, as well as certain related international patents and patent applications.

Under the Research Triangle Institute Agreement, we reimbursed Research Triangle Institute for certain past patent-related expenses and made certain annual payments to Research Triangle Institute to support research conducted at Research Triangle Institute through March 1999. In addition, we are obligated to pay Research Triangle Institute a royalty on gross revenues to Guilford from products derived from the licensed technology and from sublicensee proceeds and to make certain minimum royalty payments following the first commercial sale of such products. Guilford must use commercially reasonable efforts to develop products related to the licensed technology and to meet certain performance milestones. Our failure to perform our obligations under the RTI Agreement in the future could result in termination of the license.

United States Government Rights

Aspects of the technology licensed by us under agreements with third party licensors may be subject to certain government rights. Government rights in inventions conceived or reduced to practice under a government-funded program may include a non-exclusive, royalty-free worldwide license to practice or have practiced those inventions for any governmental purpose. In addition, the U.S. government has the right to grant licenses which may be exclusive under any of such inventions to a third party if it determines that: (1) adequate steps have not been taken to commercialize such inventions; (2) the action is necessary to meet public health or safety needs; or (3) the action is necessary to meet requirements for public use under federal regulations. The U.S. government also has the right to take title to a subject invention if there is a failure to disclose the invention and elect title within specified time limits. In addition, the U.S. government may acquire title in any country in which a patent application is not filed within specified time limits. Federal law requires any licensor of an invention that was partially funded by the federal government to obtain a covenant from any exclusive licensee to manufacture products using the invention substantially in the United States. Further, the government rights include the right to use and disclose without limitation technical data relating to licensed technology that was developed in whole or in part at government expense. Our principal technology license agreements contain provisions recognizing these government rights.

Sales, Marketing and Distribution

In general, our strategy is to establish strategic alliances with larger pharmaceutical companies where possible to develop and promote products that require extensive development, sales and marketing resources. Within the United States, we may seek to retain co-promotion rights with respect to some or all compounds or indications in any such strategic alliances, or we may elect to market and distribute our products directly where the commercial prospects so warrant.

Aventis Agreement

In June 1996, we entered into a marketing, sales and distribution rights agreement and other related agreements with Aventis. Under these agreements Aventis has worldwide, with the exclusion of Scandinavia and Japan, marketing, sales, promotion and distribution rights for GLIADEL® Wafer. Upon execution of these agreements, we received $7.5 million for 281,531 shares of our common stock. Furthermore, in addition to an aggregate of $27.5 million in rights payments made by Aventis upon execution of the agreements in June 1996 and FDA clearance of the GLIADEL® Wafer NDA in September 1996, the agreements with Aventis currently provide for up to an additional

$30.5 million in payments, including $7.5 million in the form of an equity investment, in the event that certain regulatory and other milestones are achieved. We caution you that we cannot be sure that any or all of these milestones will be attained and that certain of these payments are contingent on international regulatory filings and clearances, the timing and extent of which are largely within the control of Aventis.

Aventis may, under certain circumstances, fund up to approximately $17 million for the development of higher dose forms of GLIADEL® Wafer that we are developing and for certain additional clinical studies related to GLIADEL® Wafer. We have the right under certain circumstances to borrow up to an aggregate of $7.5 million to expand our GLIADEL® Wafer manufacturing and related facilities.

In addition to the payments outlined above, we act as the exclusive manufacturer of GLIADEL® Wafer and receive transfer price payments and royalties based on any "net sales", as defined in the agreements with Aventis, of GLIADEL® Wafer. Aventis' exclusive rights terminate in a particular country upon the later of the expiration of the last to expire of certain patents applicable in that country or the last commercial sale of GLIADEL® Wafer in that country. Aventis also has an exclusive 90-day period following development by Guilford of new polymer technology for brain cancer to make an offer to license such technology.

Amgen Collaboration

As described in more detail above under "Product and Development Programs — Neurological Programs", in August 1997, we entered into a collaboration with Amgen to research, develop and commercialize FKBP neuroimmunophilin ligands, as well as any other compounds that may result from the collaboration, for all human therapeutic and diagnostic applications. Under this agreement, Amgen initially paid Guilford a total of $35 million and agreed to fund future FKBP neuroimmunophilin ligand technology research up to $13.5 million. Amgen also agreed to pay Guilford a total of $392 million in milestone payments if Amgen achieves specified development objectives.

We will receive royalties on any future sales of products resulting from the collaboration. Amgen has agreed to fund, develop and commercialize the FKBP neuroimmunophilin ligand technology. Under limited circumstances, Guilford has the option to conduct certain Phase I and Phase II clinical trials on one product candidate and has the right to co-promote in the United States one product resulting from the collaboration. Subject to its obligation to fund two years of research at Guilford, Amgen has the right to discontinue all its development and commercialization activities under the collaboration at any time.

Other Agreements

In October 1995, we entered into an agreement appointing Orion Corporation Pharma distributor for GLIADEL® Wafer in Scandinavia, and in December 1995 we entered into an agreement with Daiichi Radioisotope Laboratories, Ltd. for the marketing, sale and distribution of DOPASCAN® Injection in Japan, Korea and Taiwan.

Competition

We are involved in evolving technological fields in which developments are expected to continue at a rapid pace. Guilford's success depends upon its ability to compete effectively in the research, development and commercialization of products and technologies in its areas of focus. Competition from pharmaceutical, chemical and biotechnology companies, universities and research institutes is intense and expected to increase. Many of these competitors have substantially greater research and development capabilities, experience and manufacturing, marketing, financial and managerial resources than Guilford and represent significant competition for Guilford. Acquisitions of competing companies by large pharmaceutical or other companies could enhance the financial, marketing and

other resources available to these competitors. These competitors may develop products which are superior to those under development by Guilford.

We are aware of several competing approaches under development for the treatment of malignant glioma including using radioactive seeds for interstitial radiotherapy, increasing the permeability of the blood-brain barrier to chemotherapeutic agents, sensitizing cancer cells to chemotherapeutic agents using gene therapy and developing chemotherapeutics directed to specific receptors in brain tumors.

A number of companies are working on products for the treatment of ovarian cancer, using approaches ranging from novel chemotherapeutics to antibody technologies. Further, controlled release polymers and liposomes are being explored by various companies to enhance the efficacy of current and novel therapies.

A number of companies have shown interest in trying to develop neurotrophic agents to promote nerve growth and repair in neurodegenerative disorders and traumatic central nervous system injuries. However, much of this activity has focused on naturally occurring growth factors. Such large molecules generally cannot cross the blood-brain barrier and thus present problems in administration and delivery. One company has announced that certain of its neuroimmunophilin ligands showed positive results in stimulating nerve growth in an animal model of nerve crush, and has disclosed that it has made patent filings covering compounds and uses in connection with nerve growth promotion. This company has also announced that it has begun a phase II clinical trial for peripheral neuropathy using a neuroimmunophilin compound it originally was developing for multiple drug resistance in cancer patients. In addition, another company announced that IGF-1 showed positive results in clinical trials of a peripheral neurodegenerative disorder.

There is intense competition to develop an effective and safe neuroprotective drug or biological agent. Calcium channel antagonists, calpain inhibitors, adenosine receptor antagonists, free radical scavengers, superoxide dismutase inducers, proteoloytic enzyme inhibitors, phospholipase inhibitors and a variety of other agents are under active development by others. Glutamate or NMDA receptor antagonists are under development by several other companies.

The anesthesia/sedation field is concentrated in the United States mainly among four major companies, with several other companies doing research in the field. There are numerous products currently on the market that are accepted as relatively safe and effective anesthetic agents and sedation agents. We cannot be sure that we can successfully develop GPI-15715, our propofol pro-drug product candidate, into a safe and effective drug or that it will be cleared for marketing. Even if we do develop it into a safe and effective drug and it is cleared for marketing, the commercial prospect of GPI-15715 will heavily depend on its safety and efficacy profile relative to alternatives then available in the market.

We believe that two other companies and their affiliates, as well as some university researchers, are clinically evaluating imaging agents for dopamine neurons. In addition, a variety of radiolabeled compounds for use with Positron Emission Tomography, or "PET", scanners have been used to image dopamine neurons successfully in patients with Parkinson's disease. PET scanning is currently only available in a limited number of hospitals in the United States and Europe.

In the field of cocaine addiction, academic and government groups have studied most of the investigated compounds to date. Further, much of this work has been with known agents, such as carbamazepine, that are commercially available for other indications. Guilford is aware of another company that is investigating the use of butylcholinesterase as a treatment for acute cocaine overdose. We are aware of one company that is investigating an immunological approach in an attempt to develop a cocaine vaccine. We are not aware of other commercial research programs targeting specific cocaine antagonists, which do not interfere with normal dopamine neuron function.

Any product candidate that we develop and for which we gain regulatory approval, including GLIADEL® Wafer, must then compete for market acceptance and market share. For certain of our

product candidates, an important factor will be the timing of market introduction of competitive products. Accordingly, the relative speed with which we and competing companies can develop products, complete the clinical testing and approval processes, and supply commercial quantities of the products to the market is expected to be an important determinant of market success. Other competitive factors include

- the capabilities of our collaborators,
- product efficacy and safety,
- timing and scope of regulatory approval,
- product availability,
- marketing and sales capabilities,
- reimbursement coverage,
- the amount of clinical benefit of our product candidates relative to their cost, method of administration,
- price, and
- patent protection.

Our competitors may develop more effective or more affordable products or achieve earlier product development completion, patent protection, regulatory approval or product commercialization than Guilford. The achievement of any of these goals by our competitors could have a material adverse effect on our business, financial condition and results of operations.

Product Liability and Insurance

Product liability risk is inherent in the testing, manufacture, marketing and sale of Guilford's product candidates, and there can be no assurance that Guilford will be able to avoid significant product liability exposure. While Guilford currently maintains $15 million of product liability insurance covering clinical trials and product sales, we cannot be sure that this or any future insurance coverage that we obtain will be adequate or that our insurance will cover any claims. Guilford's insurance policies provide coverage on a claims-made basis and are subject to annual renewal. Product liability insurance varies in cost, can be difficult to obtain and may not be available to Guilford in the future on acceptable terms, or at all.

Employees

At December 31, 1999, Guilford employed 228 individuals. Of these 228 employees, 193 were employed in the areas of research and product development and in manufacturing and quality control of GLIADEL. The remaining 35 employees performed general and administrative functions, including executive, finance and administration, legal and business development. None of Guilford's employees are currently represented by a labor union. To date, we have experienced no work stoppages related to labor issues and believe our relations with our employees are good.

All employees are required to enter into a confidentiality agreement with Guilford. Hiring and retaining qualified personnel are important factors for Guilford's future success. We are likely to continue to add personnel particularly in the areas of research, clinical research and operations, including manufacturing. Intense competition exists for these qualified personnel from other biotechnology and biopharmaceutical companies as well as academic, research and governmental organizations. Guilford cannot be sure that it will be able to continue to hire qualified personnel and, if hired, that it will be able to retain these individuals.

Item 1A. Executive Officers and Other Significant Employees of Registrant

Craig R. Smith, M.D., age 54, joined Guilford as a Director at its inception in July 1993. Dr. Smith was elected President and Chief Executive Officer in August 1993 and was elected Chairman of the Board in January 1994. Prior to joining Guilford, Dr. Smith was Senior Vice President for Business and Market Development at Centocor, Inc., a biotechnology corporation. Dr. Smith joined Centocor in 1988 as Vice President of Clinical Research after serving on the Faculty of the Department of Medicine at Johns Hopkins Medical School for 13 years. Dr. Smith received his M.D. from the State University of New York at Buffalo in 1972 and received training in Internal Medicine at Johns Hopkins Hospital from 1972 to 1975. Dr. Smith is a member of the board of directors of CellGate, Inc.

John P. Brennan, age 57, joined Guilford as Vice President, Operations in January 1994 and became Senior Vice President, Operations in January 1997. In February 1999, Mr. Brennan was promoted to Senior Vice President, Technical Operations and General Manager, Drug Delivery Business. From 1980 to 1993, he was Vice President, Technical Operations and Manufacturing for G.D. Searle and Co., a pharmaceutical company, and was responsible for the operation of manufacturing plants in North America, Latin America and Europe and the worldwide pharmaceutical and process technology from 1980 to 1993. From 1977 to 1980, Mr. Brennan was General Manager of the E.R. Squibb & Sons, Inc. manufacturing facility in Humacao, Puerto Rico. Mr. Brennan held various technical positions at SmithKline Corporation from 1960 to 1977. Mr. Brennan has over 39 years of experience in the pharmaceutical industry. Mr. Brennan received his B.S. in Chemistry from the Philadelphia College of Pharmacy and Science in 1968 and attended the Wharton Graduate Management Program in 1976.

Andrew R. Jordan, age 52, joined Guilford as Vice President, Secretary, Treasurer and Chief Financial Officer in September 1993 and became Senior Vice President, Treasurer and Chief Financial Officer in January 1997. Prior to joining Guilford, Mr. Jordan held various positions with KPMG LLP, a public accounting firm, beginning in 1973, including partner since 1983. Mr. Jordan's experience at KPMG LLP included advising early-stage and emerging technology companies and initial and secondary public equity and debt offerings. He received his B.A. from Rutgers College in 1969 and his MBA from Rutgers Graduate School of Business in 1973 and is a Certified Public Accountant.

Peter D. Suzdak, Ph.D., age 41, joined Guilford in March 1995 as Vice President, Research. In February 1999, Dr. Suzdak was promoted to Senior Vice President, Research & Development. Prior to joining Guilford, Dr. Suzdak was Director of Neurobiology at Novo Nordisk A/S and was responsible for all neurobiology research from 1993 to 1995, and Department Head for Receptor Neurochemistry from 1988 to 1992 as well as a member of the drug discovery management group from 1989 to 1995. Prior thereto, Dr. Suzdak was a Pharmacology Research Associate in the Clinical Neuroscience Branch of the National Institute of Mental Health in Bethesda, Maryland from 1985 to 1988. Dr. Suzdak received his Ph.D. in Neuroscience from the University of Connecticut and a B.S. in Pharmacy from St. Johns University.

Thomas C. Seoh, age 42, joined Guilford in April 1995 as Vice President, General Counsel and Secretary. In August 1999, Mr. Seoh was promoted to Senior Vice President, General Counsel and Secretary. From 1992 to 1995, Mr. Seoh was affiliated with the ICN Pharmaceuticals, Inc. ("ICN") group, as Vice President and Associate General Counsel of ICN from 1994 to 1995, Vice President, General Counsel and Secretary of Viratek, Inc. from 1993 to 1994 and Deputy General Counsel of SPI Pharmaceuticals, Inc. from 1992 to 1994, providing legal function support for pharmaceutical operations, research and development and corporate development. From 1990 to 1992, Mr. Seoh was General Counsel and Secretary of Consolidated Press U.S., Inc., the North American holding corporation of the Sydney, Australia-based Consolidated Press group. Prior thereto, Mr. Seoh was associated with the New York and London law offices of Lord, Day & Lord, Barrett Smith. Mr. Seoh received his J.D. and A.B. from Harvard University.

William C. Vincek, Ph.D., age 52, joined Guilford as Vice President, Corporate Quality in August 1997. From November 1993 until Dr. Vincek joined Guilford, he was Group Director, CMC & Preclinical Regulatory Affairs and Global Research and Development GMP Quality Assurance at Glaxo Wellcome, Inc. Prior thereto from 1984 until October 1993, Dr. Vincek held various positions at SmithKline Beecham Pharmaceuticals and related entities, most recently from July 1992 until October 1993 as Director, Pharmaceutical Analysis Department. Dr. Vincek received his Ph.D. in Medicinal Chemistry from the University of Kansas, where he also received an M.S. in Medicinal Chemistry. Dr. Vincek received a B.S. in Chemistry from Colorado State University.

Dana C. Hilt, M.D., age 46, joined Guilford as Vice President, Clinical Research in May 1998. As part of Guilford's reorganization in February 1999, Dr. Hilt's title was changed to Vice President, Clinical Research and Drug Metabolism. Prior to joining Guilford, Dr. Hilt was employed by Amgen, most recently as Director, Neuroscience from 1996 to 1998, earlier as Associate Director, Neuroscience from 1993 to 1996. While at Amgen, Dr. Hilt's duties included overseeing aspects of basic research, clinical trials, regulatory strategy and manufacturing for certain of Amgen"s neurological product programs. Prior to joining Amgen, Dr. Hilt held a variety of positions at the University of Maryland School of Medicine and the National Institutes of Health. Dr. Hilt received his B.S. degree in Chemistry from the University of Maine, his M.D. from Tufts University School of Medicine, and received training in Internal Medicine at Harvard Medical School and Neurology at Johns Hopkins Hospital.

Nancy J. Linck, Ph.D., J.D., age 58, joined Guilford as Vice President, Intellectual Property in November 1998. From 1994 to 1998, Dr. Linck was Solicitor for the U.S. Patent and Trademark Office, where she acted as general counsel for the Commissioner of Patents and Trademarks. From 1987 to 1994, Dr. Linck worked as a patent and trademark litigator at the intellectual property law firm of Cushman, Darby & Cushman, first as an Associate from 1987 to 1990, and later as a Partner from 1991 to 1994. Since 1995, Dr. Linck has been engaged as an Adjunct Professor of Law, first at George Washington University School of Law and presently at Georgetown University Law Center. Dr. Linck received her B.S. in Chemistry from the University of California, Berkeley, her M.S. and Ph.D. in Inorganic Chemistry from the University of California, San Diego, and her J.D. from Western New England College School of Law.

Denise Battles, age 45, joined Guilford as Director of Quality Assurance in August 1994 and became Senior Director of Product Compliance in August 1997. Ms. Battles was promoted to Vice President of Corporate Quality in August 1999. Prior to joining Guilford, Ms. Battles was employed by Pharmaceutical Systems, Incorporated as the Director of Quality Assurance from 1993 to 1994. Prior thereto, Ms. Battles held various positions with Quality Control and Quality Assurance at Baxter Healthcare Corporation, including Director of Quality Assurance from 1990 to 1993. Ms. Battles received her B.S. in Biology from Fisk University in 1977 and received training at the Lake Forest Graduate School of Management.

Item 2. Properties.

In August 1994, Guilford entered into a master lease for an approximately 83,000 square foot building in Baltimore, Maryland. Guilford currently occupies 23,000 square feet for office space, 18,000 square feet for manufacturing space for GLIADEL and potentially other polymer-based products, and 42,000 square feet of research and development laboratories. Guilford added approximately 5,000 square feet to its animal handling facilities in 1998. The master lease expires in July 2005. Two five-year renewal options are available to Guilford or Guilford may exercise a purchase option any time after the ninth year of the lease for the then-current fair market value.

In February 1998, Guilford entered into an operating lease with a trust affiliated with First Union National Bank respecting the construction and occupancy of a new laboratory and office facility, consisting of approximately 73,000 square feet. Guilford began moving personnel into the facility in June 1999 and consolidated all of its operations into its current headquarters and the new facility during the third quarter of 1999. The lease expires in February 2005, at which time Guilford has an

option (1) to purchase the property or (2) to sell the property on behalf of the trust, subject to certain limitations and related obligations. In addition, Guilford may, with the consent of First Union, enter into a new lease arrangement. See Exhibit 13.01, "Management's Discussion of Financial Condition and Results of Operations — Liquidity and Capital Resources" for a more complete description of Guilford's arrangements with First Union.

Item 3. Legal Proceedings

We are not a party to any material legal proceedings.

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

None.

Item 4A. Risk Factors

An investment in our stock is very speculative and involves a high degree of risk. In addition to the other information contained in this annual report, including the reports we incorporate by reference, you should consider the following important factors carefully in evaluating our company and its business before purchasing shares of our stock.

We have a history of losses and our future profitability is uncertain.

We cannot be sure that we will be able to achieve significant and sustained revenues or realize sustained profitable operating results in the future. Guilford was founded in July 1993 and, with the sole exception of 1996, we have not earned a profit in any year since inception. Our losses stem mainly from the significant amount of money that we have spent on research and development. As of December 31, 1999, we had an accumulated deficit of approximately $83 million. We expect to have significant additional losses over the next several years.

Most of our product candidates are in research or early stages of pre-clinical and clinical development. Except for GLIADEL, none of our product candidates has been marketed and sold to the public. At this time, nearly all of our revenues have come from:

- payments from Aventis from the sale and distribution of GLIADEL® Wafer,
- one-time signing fees from our corporate partners under our collaboration agreements supporting the research, development and commercialization of our product candidates,
- one-time payments from our corporate partners upon the achievement of specified regulatory or development milestones; for example, Aventis' payment to us in July 1999 relating to approval in France to market and sell GLIADEL for the recurrent surgery indication, and
- periodic research funding under our collaboration with Amgen.

We do not expect current and anticipated revenues from GLIADEL® Wafer to be sufficient to support all our anticipated future activities. Whether GLIADEL® Wafer sales will ever generate any significant revenues continues to remain uncertain. In addition, we do not anticipate generating revenues from the sale of our product candidates for the next several years, if ever. We will require payments from our current corporate partners, principally Aventis and Amgen, and any future corporate partners, to fund our ongoing activities.

Whether we will ever recognize significant revenues from Amgen in the form of milestone payments or royalties paid on product sales is also subject to significant risk and uncertainty. These risks are part of each of the following activities, among others:

- new product development,
- the conduct of pre-clinical animal studies and human clinical trials,
- applying for and obtaining regulatory approval to market and sell product candidates,

- scale-up of the processes for making product candidates in quantities and qualities needed for research and development purposes to commercial scale manufacture needed to support marketing and sales of new products, and
- commercialization of new products.

We discuss these and other risks in greater detail below in this "Risk Factors" section.

Whether we will ever be able to achieve sustained profitability in the future will depend on many factors, including:

- the successful marketing of GLIADEL® Wafer by Aventis,
- receipt of regulatory clearance to market and sell GLIADEL® Wafer in Europe,
- receipt of regulatory clearance to market and sell GLIADEL® Wafer for patients undergoing initial surgery for malignant glioma in the United States as well as Europe and other countries,
- the successful development and commercialization of product candidates that result from our collaboration with Amgen, and
- our ability to enter into additional collaborative arrangements and license agreements with other corporate partners for our product candidates and earlier stage technologies as we develop them.

We will need to conduct substantial additional research, development and clinical trials. We will also need to receive necessary regulatory clearances. We expect that these research, development and clinical trial activities, and regulatory clearances, together with future general and administrative activities, will result in significant expenses for the foreseeable future.

Our results of operations are likely to fluctuate.

Our revenues and expenses have fluctuated significantly in the past because of the nature of their sources. This fluctuation has in turn caused our results of operations to vary significantly from quarter to quarter and year to year. We expect the fluctuations in our revenues and expenses to continue and thus our results of operations should also continue to vary significantly. These fluctuations are due to a variety of factors, including:

- the timing and amount of sales of GLIADEL® Wafer to Aventis and Aventis' sales to others,
- the timing and realization of milestone and other payments from our corporate partners, including Aventis and Amgen,
- the timing and amount of expenses relating to our research and development, product development, and manufacturing activities, and
- the extent and timing of costs related to our activities to obtain patents on our inventions and to extend, enforce and/or defend our patent and other rights to our intellectual property.

We are dependent on GLIADEL® Wafer and Aventis for revenues.

Our near term prospects depend to a large extent on sales by Aventis of GLIADEL® Wafer, our only commercial product to date. GLIADEL® Wafer was commercially launched in the United States in February 1997. We currently do not know whether the product will ever gain broad market acceptance or the extent of the marketing efforts necessary to achieve broad market acceptance. If GLIADEL® Wafer fails to gain market acceptance, that failure would have a material adverse effect on the likelihood of increasing the revenues that we receive from sales of GLIADEL® Wafer.

To date, we have received clearance from the FDA to market GLIADEL® Wafer in the United States for a limited subset of patients suffering from brain cancer. This clearance extends to those patients for whom surgical tumor removal, commonly referred to as "resection", is indicated and who have recurrent forms of the brain cancer glioblastoma multiforme. A recurrent form of glioblastoma

multiforme is one in which the cancer has returned after initial surgery to remove a brain tumor. The number of patients undergoing recurrent surgery for glioblastoma multiforme is very limited, and we believe the total annual incidence of glioblastoma multiforme in the United States is less than 10,000.

In order to expand the medical uses, commonly referred to as "indications", for which Aventis may market GLIADEL® Wafer, we and Aventis must successfully complete additional lengthy clinical trials. Thereafter, we and Aventis will have to apply to the FDA and international health regulatory authorities for clearance to market GLIADEL® Wafer for patients undergoing initial surgery for glioblastoma multiforme and potentially other brain cancers. We cannot be sure that we and Aventis will be able to successfully complete these clinical trials or receive the desired regulatory clearance. If GLIADEL® Wafer fails to receive regulatory clearance, that failure would limit Aventis' ability to market GLIADEL® Wafer for use in patients beyond the current narrow indication and would have a material adverse effect on our business prospects.

In addition, Aventis has filed for marketing clearance for the current indication for GLIADEL® Wafer in a number of foreign countries, and as of the date of this annual report, Aventis has received international regulatory approvals to market and sell GLIADEL® Wafer in only a limited number of foreign countries, including France and Germany. Aventis may not be able to obtain any other international regulatory approvals for GLIADEL® Wafer. If Aventis fails to obtain those approvals, the geographic market for GLIADEL® Wafer would remain limited, which reduces the likelihood of increasing the revenues that we receive from sales of GLIADEL® Wafer.

We have granted Aventis exclusive worldwide (excluding Scandinavia and Japan) marketing, sales and distribution rights for GLIADEL® Wafer. However, our agreements with Aventis do not impose any minimum requirements on Aventis for the purchase of GLIADEL from us or for the sale of GLIADEL® Wafer to end-users. Therefore, we have no control over the revenues we receive from the sale and distribution of GLIADEL® Wafer, which depend completely on Aventis' marketing efforts. In addition, prior to the February 1997 commercial launch of GLIADEL® Wafer in the United States, Aventis' oncology sales force had no previous experience in marketing a product to neurosurgeons. We cannot be sure that Aventis will elect to continue or increase its marketing and promotional activities for GLIADEL® Wafer or that its efforts in that regard will be successful. The inability or unwillingness of Aventis to aggressively market and promote GLIADEL® Wafer would have a material adverse effect on the revenues that we receive from sales of GLIADEL® Wafer.

GLIADEL® Wafer is also a very fragile product and can easily break into many pieces if not handled with great care. Product recalls due to excessive breakage of the GLIADEL® Wafers or for other reasons could also have a material adverse effect on our business, financial condition and results of operations.

Aventis must make designated one-time milestone payments to us upon achieving specified domestic and international regulatory approvals. By and large, Aventis is responsible for the timing and content of the applications necessary for international regulatory clearances to market and sell GLIADEL® Wafer. Thus, whether GLIADEL® Wafer will receive these clearances depends heavily on the efforts of Aventis. We cannot be sure any or all of these milestones will be satisfied in a manner so as to entitle us to receive the corresponding milestone payments from Aventis. The potential milestone payments are significant, and failure to achieve the designated regulatory objectives could have a material adverse effect on our financial condition.

The success of our Amgen collaboration is dependent on a number of factors, most of which are outside of our control.

Regulatory and development milestone payments as well as royalty amounts on product sales payable to us under our collaboration with Amgen depend on a number of factors. Many of these factors are not within our control, including:

- the selection of one or more appropriate lead compounds,
- successful design and completion of pre-clinical and clinical development activities,
- application for and obtaining regulatory clearances to market potential products,
- commercialization of products, and
- the successful preservation and extension of the patent and other intellectual property rights licensed to Amgen.

All of these activities are subject to significant risks and uncertainties. For a description of these and other material risks related to the research, development and commercialization of the FKBP neuroimmunophilin ligand technology, you should read the following sections contained in this "Risk Factors" discussion:

- "We face technological uncertainties related to research, development and commercialization,"
- "We may be unable to protect our proprietary rights, permitting competitors to duplicate our products and services,"
- "We are dependent on licensed intellectual property,"
- "Pre-clinical and clinical trial results for our products may not be favorable,"
- "Our products use novel alternative technologies and therapeutic approaches which have not been widely studied," and
- "Our business is dependent on our ability to keep pace with the latest technological changes."

Moreover, under the terms of our collaboration with Amgen, we have no control over the development activities regarding the FKBP neuroimmunophilin ligand technology, which have been left to the sole discretion of Amgen. Our agreement with Amgen also does not specify a binding timetable for achieving development and commercialization goals with respect to the FKBP neuroimmunophilin ligand technology. If Amgen determines to conduct clinical trials on a product candidate resulting from our collaboration, Amgen still may not be able successfully to complete those clinical trials and then receive clearance from the FDA or foreign regulatory authorities to market and sell any such products.

The FKBP neuroimmunophilin ligand technology we have licensed to Amgen represents a new approach to the treatment of certain types of neurological and other diseases and conditions. We and Amgen have very limited experience in taking the kinds of compounds likely to result from our work and formulating them into final drug products appropriate for sale to the public. In addition, both of us have limited experience with the scale-up of such compounds from the quantity and quality needed to support research and development efforts to quantities needed to support commercial scale distribution. Also, both we and Amgen have limited experience with the manufacture of compounds of this type for commercial sale. There is a risk that Amgen will not be successful in scaling-up and manufacturing any such compounds needed for commercial sale. For a more complete description of the kinds of risks associated with product manufacture, you should read the section entitled "We have limited manufacturing capabilities" below.

If Amgen is able to obtain all regulatory approvals necessary to market a product resulting from our collaboration, our agreement does not specify any minimum sales requirements for Amgen. Thus, any royalty amounts payable to us in the future will depend entirely on the sales and marketing efforts of Amgen, an activity over which we will have no control. In addition, our agreement with

Amgen does not prevent Amgen from pursuing technologies for product candidates competitive with the FKBP neuroimmunophilin ligand technology in the future.

We have limited manufacturing capabilities.

To commercialize GLIADEL® Wafer, we must be able to manufacture this product in sufficient quantities, in compliance with regulatory requirements, and at acceptable costs. We manufacture GLIADEL® Wafer at our manufacturing facility in Baltimore, Maryland, which consists of production laboratories and redundant cleanrooms. We estimate that the facility currently has the capacity to manufacture approximately 8,000 GLIADEL® Wafer treatments per year.

Although we believe this GLIADEL® Wafer manufacturing facility meets the FDA's current requirements for good manufacturing practices, which are commonly referred to as "cGMP", and the FDA has inspected the facility in the past, we have manufactured only limited quantities of GLIADEL® Wafer in the facility. We cannot be sure that we will be able to continue to satisfy applicable regulatory standards, including cGMP requirements, and other requirements relating to the manufacture of GLIADEL® Wafer in the facility.

We also face risks inherent in the operation of a single facility for manufacture of GLIADEL® Wafer. These risks include:

- unforeseen plant shutdowns due to personnel, equipment or other factors, and
- the possible inability of the facility to produce GLIADEL® Wafer in quantities sufficient to meet demand.

Any delay in the manufacture of GLIADEL® Wafer could result in delays in product shipment. Delays in product shipment would have a material adverse effect on our business, financial condition and results of operations.

Currently, we have no manufacturing capabilities for our product candidates, including DOPASCAN® Injection. Consequently, in order to complete the commercialization process of any of our product candidates, we must either acquire, build or expand our internal manufacturing capabilities or rely on third parties to manufacture these product candidates. We cannot be sure that we or our corporate partners, including Amgen, will be able to (1) acquire, build or expand facilities that will meet quality, quantity and timing requirements or (2) enter into manufacturing contracts with others on acceptable terms, or at all. Our inability, or that of our corporate partners, to accomplish these tasks would impede our efforts to bring our product candidates to market, which would adversely affect our business.

Third-party manufacturers must also comply with FDA, Drug Enforcement Administration, and other regulatory requirements for their facilities, including the FDA's cGMP regulations. In addition, manufacture of product candidates on a limited basis for investigational use in animal studies or human clinical trials does not guarantee that large-scale, commercial production is viable. Small changes in methods of manufacture can affect the safety, efficacy, controlled release or other characteristics of a product. Changes in methods of manufacture, including commercial scale-up, can, among other things, require the performance of new clinical studies. Moreover, if we decide to manufacture one or more of our product candidates ourselves, we would incur substantial start-up expenses and need to expand our facilities and hire additional personnel.

We face technological uncertainties related to research, development and commercialization.

The research, development and commercialization of pharmaceutical drugs inherently involve significant risk. Before we or our corporate partners can be in a position to commercialize a new product (i.e., to market, distribute and sell the product), each of us will have to:

- expend substantial capital and effort to develop our product candidates further, which includes conducting extensive and expensive pre-clinical animal studies and human clinical trials,

- apply for and obtain regulatory approval to market and sell such product candidates, and
- conduct other costly activities related to preparation for product launch, among many other activities.

In some of our research programs, we are using compounds that we consider to be "prototype" compounds in the research phase of our work. By prototype compounds we mean compounds that we are using primarily to establish that a relevant scientific mechanism of biological or chemical action could have commercial application in diagnosing, treating or preventing disease. We generally do not consider our prototype compounds to be lead compounds acceptable for further development into a product(s) because of factors that render them unsuitable as drug candidates. Such factors include sub-optimal metabolic or pharmacokinetic characteristics or unfavorable patent coverage. In order to develop commercial products, we will need to conduct research using other compounds that share the key aspects of the prototype compounds but do not have the unsuitable characteristics. We cannot be sure that this will always be possible.

In addition, our product candidates are subject to the risks of failure inherent in the development of products based on new and unproved technologies. These risks include the possibility that:

- our new approaches will not result in any products that gain market acceptance;
- a product candidate will prove to be unsafe or ineffective, or will otherwise fail to receive and maintain regulatory clearances necessary for marketing,
- a product, even if found to be safe and effective, could still be difficult to manufacture on the large scale necessary for commercialization or otherwise not be economical to market,
- a product will unfavorably interact with other types of commonly used medications, thus restricting the circumstances in which it may be used,
- proprietary rights of third parties will preclude us from manufacturing or marketing a new product, or
- third parties will market superior or more cost-effective products.

As a result, our activities, either directly or through corporate partners, may not result in any commercially viable products.

We are dependent on collaborations with third parties for the development and commercialization of our products.

Our resources are limited, particularly because we are developing our technologies for a variety of different diseases. Our business strategy requires that we enter into various arrangements with:

- corporate partners, such as Aventis and Amgen,
- academic investigators at universities, such as Johns Hopkins and others,
- licensors of technologies, such as Johns Hopkins, Massachusetts Institute of Technology and RTI,
- licensees of our technologies, such as Daiichi Radioisotope Laboratories, Ltd. and others.

Our success depends in large part upon the efforts of these parties.

Like many small biopharmaceutical companies, our business strategy includes finding larger pharmaceutical companies to collaborate with us to support the research, development and commercialization of our product candidates. In trying to attract corporate partners to collaborate with us in the research, development and commercialization process, we face serious competition from other small biopharmaceutical companies and even the in-house research and development staffs of the larger pharmaceutical companies themselves. If we are unable to enter into such arrangements with corporate partners, this failure may severely limit our ability to proceed with the research,

development, manufacture or sale of product candidates. For example, we are actively seeking corporate partners to assist in the development of DOPASCAN® Injection as well as our NAALADase and PARP inhibitor neuroprotective drug programs, but we may not find suitable corporate partners for these programs.

It is common in many corporate partnerships in our industry for the larger partner to have responsibility for conducting pre-clinical studies and human clinical trials and/or preparing and submitting applications for regulatory approval of potential pharmaceutical or other products. That is the case with some of our current corporate partnerships, including our collaboration with Amgen. It is possible that this will also be the case with future arrangements into which we may enter. If one of our collaborative partners fails to develop or commercialize successfully any of our product candidates, we would not be able to remedy this failure would and the failure could materially and adversely affect our business.

Furthermore, larger pharmaceutical companies often explore multiple technologies and products for the same medical conditions. Therefore, they are likely to enter into collaborations with our competitors for products addressing the same medical conditions targeted by our technologies. Thus our collaborators, including Amgen, may pursue alternative technologies or product candidates either on their own or in collaboration with others, including our competitors, in order to develop treatments for the diseases or disorders targeted by our collaborative arrangements. Depending on how other product candidates advance, a corporate partner may slow down or abandon its work on our product candidates or terminate its collaborative arrangement with us in order to focus on these other prospects.

We also depend to a large extent on technology license agreements with third parties, including our agreements with Johns Hopkins relating to the neuroimmunophilin ligand technology. This license agreement and others we have require that we meet a specified schedule for achieving designated research, development and regulatory milestones and that we spend minimum amounts of money to develop the technology, as well as make specified payments from proceeds from corporate partners and royalty payments. If we are unable to meet or agree upon these requirements under a license, our licensor could terminate the license and thus deprive us of access to key technology. A deprivation of this type could have a material adverse effect on our business.

We may be unable to obtain the additional capital needed to operate and grow our business.

We will require substantial funds in order to continue our research and development programs and pre-clinical and clinical testing and to manufacture and, where applicable, market our products. We cannot be sure that we will be able to obtain any future funds that we may require on acceptable terms, or at all. Under our operating lease with a trust affiliated with First Union National Bank for our new research and development facility, we are required to hold, in the aggregate, unrestricted cash, cash equivalents and investments of $40 million at all times during the term of the lease. In addition, we are required to maintain specified amounts of cash, $19.1 million restricted at December 31, 1999, as collateral at First Union under this arrangement and other loan agreements with First Union. These requirements may limit our ability to access our capital in the future.

Our capital requirements depend on numerous factors, including:

- the progress of our research and development programs,
- the progress of pre-clinical and clinical testing,
- the time and costs involved in obtaining regulatory approvals,
- the cost of filing, prosecuting, defending and enforcing any patent claims and other intellectual property rights,
- competing technological and market developments,

- changes in our existing research relationships with universities and others,
- our ability to establish collaborative arrangements with large pharmaceutical companies and others,
- the requirements and timing of entering into technology licensing agreements and other similar arrangements, and
- the progress of efforts to scale-up manufacturing processes.

We may use our existing resources before we may otherwise expect because of changes in our research and development and commercialization plans or other factors affecting our operating expenses or capital expenditures, including potential acquisitions of other businesses, assets or technologies.

Our ability to raise future capital on acceptable terms depends on conditions in the public and private equity markets and our performance, as well as the overall performance of other companies in the biopharmaceutical and biotechnology sectors.

Our stock price is volatile.

The market price of our stock has been and is likely to continue to be highly volatile, and an investment in our shares involves substantial risks. The market prices for shares of smaller biotechnology companies like ours have a history of being highly volatile. Furthermore, the stock market generally and the market for stocks of companies with lower market capitalizations, like us, have from time to time experienced and likely will again experience significant price and volume fluctuations that are unrelated to the operating performance of a particular company.

From time to time, stock market professionals publish research reports covering our business and our future prospects. A number of factors may limit our ability to meet the expectations of securities analysts or investors and thus may adversely affect our stock price. These factors include:

- announcements by us or our competitors of clinical results, technological innovations, product sales, new products or product candidates,
- developments or disputes concerning patent or proprietary rights,
- regulatory developments affecting our products,
- period-to-period fluctuations in the results of our operations, and
- market conditions for emerging growth companies and biopharmaceutical companies.

We may be unable to protect our proprietary rights, permitting competitors to duplicate our products and services.

Any success that we have will depend in large part on our ability to:

- obtain, maintain and enforce intellectual property protection for our products and processes,
- license rights to patents from third parties,
- maintain trade secret protection, and
- operate without infringing upon the proprietary rights of others.

Intellectual property for our technologies and products will be a crucial factor in our ability to develop and commercialize our products. Large pharmaceutical companies consider a strong patent estate critical when they evaluate whether to enter into a collaborative arrangement to support the research, development and commercialization of a technology. Without the prospect of reasonable intellectual property protection, it would be difficult for a corporate partner, or our company for that matter, to justify the time and money that is necessary to complete the development of a product.

The rules and criteria for receiving and enforcing a patent for pharmaceutical and biotechnological inventions are in flux and are unclear in many respects. The ultimate scope of patent protection afforded these types of patents remains uncertain, and a number of our product candidates are subject to this uncertainty.

Many others, including companies, universities and other research organizations, work in the areas of our business, and we cannot be sure that the claims contained in our issued patents will be interpreted as broadly as we would like in light of the inventions of these other parties. In addition, we cannot be sure that the claims set forth in our pending patent applications will issue in the form submitted. These claims may be narrowed or stricken, and the applications may not ever ultimately result in valid and enforceable patents. Thus, we cannot be sure that our patents and patent applications will adequately protect our product candidates.

We are aware that other companies have been issued patents, and have filed or may be engaged in filing patent applications, that claim matter relating to polymer drug delivery technology, including polymer-based oncology products, and neurological therapeutics and diagnostics, including small molecule neuroimmunophilin ligands and neuroprotectants. While we do not believe that we are infringing valid third-party patents of which we are aware, we cannot give you any assurance as to the ability of our patents and patent applications to adequately protect our products or product candidates. In addition, our products or product candidates may infringe or be dominated by patents that have issued or may issue in the future to third parties. Also, our neurotropic product candidates may infringe or be dominated by patents that have been issued or may be issued to third parties.

In order to protect our intellectual property position with respect to our neuroimmunophilin ligands, we filed an opposition in 1998 in an effort to prevent the final issuance of a European patent to the company we reference in the immediately preceding paragraph. While we do not believe the claims of this European patent are valid, any final issuance could result in future litigation if this company were to allege that we infringed the claims of this patent in Europe.

Furthermore, we cannot be sure that any or all of the patent applications assigned or licensed to us from third parties will be granted. We cannot offer assurances that we will develop additional products or processes that are patentable, or that any patents issued to us, or licensed by us, will provide us with any competitive advantages or adequate protection for our products. We also cannot be sure that others will not successfully challenge, circumvent or invalidate any of our existing or future patents or intellectual property.

Our policy is to control the disclosure and use of our know-how and trade secrets by entering into confidentiality agreements with our employees, consultants and third parties. There is a risk, however, that:

- these parties will not honor our confidentiality agreements,
- others will independently develop equivalent or competing technology,
- disputes will arise concerning the ownership of intellectual property or the applicability of confidentiality obligations, or
- disclosure of our trade secrets will occur regardless of these contractual protections.

In our business, we often work with consultants and research collaborators at universities and other research organizations. To the extent that any of these consultants or research collaborators uses intellectual property owned by others as part of their work with us, disputes may arise between us and these other parties as to which one of us has the rights to intellectual property related to or resulting from the work done.

We support and collaborate in research conducted in universities, such as Johns Hopkins, and in governmental research organizations, such as the National Institutes of Health. We cannot be sure that we will have or be able to acquire exclusive rights to the inventions or technical information that result from work performed by university personnel or at these organizations. Also, disputes may arise as to which party should have rights in research programs that we conduct on our own or in

collaboration with others that are derived from or related to the work performed at the university or governmental research organization. In addition, in the event of a contractual breach by us, some of our collaborative research contracts provide that we must return the technology rights, including any patents or patent applications, to the contracting university or governmental research organization.

Questions of infringement of intellectual property rights, including patent rights, may involve highly technical and subjective analyses. Some or all of our existing or future products or technologies may now or in the future infringe the rights of other parties. These other parties might initiate legal action against us to enforce their claims, and our defense of the claims might not be successful.

We may incur substantial costs if we must defend against charges of infringement of patent or proprietary rights of third parties. We may also incur substantial costs if we find it necessary to protect our own patent or proprietary rights by bringing suit against third parties, including suits involving our neurotrophic product candidates. We could also lose rights to develop or market products or be required to pay monetary damages or royalties to license proprietary rights from third parties. In response to actual or threatened litigation, we may seek licenses from third parties or attempt to redesign our products or processes to avoid infringement. We cannot be sure that we will be able to obtain licenses on acceptable terms, or at all, or successfully redesign our products or processes.

In addition to the risk that we could be a party to patent infringement litigation, the U.S. Patent and Trademark Office, or its foreign counterparts, could require us to participate in patent interference proceedings that it declares. These proceedings are often expensive and time-consuming, even if we were to prevail in such a proceeding. We may also be forced to initiate legal proceedings to protect our patent position or other proprietary rights. These proceedings typically are costly, protracted, and offer no assurance of success.

Under our collaboration, Amgen is responsible for preparing, filing, prosecuting, maintaining and defending patent applications and patents relating to the FKBP neuroimmunophilin ligand technology. We cannot be sure that Amgen will pursue these activities in the same manner or as vigorously as we would if we had that responsibility. Furthermore, Amgen has the option to take the lead in bringing actions to enforce patent rights relating to the FKBP neuroimmunophilin ligand technology and to defend against third party infringement suits regarding that technology. While Amgen and Guilford have agreed to consult with each other on such matters, in the event of disagreement, Amgen's decisions will control.

We are dependent on licensed intellectual property.

We have licensed intellectual property, including patents, patent applications and know-how, from universities and others, including intellectual property underlying GLIADEL® Wafer, DOPASCAN® Injection and the neuroimmunophilin ligand technology. Some of our product development programs depend on our ability to maintain rights under these licenses. Under the terms of our license agreements, we are generally obligated to:

- exercise diligence in the research and development of these technologies,
- achieve specified development and regulatory milestones,
- expend minimum amounts of resources in bringing potential products to market,
- make specified royalty and milestone payments to the party from which we have licensed the technology, and
- reimburse patent costs to these parties.

In addition, these license agreements obligate us to abide by record-keeping and periodic reporting obligations. Each licensor has the power to terminate its agreement if we fail to meet our obligations under that license. We may not be able to meet our obligations under these license

agreements. Furthermore, these obligations may conflict with our obligations under other agreements that we have.

If we default under any of these license agreements, we may lose our right to market and sell any products based on the licensed technology. Losing our marketing and sales rights would have a material and adverse effect on our business, financial condition and results of operations. Our license agreements require that we pay a royalty on sales of GLIADEL® Wafer to the university that licensed us the technology underlying that product. In addition, we will have to pay milestone and/or royalty payments in connection with the successful development and commercialization of DOPASCAN® Injection and any products that result from the NIL and PARP technologies.

In the future, to support our product development efforts, we may need research materials or scientific information that researchers at universities or other organizations generate. We cannot be sure that we will be able to obtain this scientific information or research materials in a timely manner or at all.

Revenues from our products are dependent in part on reimbursement from healthcare payors, which is uncertain.

Sales of our product candidates will depend in part on the availability of reimbursement from third-party healthcare payors, such as government insurance plans, including Medicare and Medicaid in the United States, private insurance and managed care plans. Reimbursement policies for GLIADEL® Wafer remain uncertain, both domestically and internationally. We cannot be sure that any reimbursement will be available for GLIADEL® Wafer or any of our product candidates under development. Furthermore, even if reimbursement is available, we cannot be sure that it will be available at price levels sufficient to realize an appropriate return on our investment in GLIADEL® Wafer or our other products in development.

We are dependent on one source of supply for several of our key product components.

Currently, we are able to purchase some of the key components for GLIADEL® Wafer and our product candidates only from single source suppliers. These vendors are subject to many strict regulatory requirements regarding the supply of these components. We cannot be sure that these suppliers will comply, or have complied, with applicable regulatory requirements or that they will otherwise continue to supply us with the key components we require. If suppliers are unable or refuse to supply us, or will supply us only at a prohibitive cost, we may not be able to access additional sources at acceptable prices, on a timely basis, if ever.

The current formulation of GLIADEL® Wafer utilizes the chemotherapeutic agent BCNU, which is also known as "carmustine." Currently we have the option to procure BCNU from only two sources in the United States, and we are not aware of any supplier outside of the United States. We currently obtain BCNU from one of these two U.S. suppliers on a purchase order basis and not through any long-term supply agreement. If we fail to receive key supplies necessary for the manufacture of GLIADEL on a timely basis at a reasonable cost, delays in product shipment could result. Delays of this type would have a material adverse effect on our business.

The manufacture of DOPASCAN® Injection requires that a precursor compound be labeled with a radioactive isotope of iodine, known as Iodine-123, to form the final product. Only a limited number of companies worldwide are capable of performing the necessary "radioiodination" of the precursor and distribution of the final product. Currently, we do not have any arrangement for the manufacture and supply of DOPASCAN® Injection nor do we have the internal capability to manufacture DOPASCAN® Injection ourselves. Consequently, we will not be in a position to commence Phase III or other clinical trials for DOPASCAN® Injection until we locate a qualified supplier.

We have assessed the companies that we believe are currently capable of manufacturing a product like DOPASCAN® Injection. Based on this assessment, we believe a significant risk exists

that we may not be able to find a manufacturer who can meet the quality and cost requirements required to conduct the Phase III clinical trials that will be necessary to support application to the FDA for regulatory approval. Inability to come to agreement with a suitable manufacturer for the clinical and commercial supply of DOPASCAN® Injection on acceptable terms would prevent us from developing this product candidate further.

The U.S. Government holds rights which may permit it to license to third parties technology we currently hold the exclusive right to use.

The U.S. government holds rights that govern aspects of certain of the technologies licensed to us by third party licensors. These government rights in inventions conceived or reduced to practice under a government-funded program may include a non-exclusive, royalty-free, worldwide license for the government to practice or have practiced resulting inventions for any governmental purpose. In addition, the U.S. government has the right to grant to others licenses that may be exclusive under any of these inventions if the government determines that:

- adequate steps have not been taken to commercialize such inventions,
- the grant is necessary to meet public health or safety needs, or
- the grant is necessary to meet requirements for public use under federal regulations.

The U.S. government also has the right to take title to a subject invention if we fail to disclose the invention, and may elect to take title within specified time limits. The U.S. government may acquire title in any country in which we do not file a patent application within specified time limits.

Federal law requires any licensor of an invention partially funded by the federal government to obtain a commitment from any exclusive licensee, such as us, to manufacture products using the invention substantially in the United States. Further, these rights include the right of the government to use and disclose technical data relating to licensed technology that was developed in whole or in part at government expense. Our principal technology license agreements contain provisions recognizing these rights.

We have entered into a contract with the U.S. Army, funded by the Office of National Drug Control Policy, commonly referred to as the "Drug Czar", to provide financial support for research being conducted by us on a potential cocaine inhibitor. That contract permits the U.S. government to obtain unlimited rights to data developed in the course of our performance if we do not use the data within five years after termination of the contract to conduct further laboratory investigation and/or clinical trials aimed at developing a commercial product to combat drug abuse.

Pre-clinical and clinical trial results for our products may not be favorable.

In order to obtain regulatory approval for the commercial sale of any of our product candidates, we must conduct both pre-clinical studies and human clinical trials. These studies and trials must demonstrate that the product is safe and effective for the clinical use for which we are seeking approval. Together with Aventis, we commenced a Phase III clinical trial for GLIADEL in December 1997 in patients undergoing initial surgery for the brain cancer malignant glioma. We cannot be sure that the results of this or other clinical trials we may conduct in the future will be successful. Adverse results from this or any future trial would have a material adverse effect on our business.

We also face the risk that we will not be permitted to undertake or continue clinical trials for any of our product candidates in the future. Even if we are able to conduct such trials, we may not be able to demonstrate satisfactorily that the products are safe and effective and thus qualify for the regulatory approvals needed to market and sell them. Results from pre-clinical studies and early clinical trials are often not accurate indicators of results of later-stage clinical trials that involve larger human populations.

We are subject to extensive governmental regulation, which may change and harm our business.

Our research, pre-clinical development and clinical trials, and the manufacturing and marketing of our product candidates, are subject to extensive regulation by numerous governmental authorities in the United States and other countries, including the FDA and the DEA. Controlled drugs such as GLIADEL® Wafer and radiolabeled drugs such as DOPASCAN® Injection are subject to additional requirements. Except for GLIADEL® Wafer, none of our product candidates has received marketing clearance from the FDA. In addition, none of our product candidates has received clearance from any foreign regulatory authority for commercial sale, except with respect to GLIADEL® Wafer, which has received marketing clearance in a limited number of foreign countries.

As a condition to approval of our product candidates under development, the FDA could require additional pre-clinical, clinical or other studies. Any requirement that we perform additional pre-clinical, clinical or other studies, or purchase clinical or other data from other companies could delay, or increase the expense of, approval of our product candidates, which could have a material adverse effect on our business.

In order to obtain FDA approval of a new drug product for a specific clinical use, we must demonstrate to the satisfaction of the FDA that the product is safe and effective for its intended use. We must also demonstrate that the product is capable of being manufactured in accordance with applicable regulatory standards. Significant risks exist that:

- we will not be able to satisfy the FDA's requirements with respect to any of our drug product candidates or with respect to the proposed expanded labeling for GLIADEL® Wafer for patients undergoing initial surgery for malignant glioma, or
- even if the FDA does approve our product candidates or expanded labeling, the FDA will approve less than the full scope of uses or labeling that we seek.

Failure to obtain regulatory drug approvals on a timely basis could have a material adverse effect on our business.

Even if we are able to obtain necessary FDA approval, the FDA may nevertheless require post-marketing testing and surveillance to monitor the approved product and continued compliance with regulatory requirements. The FDA may withdraw product approvals if we or our corporate partners, such as Aventis in the case of GLIADEL® Wafer, do not maintain compliance with regulatory requirements. The FDA may also withdraw product approvals if problems concerning safety or efficacy of the product occur following approval.

The process of obtaining FDA and other required approvals or licenses and of meeting other regulatory requirements to test and market drugs, including controlled substances and radiolabeled drugs, is rigorous and lengthy. It has required, and will continue to require, that we expend substantial resources. We will need to conduct clinical trials and other studies on all of our product candidates before we are in a position to file a new drug application for marketing and sales approval. Unsatisfactory clinical trial results and other delays in obtaining regulatory approvals or licenses would prevent the marketing of the products we are developing. Until we receive the necessary approvals or licenses and meet other regulatory requirements, we will not receive revenues or royalties related to product sales.

In addition to the requirements for product approval, before a pharmaceutical product may be marketed and sold in some foreign countries, the proposed pricing for the product must be approved as well. Products may be subject to price controls or limits on reimbursement. The requirements governing product pricing and reimbursement vary widely from country to country and can be implemented disparately at the national level. We cannot guarantee that any country which has price controls or reimbursement limitations for pharmaceuticals will allow favorable reimbursement and pricing arrangements for our products or those of our corporate partners, including Aventis and its applications for GLIADEL® Wafer outside the United States.

Where applicable, we hope to capitalize on current FDA regulations and the new provisions of the FDA Modernization Act of 1997. These regulations or provisions permit "fast track", expedited or accelerated approval or more limited "treatment use" of, and cost recovery for, certain experimental drugs under limited circumstances. The fast track and treatment provisions, and FDA's accelerated, expedited and treatment regulations apply generally only to:

- drug products intended to treat severely debilitating or serious or life-threatening diseases, and
- drug products that provide meaningful therapeutic benefit to patients over existing treatments, that potentially address an unmet medical need, or that are for diseases for which no satisfactory or comparable therapy exists.

The FDA Modernization Act contains provisions patterned after the accelerated approval regulations and other provisions pertaining to expanded access, i.e., treatment uses. Since some of the new statutory provisions and current FDA regulations are different from one another, it is unclear how they will apply, if at all, to our drug candidates. We cannot be sure that our drug candidates will qualify for fast track, accelerated or expedited approvals or for treatment use and cost recovery.

Because controlled drug products and radiolabeled drugs are subject to special regulations in addition to those applicable to other drugs, some of our products and product candidates, including DOPASCAN® Injection, are or may be subject to regulation by the DEA as controlled substances and by the Nuclear Regulatory Commission as radiolabeled drugs. The NRC licenses persons who use nuclear materials and establishes standards for radiological health and safety. The DEA is responsible for the control of manufacture, distribution and dispensing of controlled substances, including the equipment and raw materials used in their manufacture and packaging in order to prevent such articles from being diverted into illicit channels of commerce. Registration is required and other activities involving controlled substances are subject to a variety of record keeping and security requirements, and to permits and authorizations and other requirements. States often have requirements for controlled substances, as well. Certain exceptions are granted by the DEA from requirements for permits and authorizations to export or import materials related to or involving controlled substances. If we are unable to continue to obtain exceptions from the DEA for shipment abroad or other activities, as we have in the past, this situation could have a material adverse effect on us.

We have obtained registrations for our facilities from the DEA. We have also obtained exceptions from the DEA with respect to various of our activities involving DOPASCAN® Injection, including the shipment of specified quantities of a precursor of this product candidate to an overseas collaborative partner. However, we cannot be sure that these exceptions will be sufficient to cover our future activities or that the DEA will not revoke the exceptions. We also cannot be sure that we will be able to meet the other requirements to test, manufacture and market controlled substances or radiolabeled drugs, or that we will be able to obtain additional necessary approvals, permits, authorizations, registrations or licenses to meet state, federal and international regulatory requirements to manufacture and distribute these products. The FDA Modernization Act required the FDA to issue and finalize within one and one-half years regulations governing the approval of radiolabeled drugs. Final regulations were issued in May 1999. These cover general factors relevant to safety and effectiveness, possible indications for radiopharmaceuticals, and the evaluation criteria for safety and effectiveness. We do not know and cannot predict how these and other provisions may affect the potential for approval of DOPASCAN® Injection.

Our products use novel alternative technologies and therapeutic approaches which have not been widely studied.

Many of our product development efforts focus on novel alternative therapeutic approaches and new technologies that have not been widely studied. Applications for these approaches and technologies include, among other things, the treatment of brain cancer, the diagnosis and monitoring of Parkinson's disease, the promotion of nerve growth and the prevention of neuronal damage. These

approaches and technologies may not be successful. We are applying these approaches and technologies in our attempt to discover new treatments for conditions that are also the subject of research and development efforts of many other companies. Our competitors may succeed in developing technologies or products that are more effective or economical than those we are developing. Rapid technological change or developments by others may result in our technology or product candidates becoming obsolete or noncompetitive.

Our business is dependent on our ability to keep pace with the latest technological changes.

The technological areas in which we work continue to evolve at a rapid pace. Our future success depends upon maintaining our ability to compete in the research, development and commercialization of products and technologies in our areas of focus. Competition from pharmaceutical, chemical and biotechnology companies, universities and research institutions is intense and expected to increase. Many of these competitors have substantially greater research and development capabilities and experience and manufacturing, marketing, financial and managerial resources than we do, and represent significant competition for us.

Acquisitions of competing companies by large pharmaceutical companies or other companies could enhance the financial, marketing and other resources available to these competitors. These competitors may develop products that are superior to those we are developing. We are aware of the development by other companies and research scientists of alternative approaches to:

- the treatment of malignant glioma,
- the diagnosis of Parkinson's disease,
- the promotion of nerve growth and repair,
- the treatment and prevention of neuronal damage, and
- the treatment of cocaine addiction.

Our competitors may develop products that render our products or technologies noncompetitive or obsolete. In addition, we may not be able to keep pace with technological developments.

Our products must compete with others to gain market acceptance.

Any product candidate that we develop and for which we gain regulatory approval, including GLIADEL® Wafer, must then compete for market acceptance and market share. An important factor will be the timing of market introduction of competitive products. Accordingly, we expect that the relative speed with which we and competing companies can develop products, complete the clinical testing and approval processes, and supply commercial quantities of the products to the market will be an important element of market success.

Significant competitive factors include:

- capabilities of our collaborators,
- product efficacy and safety,
- timing and scope of regulatory approval,
- product availability,
- marketing and sale capabilities,
- reimbursement coverage from insurance companies and others,
- the amount of clinical benefit of our product candidates relative to their cost,
- the method of administering a product,

- price, and
- patent protection.

Our competitors may develop more effective or more affordable products or achieve earlier product development completion, patent protection, regulatory approval or product commercialization than we do. Our competitors' achievement of any of these goals could have a material adverse effect on our business.

We have limited clinical and regulatory compliance capabilities.

We have limited resources in the areas of product testing and regulatory compliance. Consequently, in order to carry our products through the necessary regulatory approvals and prepare our product candidates for commercialization and marketing, we will have to:

- expend capital to acquire and expand such capabilities,
- reach collaborative arrangements with third parties to provide these capabilities, or
- contract with third parties to provide these capabilities.

We are subject to risks of product liability.

We may potentially become subject to large liability claims and significant defense costs as a result of the design, manufacture or marketing of our products, including GLIADEL® Wafer, or the conduct of clinical trials involving these products. A product liability-related claim or recall could have a material adverse effect on us. We currently maintain only $15 million of product liability insurance covering clinical trials and product sales. We cannot be sure that this existing coverage or any future insurance coverage we obtain will be adequate. Furthermore, we cannot be sure that our insurance will cover any claims made against us.

Product liability insurance varies in cost. It can be difficult to obtain, and we may not be able to purchase it in the future on terms acceptable to us, or at all. We also may not be able to otherwise protect against potential product liability claims. If this occurs, it could prevent or inhibit the clinical development and/or commercialization of any products we are developing.

We are dependent on qualified personnel and consultants.

We depend heavily on the principal members of our management and scientific staff, including Craig R. Smith, M.D., our Chief Executive Officer, and Solomon H. Snyder, M.D., who is a member of our Board of Directors and a consultant to our company. Both Dr. Smith and Dr. Snyder have extensive experience in the biotechnology industry and provide us with unique access to their contacts in the scientific community. The loss of the services of either of these individuals or other members of our senior management team could have a material adverse effect on our business.

We have entered into a consulting agreement with Dr. Snyder and an employment agreement with Dr. Smith, each of which provides protection for our proprietary rights. Nevertheless, either Dr. Snyder or Dr. Smith may terminate his relationship with us at any time. Accordingly, we cannot be sure that either of these individuals or any of our other employees or consultants will remain with us. In the future they may take jobs or consulting positions with our competitors. These employees or consultants may also choose to organize competing companies or ventures.

Our planned activities will require individuals with expertise in many areas including:

- medicinal chemistry and other research specialties,
- pre-clinical testing,
- clinical trial management,
- regulatory affairs,

- manufacturing, and
- business development.

These planned activities will require additional personnel, including management personnel, and will also require existing management personnel to develop added expertise. Recruiting and retaining qualified personnel, collaborators, advisors and consultants will be critical to our activities. We cannot be sure that we will be able to attract and retain the personnel necessary for the development of our business. Furthermore, many pharmaceutical, biotechnology and health care companies and academic and other research institutions compete intensely for experienced scientists. If we are not able to hire the necessary experienced scientists or develop the necessary expertise, this inability could have a material adverse effect on us. In addition, we also depend on the support of our collaborators at research institutions and our consultants.

We currently lack sales and marketing experience.

We currently do not have a sales force, and we have no experience in marketing or selling a product in a commercial setting. If we decide to establish an in-house sales force, our efforts may not be successful in this regard. In addition, if we succeed in bringing additional products to market, our sales force will have to compete with many other companies that currently have extensive and well-funded marketing and sales operations. We cannot be sure that our marketing and sales efforts would compete successfully against these other companies.

Our business involves using hazardous and radioactive materials and animal testing, all of which may result in environmental liability.

Our research and development processes involve the controlled use of hazardous and radioactive materials. We and our collaborative partners are subject to international, federal, state and local laws and regulations governing the use, manufacture, storage, handling and disposal of hazardous and radioactive materials. We believe that the safety procedures relating to our in-house research and development and manufacturing efforts comply in all material respects with the standards prescribed by such laws and regulations. However, we cannot completely eliminate the risk of accidental contamination or injury from these materials. Moreover, we cannot be sure that our collaborative partners are currently complying with the governing standards. We also cannot be sure that we and our collaborative partners will be in compliance with such standards in the future. If a regulatory authority determines that we or our collaborative partners are not complying with the governing laws and regulations, that determination could have a material adverse effect on our business, operations or finances. In addition, we and/or our collaborative partners could be held liable for damages, fines or other liabilities, which could exceed our resources.

We believe that we are and will continue to be in compliance in all material respects with applicable environmental laws and regulations and currently do not expect to make material capital expenditures for environmental control facilities in the near term. However, we may have to incur significant costs to comply with environmental laws and regulations in the future. In addition, future environmental laws or regulations may have a material adverse effect on our operations, business or assets.

Many of the research and development efforts we sponsor involve the use of laboratory animals. Changes in laws, regulations or accepted clinical procedures may adversely affect these research and development efforts. Social pressures that would restrict the use of animals in testing or actions against us or our collaborators by groups or individuals opposed to testing using animals could also adversely affect these research and development efforts.

Effecting a change of control of Guilford would be difficult, which may discourage offers for shares of our common stock.

Our certificate of incorporation and the Delaware General Corporation Law contain provisions that may delay or prevent an attempt by a third party to acquire control of us. These provisions include the requirements of Section 203 of the Delaware General Corporation Law. In general, Section 203 prohibits designated types of business combinations, including mergers, for a period of three years between us and any third party who owns 15% or more of our common stock. This provision does not apply if:

- our Board of Directors approves of the transaction before the third party acquires 15% of our stock,
- the third party acquires at least 85% of our stock at the time its ownership goes past the 15% level, or
- our Board of Directors and two-thirds of the shares of our common stock not held by the third party vote in favor of the transaction.

We have also adopted a stockholder rights plan intended to deter hostile or coercive attempts to acquire us. Under the plan, if any person or group acquires more than 20% of our common stock without approval of the Board of Directors under specified circumstances, our other stockholders have the right to purchase shares of our common stock, or shares of the acquiring company, at a substantial discount to the public market price. The plan thus makes an acquisition much more costly to a potential acquirer.

Our certificate of incorporation also authorizes us to issue up to 4,700,000 shares of preferred stock in one or more different series with terms fixed by the Board of Directors. We do not have to obtain stockholder approval to issue preferred stock in this manner. Issuance of these shares of preferred stock could have the effect of making it more difficult for a person or group to acquire control of us. No shares of our preferred stock are currently outstanding. While our Board of Directors has no current intentions or plans to issue any preferred stock, issuance of these shares could also be used as an anti-takeover device.

PART II

Item 5. Market for Registrant's Common Equity and Related Stockholder Matters

We include the information set forth under the caption "Stock Description and Form 10-K" on the inside back cover of Guilford's 1999 Annual Report to Stockholders which is included as Exhibit 13.01 to this annual report, and we incorporate by reference that portion into Part II of this report.

We have never declared or paid any cash dividends and do not intend to do so for the foreseeable future. Under our various loan and lease agreements with certain financial institutions, we may not declare, during the term of these agreements, any cash dividends on our common stock without the prior written consent of these financial institutions and, in certain cases, the Maryland Industrial Development Financing Authority.

Item 6. Selected Consolidated Financial Data

We incorporate by reference herein the information set forth under the caption "Selected Financial Data" in the 1999 Annual Report to Stockholders. We have filed this information as Exhibit 13.01 to this annual report. You should read this information in conjunction with the Consolidated Financial Statements of the Company and notes thereto.

Item 7. Management's Discussion and Analysis of Results of Operations and Financial Condition

We incorporate by reference herein the information set forth under the caption "Management's Discussion and Analysis of Results of Operations and Financial Condition" in the 1999 Annual Report to Stockholders. We have filed this information as Exhibit 13.01 to this annual report.

Item 7A. Quantitative and Qualitative Disclosures About Market Risk

We have exposure to changing interest rates. Our investment portfolio includes investment grade debt instruments. These instruments are subject to interest rate risk and are volatile to interest rate fluctuations. Due to the short duration and conservative nature of these instruments, we do not believe that we have a material exposure to interest rate risk related to our investment portfolio.

Substantially all of our financial obligations have variable rates of interest. By entering into certain interest rate swap agreements with a commercial bank ("counter party"), we have effectively fixed the interest rates for these floating rate financial obligations. In the event of non-performance by the counter party, we could be exposed to market risk related to interest rates. We describe our exposure to interest rate risk in Notes 4 and 7, "Interest Rate Swap Agreements" and "Indebtedness," respectively, to the footnotes to our Consolidated Financial Statements. We have filed this information as Exhibit 13.01 to this annual report.

Item 8. Financial Statements and Supplementary Data

We incorporate by reference herein the consolidated financial statements and notes thereto and independent auditors' report thereon which are included in the 1999 Annual Report to Stockholders required by this Item 8. We have filed this information as Exhibit 13.01 to this annual report.

Item 9. Changes in and Disagreements with Accountants on Accounting and Financial Disclosure

Not Applicable.

Item 10. Directors and Executive Officers of the Registrant

The information concerning our executive officers is contained in Item 1A of Part I. The information concerning the Company's directors and with regard to Item 405 of Regulation S-K is hereby incorporated by reference from the information to be contained under the caption "Board of Directors" and "Section 16(a) Beneficial Ownership Reporting Compliance" in our 2000 Proxy Statement, which we will file no later than 120 days following December 31, 1999.

PART III

Item 11. Executive Compensation

The information required by this item is hereby incorporated by reference from the information to be contained under the caption "Executive Compensation" in our 2000 Proxy Statement, which we will file no later than 120 days following December 31, 1999.

Item 12. Security Ownership of Certain Beneficial Owners and Management

The information required by this item is hereby incorporated by reference from the information to be contained under the caption "Beneficial Ownership of Common Stock" in our 2000 Proxy Statement, which we will file no later than 120 days following December 31, 1999.

Item 13. Certain Relationships and Related Transactions

The information required by this item is hereby incorporated by reference from the information to be contained under the caption "Beneficial Ownership of Common Stock" and "Certain Relationships and Related Party Transactions" in our 2000 Proxy Statement, which we will file no later than 120 days following December 31, 1999.

PART IV

Item 14. Exhibits, Financial Statement Schedules, and Reports on Form 8-K

(a)(1) Financial Statements

The following Consolidated Financial Statements of Guilford and Independent Auditors' Report beginning on page 41 in Guilford's 1999 Annual Report to Stockholders are included in Exhibit 13.01 to this report and are incorporated into Item 8 of this report:

Independent Auditors' Report

Consolidated Balance Sheets as of December 31, 1999 and 1998

Consolidated Statements of Operations for the Years Ended December 31, 1999, 1998 and 1997

Consolidated Statements of Changes in Stockholders' Equity for the Years Ended December 31, 1999, 1998 and 1997

Consolidated Statements of Cash Flows for the Years Ended December 31, 1999, 1998 and 1997

Notes to Consolidated Financial Statements

(a)(2) Financial Statement Schedules

Independent Auditors' Report

Schedule II — Valuation and Qualifying Accounts

Independent Auditors' Report

The Board of Directors and Stockholders
Guilford Pharmaceuticals Inc.:

Under date of February 11, 2000, we reported on the consolidated balance sheets of Guilford Pharmaceuticals Inc. and subsidiaries as of December 31, 1999 and 1998, and the related consolidated statements of operations, changes in stockholders' equity, and cash flows for each of the years in the three-year period ended December 31, 1999, which are included in the Form 10-K. In connection with our audits of the aforementioned consolidated financial statements, we also audited the related consolidated financial statement schedule as listed in the accompanying index. This financial statement schedule is the responsibility of the Company's management. Our responsibility is to express an opinion on this financial statement schedule based on our audits.

In our opinion, such financial statement schedule, when considered in relation to the basic consolidated financial statements taken as a whole, presents fairly, in all material respects, the information set forth therein.

/s/ KPMG LLP

Philadelphia, Pennsylvania
February 11, 2000

GUILFORD PHARMACEUTICALS INC. AND SUBSIDIARIES
VALUATION AND QUALIFYING ACCOUNTS AND RESERVES
SCHEDULE II
(in thousands)

Classification	Balance @ 12/31/96	Charged to Costs and Expenses	Deductions	Balance @ 12/31/97
Inventory Reserve	$ —	$257	$ —	$257

Classification	Balance @ 12/31/97	Charged to Costs and Expenses	Deductions	Balance @ 12/31/98
Inventory Reserve	$257	$ —	$ —	$257

Classification	Balance @ 12/31/98	Charged to Costs and Expenses	Deductions	Balance @ 12/31/99
Inventory Reserve	$257	$ —	$ —	$257

All other schedules are omitted because they are not applicable or the required information is included in the Consolidated Financial Statements or notes thereto.

(a)(3) Exhibits

The following exhibits are filed with this Form 10-K or incorporated herein by reference to the document set forth next to the exhibit listed below:

Exhibit Number*	Description
3.01A	Amended and Restated Certificate of Incorporation of the Company.
3.01B	Certificate of Amendment to Amended and Restated Certificate of Incorporation.
3.02A	Amended and Restated By-laws of the Company.
3.02B	Amendments to Amended and Restated By-laws of the Company (incorporated by reference to the Registrant's Quarterly Report on Form 10-Q for the quarter ended June 30, 1998 and the Registrant's Annual Report on Form 10-K for the year ended December 31, 1998).
4.01	Specimen Stock Certificate.
4.02A	Stockholder Rights Agreement dated September 26, 1995.
4.02B	Form of Amendment No. 1 to Stockholder Rights Agreement (incorporated by reference to Form 8-K, filed October 20, 1998).
10.01A	1993 Employee Share Option and Restricted Share Plan ("1993 Option Plan").
10.01B	Amendments to 1993 Option Plan.
10.01C	1998 Employee Share Option and Restricted Share Plan as amended ("1998 Option Plan") (incorporated by reference to Form S-8, filed on February 22, 2000).
10.01D	Amendment to 1998 Option Plan (incorporated by reference to Form 10-K filed on March 30, 1999).
10.02A	Series A Preferred Stock Purchase Agreement, dated September 30, 1993, as amended between the Company and holders of its Series A Preferred Stock ("Series A Agreement").
10.02B	Amendment, dated August 25, 1994, to Series A Agreement.
10.02C	Amendment, dated February 15, 1995, to Series A Agreement.
10.03A†	License Agreement, effective March 18, 1994, between the Company and Research Triangle Institute, a not-for-profit Corporation existing under the laws of North Carolina.
10.03B	Appendix A to Exhibit 10.04.
10.04†	License Agreement, dated March 15, 1994, between the Company and Scios Nova.
10.05	Employment Agreement between the Company and Craig R. Smith, M.D.
10.06	Employment Agreement between the Company and Andrew R. Jordan.
10.07	Employment Agreement between the Company and John P. Brennan.
10.08	(Intentionally Omitted)
10.09	Employment Agreement between the Company and William C. Vincek, Ph.D.
10.10	Employment Agreement between the Company and Peter D. Suzdak.
10.11	Employment Agreement between the Company and Nicholas Landekic.
10.12	Employment Agreement between the Company and Thomas C. Seoh.
10.13A	Amendments to certain executive officer employment letter Agreements.
10.13B	Form of Change in Control Severance Agreement (incorporated be reference to the Form 10-Q for the quarter ended September 30, 1998).
10.13C	Severance Provisions from Employment Letter Agreement, effective September 21, 1998, with Nancy J. Linck (incorporated be reference to the Form 10-Q for the quarter ended September 30, 1998).
10.14	(Intentionally Omitted)
10.15A	Consulting Agreement, dated August 1, 1993, as amended on February 28, 1994, between the Company and Solomon H. Snyder, M.D (the "Snyder Consulting Agreement").
10.15B	September 1, 1995 amendment to Snyder Consulting Agreement.

Exhibit Number*	Description
10.15C	November 19, 1997 amendment to Snyder Consulting Agreement.
10.15D	September 1, 1998 and January 1, 1999 amendments to Snyder Consulting Agreement (incorporated by reference to Form 10-K filed March 30, 1999).
10.16A†	License Agreement, dated December 20, 1993, between the Company and The Johns Hopkins University ("JHU Agreement").
10.16B	Appendix B to JHU Agreement.
10.16C†	Amended and Restated License Agreement, effective November 25, 1998, between the Company and Johns Hopkins (incorporated by reference to Form 10-K filed March 30, 1999).
10.17	Form of Director and Officer Indemnification Agreement.
10.18	Form of Tax Indemnity Agreement.
10.19A	Guilford Pharmaceuticals Inc. Directors' Stock Option Plan.
10.19B	Amendments to Directors' Stock Option Plan (incorporated by reference to Form 10-K filed on March 30, 1999).
10.19C	Amendment to Form of Directors' Stock Option Agreement (incorporated by reference to Form 10-K filed March 30, 1999).
10.20	Lease Agreement, dated August 30, 1994, between Crown Royal, L.P. and the Company.
10.21A	Lease Agreement, dated June 9, 1997 between SN Properties, Inc. and the Company ("Freeport Lease").
10.21B	Amendment, dated February 10, 1998, to Freeport Lease.
10.22(1)	Employment Letter Agreement, effective March 8, 1998, between the Company and Gregory M. Hockel, Ph.D.
10.23(1)	Employment Letter Agreement, effective January 27, 1998, between the Company and Dana C. Hilt, M.D.
10.24	Exchange and Registration Rights Agreement, dated February 17, 1995, among the Company and the Abell Foundation, Inc., and the several holders named in Appendix I.
10.25A	Loan and Financing Agreement between the Maryland Economic Development Corporation ("MEDCO"), the Company and Signet Bank/Maryland ("Signet") ("L&F Agreement").
10.25B	Amendment No. 1, dated June 30, 1998, to L&F Agreement (incorporated be reference to the Form 10-Q for the quarter ended June 30, 1998).
10.26	Leasehold Deed of Trust by and between the Company and Janice E. Godwin and Ross Chaffin (as trustees) for the benefit of MEDCO and Signet.
10.27A	Insurance Agreement between the Maryland Industrial Development Financing Authority and Signet ("Insurance Agreement").
10.27B	Letter, dated April 2, 1996, amending Insurance Agreement.
10.27C	Amendment No. 2, dated June 29, 1998, to Insurance Agreement (incorporated by reference to the Form 10-Q for the quarter ended June 30, 1998).
10.28†	License Agreement, dated December 9, 1995, by and between the Company and Daiichi Radioisotope Laboratories, Ltd.
10.29†	License and Distribution Agreement, dated October 13, 1995, by and between the Company and Orion Corporation Farmos.
10.30	Employment Letter Agreement, effective June 10, 1998, between the Company and David H. Bergstrom, Ph.D.
10.31	Master Lease Agreement, dated March 19, 1998, by and between Comdisco Laboratory and Scientific Group, a Division of Comdisco Healthcare Group, Inc., and the Company (incorporated by reference to Form 10-Q for the quarter ended March 31, 1998).

Exhibit Number*	Description
10.32†	Bulk Pharmaceutical Sales Contract, dated September 23, 1994, between the Company and Aerojet-General Corporation.
10.33	Equipment Lease, dated September 18, 1996, between the Company and General Electric Capital Corporation.
10.34	Term Loan, dated April 30, 1996, as amended on December 6, 1996, by and between the Company and Signet Bank.
10.35A	Marketing, Sales and Distribution Rights Agreement between Aventis S.A (formerly known as Rhône-Poulenc Rorer Pharmaceuticals Inc.) ("Aventis"), the Company and GPI Holdings, Inc., dated June 13, 1996 ("MSDA").
10.35B†	Amendment No. 1 to MDSA, dated September 25, 1998 (incorporated by reference to Form 8-K, filed October 2, 1998).
10.36	Manufacturing and Supply Agreement between Aventis and the Company, dated June 13, 1996.
10.37A	Stock Purchase Agreement between the Company and Aventis, dated June 13, 1996 ("Aventis Stock Purchase Agreement").
10.37B	Amendment No. 1 to Aventis Stock Purchase Agreement, dated September 25, 1998 (incorporated by reference to Form 8-K, filed October 2, 1998).
10.38	Loan Agreement between the Company and Aventis Inc., dated June 13, 1996.
10.39	(Intentionally Omitted)
10.40†	Collaboration and License Agreement, dated December 15, 1997 and effective as of August 20, 1997, between Amgen Inc. ("Amgen"), GPI NIL Holdings, Inc. and the Company.
10.41	Stock and Warrant Purchase Agreement, dated October 1, 1997, between Amgen and the Company.
10.42	Registration Rights Agreement, dated October 1, 1997, between Amgen and the Company.
10.43	Warrant, dated October 1, 1997 issued to Amgen.
10.44	Security Agreement, dated as of February 5, 1998, between First Security Bank, National Association ("First Security"), not individually, but solely as the Owner Trustee under the Guilford Real Estate Trust 1998-1 (the "Trust") and First Union.
10.45	Amended and Restated Trust Agreement, dated as of February 5, 1998 between the Several Holders from time to time parties thereto and the Trust.
10.46	Agency Agreement, dated as of February 5, 1998, between the Company and the Trust.
10.47	Credit Agreement, dated as of February 5, 1998, among the Trust, the Several Holders from time to time parties thereto and First Union.
10.48	Participation Agreement, dated as of February 5, 1998, among the Company, the Trust, the various and other lending institutions which are parties hereto from time to time, as Holders, the various and other lending institutions which are parties hereto from time to time, as Lenders, and First Union.
10.49	Lease Agreement, dated as of February 5, 1998, between the Trust and the Company.
10.50	MIDFA Agreement, dated June 29, 1998, by and between MIDFA, First Security, the Company and First Union (incorporated by reference to Form 10-Q for the quarter ended June 30, 1998).
10.51	Insurance Agreement, dated June 29, 1998, by and between MIDFA and First Union (incorporated by reference to Form 10-Q for the quarter ended June 30, 1998).
10.52	April 1, 1999 amendment to Consulting Agreement, dated August 1, 1993, as amended, between the Company and Solomon H. Snyder, M.D. (incorporated by reference to Form 10-Q for the quarter ended March 31, 1999).

Exhibit Number*	Description
10.53	Amendment to Directors' Stock Option Plan (incorporated by reference to Form 10-Q for the quarter ended March 31, 1999).
10.54	Amendment to Form of Stock Option Agreement under the Company's 1993 and 1998 Employee Share Option and Restricted Share Plans (incorporated by reference to Form 10-Q for the quarter ended March 31, 1999).
10.55	Amendment to Form of Directors' Stock Option Agreement, effective May 18, 1999 (incorporated by reference to Form 10-Q for the quarter ended June 30, 1999).
10.56	July 1, 1999 amendment to Consulting Agreement, dated August 1, 1993 between the Company and Solomon H. Snyder, M.D. (incorporated by reference to Form 10-Q for the quarter ended June 30, 1999).
10.57	Consulting Agreement, dated July 23, 1999, between the Company and Solomon H. Snyder, M.D. (incorporated by reference to Form 10-Q for the quarter ended June 30, 1999).
10.58	Form of Severance Agreement (incorporated by reference to Form 10-Q for the quarter ended September 30, 1999).
10.59	Form of Change in Control Severance Agreement (incorporated by reference to Form 10-Q for the quarter ended September 30, 1999).
11.01	Statement re: Computation of Per Share Earnings (See Notes to Consolidated Financial Statements).
13.01	Portions of the Company's 1999 Annual Report to Stockholders (filed herewith).
21.01	Subsidiaries of Registrant (filed herewith).
23.01	Consent of KPMG LLP (filed herewith).
24.01	Power of Attorney (contained in signature page).
27.01	Financial Data Schedule (filed herewith).

* Unless otherwise noted above, all exhibits referenced above are incorporated by reference to Guilford's Annual Report on Form 10-K for the year ended December 31, 1997.

† Confidential treatment of certain portions of these agreements has been granted by the Securities and Exchange Commission.

(b) Reports on 8-K:

None.

Signatures and Power of Attorney

Pursuant to the requirements of Section 13 or 15(d) of the Securities Exchange Act of 1934, the registrant has duly caused this Report to be signed on its behalf by the undersigned, thereunto duly authorized.

March 30, 2000

GUILFORD PHARMACEUTICALS INC.

By: /s/ CRAIG R. SMITH, M.D.
Craig R. Smith, M.D.
President and Chief Executive Officer

KNOW ALL PERSONS BY THESE PRESENT, that each person whose signature appears below constitutes and appoints, Craig R. Smith, M.D., Andrew R. Jordan, Thomas C. Seoh, Stephen H. McElhennon and Michael J. Silver, and each of them, his or her true and lawful attorney-in-fact and agents, with full power of substitution and resubstitution, from such person and in each person's name, place and stead, in any and all capacities, to sign the report and any and all amendments to this report, and to file the same, with all exhibits thereto and other documents in connection therewith, with the Securities and Exchange Commission, granting unto said attorneys-in-fact and agents, full power and authority to do and perform each and every act and thing requisite and necessary to be done as fully to all intents and purposes as he or she might or could do in person, hereby ratifying and confirming all that said attorneys-in-fact and agents, and any of them, may lawfully do or cause to be done by virtue hereof.

Pursuant to the requirements of the Securities Exchange Act of 1934, this Report has been signed by the following persons in the capacities and on the date indicated.

Signature	Title	Date
/s/ CRAIG R. SMITH, M.D. Craig R. Smith, M.D.	Chief Executive Officer, President and Director (Principal Executive Officer)	March 30, 2000
/s/ ANDREW R. JORDAN Andrew R. Jordan	Sr. Vice President, Chief Financial Officer, and Treasurer (Principal Financial Officer and Principal Accounting Officer)	March 30, 2000
/s/ SOLOMON H. SNYDER, M.D. Solomon H. Snyder, M.D.	Director	March 30, 2000
/s/ RICHARD L. CASEY Richard L. Casey	Director	March 30, 2000
/s/ GEORGE L. BUNTING, JR. George L. Bunting, Jr.	Director	March 30, 2000
/s/ W. LEIGH THOMPSON, M.D., PH.D. W. Leigh Thompson, M.D., Ph.D.	Director	March 30, 2000
/s/ ELIZABETH M. GREETHAM Elizabeth M. Greetham	Director	March 30, 2000
/s/ JOSEPH KLEIN, III Joseph Klein, III	Director	March 30, 2000