Company: Guilford Pharmaceuticals, Inc. (GLFD)
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I have evaluated Guilford Pharmaceuticals, Inc. ("Guilford" or the "Company") for its potential suitability for a long investment. This report highlights the merits and risks for Guilford's future.

Conclusion: Guilford is a solid, second-tier biotechnology company with little or no risk of facing a "going concern" assessment within the next five years. The Company's current product, Gliadel, provides modest revenues and, since February, has gained top-line growth potential (up to $60 million per year). Guilford has two additional products in middle stage clinical development with neither likely to be on the US market before 2007. One of these, Aquavan anesthetic, has the greater likelihood of regulatory progress and future financial success. The bridge to Aquavan's success lies with the proposed acquisition of Aggrastat (see below). Together, these two drugs could propel Guilford into the top tier. Management's outstanding reputation and close ties to Johns Hopkins University are two added strengths.

Located in the Baltimore/Washington DC biotechnology corridor, Guilford plans to acquire Merck's Aggrastat (tirofiban), a platelet-aggregation inhibitor (anti-clotting factor) which is FDA approved to treat acute coronary syndrome ("ACS," unstable angina and non-ST elevating myocardial infarction (mild heart attacks)). The price is reasonable at ≈ $84 million, 2.4 times estimated '03 sales. Nominally competing against Johnson & Johnson's ReoPro and Millennium's Integrilin, in fact, third place Aggrastat is not approved for use in percutaneous coronary intervention ("PCI," e.g., balloon angioplasty), where the other two drugs dominate. Aggrastat's US sales were flat at ≈ $120 million over the past three years but with Merck's dropping all detailing efforts, they are expected to drop by 70 percent to ≈ $30-$35 million this year. Already demonstrated by Merck to be worse than ReoPro in PCI, only an expensive, high risk series of additional clinical trials (dose-ranging, efficacy in PCI) could get Aggrastat approved for the PCI indication, concurrently removing its stigma as worse than ReoPro. If Aggrastat succeeds in the clinic, Guilford will be a "home run."

That's a big "if." Guilford's background and expertise are in R&D and in neurology, not S&M or cardiovascular disease. It is risky for a company to venture outside of its core competencies. Wall Street is likely to take a positive, but "show me" approach as well when the deal is announced.

With over $130 million of cash (including $80 million of long-term debt), Guilford has over three years of cash at its current burn rate. Assuming Guilford closes the Aggrastat acquisition, the Company will still have ample liquidity. The Company will raise at least an additional $100 million over the next five years. If it can demonstrate progress in its clinical development programs and top-line growth of Gliadel and Aggrastat, raising the additional capital will be very achievable. The public equity markets for biotechnology companies wax and wane primarily as a function of dramatic clinical or market success, often by a single company. Biotechnology is currently in a bull phase due to the clinical success of Genentech's Avastin last spring. With a plethora of investment bank conferences in the fall and a favorable reception by Wall Street of the Aggrastat transaction, a capital raise by Guilford this year is probable.

Background

Guilford is a Maryland-based biotechnology company (surrounded by numerous other biotechnology companies) targeting both *cancer* and *neurological diseases*. The Company's scientific founder (and Scientific Advisory Board Chairman) is world-renown Dr. Solomon Snyder at The Johns Hopkins School of Medicine. The Company was formed from the science at Nova Pharmaceuticals deemed outside the focus areas of acquiror, and seed financier, California Biotechnology Inc. (renamed Scios, acquired by Johnson & Johnson in 2003). Guilford completed its IPO in June 1994. An NDA for a bio-erodible wafer containing a long established drug to treat brain cancer was filed with the FDA in February 1996 and approved that September.

While the market for the drug was small (< $50 million), at the time this was viewed as one of the most stunning examples of clinical development success by a biotechnology company within the prior decade. Guilford's history since that early approval has been less spectacular.

Introduction

Beyond its scientific links to Johns Hopkins, Guilford was originally perceived as "lower risk" due to its dual-platform foundation in (1) bioerodible polymers carrying conventional drugs for cancer and (2) drug discovery in neurological disease. It can be argued that the Company suffered from an overabundance of opportunity created by its research laboratories but was hobbled by inadequate clinical progress. Over the past ten years Guilford has developed:

Dopascan The molecule is a radioiodinated (^{123}I) cocaine derivative and has been studied as a diagnostic imaging agent for Parkinson's disease. It is not yet approved anywhere. In December 1995, Dopascan was licensed to Daiichi Pharmaceuticals for marketing in Japan, Korea and Taiwan. This past July, Daiichi filed for Japanese approval. In Europe, MAP Medical Technologies has exclusive rights to Dopascan and, in April 2002, filed in Finland for European approval. A North American partner has not been identified and clinical development in this territory will not progress until a partner is found, if ever. *There is little future financial value assignable to Dopascan.*

Paclimer Guilford had developed a second generation polymer (this a polyphosphoester) into which it planned to embed paclitaxel (generic version of Bristol-Myers Squibb's Taxol). The Company planned to file an Investigational New Drug application (IND) with the FDA for this formulation to enter the clinic for ovarian cancer. The entire paclimer project was terminated during the July 2002 restructuring. All assets remain with Guilford.

Neuroprotectants Guilford's researchers have identified molecules which prevent damage to neurons (brain cells) from ischemia (inadequate blood) due to stroke. Just as inadequate blood flow to the heart causes a heart attack, some refer to a stroke as a "brain attack." Guilford's post-synaptic **ni**tric **o**xide **s**ynthase (*NOS*) inhibitors may be useful in reducing ischemic damage. The Company's post-synaptic **p**oly(**A**DP-**r**ibose) **p**olymerase (*PARP*) inhibitors may be useful in spinal cord injury. Finally, Guilford had developed an injectable (parenteral) pre-synaptic glutamate inhibitor, specifically an **N-a**cetyl-**a**lpha-**l**inked **a**cidic **di**peptidase (*NAALADase*) inhibitor ready for clinical development as a neuroprotectant. For practical reasons, only an orally-active compound was viable as a drug candidate. None has been publicly disclosed.

In early May, Guilford licensed worldwide rights to NAALADase inhibitors for neurodegenerative diseases (excluding prostate cancer, head and spinal cord injury or drug addiction) to Pfizer. The $57+ million biobuck deal is heavily back-end loaded, with Pfizer only paying $5 million upfront and deferring a $10 million payment to March 2004. Pfizer will pay (unspecified) Guilford's R&D expenses associated drug development. Still, with no drugs in the clinic, most of the $42 million in clinical development milestone payments is at least eight-to-ten years out. *There is at best only modest future financial value assignable to the NAALADase project, based on its very early stage of development.*

Currently, Guilford has one product -- and that with revenue growth potential -- and two products in clinical development. In addition, the Company has disclosed to the investors, in strict confidence, that it plans to acquire Merck's Aggrastat, a cardiovascular drug. This report focuses on these four product opportunities.

Oncology:

There are over 100 different forms of cancer (broadly defined as inappropriate and uncontrolled cell proliferation) in humans. Traditional treatment includes the "slash and burn" approaches of surgical excision followed by radiation treatment. Chemotherapy started in the '40s based on the bone marrow suppression observed in WWI soldiers exposed to mustard gas. The first chemotherapeutics were, in fact, mustard gas derivatives. Bone marrow is a site of rapid cell proliferation (as are hair follicles); thus, anti-proliferative chemotherapy to stop rapidly growing tumors is still associated with the side-effects of suppressed new blood-cell formation (anemia) and hair-loss. Encapsulated formulations like Guilford's are designed to deliver higher concentrations of drug to the tumor while reducing side-effects elsewhere in the body.

Gliadel:

Gliadel is a wafer formulation of BCNU (bis-chloroethyl nitrosourea, a.k.a. carmustine; it is a nucleic acid alkylator) embedded in a bioerodible (first generation polyanhydride) polymer. Discovered in 1963, BCNU readily crosses the blood-brain barrier, unlike many molecules, and so has a history of use in brain cancer. Unfortunately, its circulating half-life is very short, so a slow-release formulation, such as Gliadel, provides highly localized, sustained dosing. Typically, 8 dime-sized wafers are dropped into the surgical site prior to closing, where the drug is slowly released over three weeks in order to "mop up" cancerous cells missed by the scalpel. In the pivotal clinical trial of 222 patients, the Gliadel Wafer increased the percentage of patients surviving six months from 36 to 56 percent, an improved, if modest and still grim, outcome.

Until recently, the approved product was cleared to treat only *recurrent* (i.e., at the time of a *second* surgical procedure) glioblastoma multiforme (GBM, the most common form of brain cancer), or roughly 3,000 of the 11,000 patients in the U.S. market. Assuming $11,000/treatment (8 wafers at $1,375), the total potential U.S. market is $120 million. In December 1998, Canadian authorities approved Gliadel for first-surgery use.

In December 1997, a new Phase 3 trial was begun to test Gliadel in first line surgery at 42 sites worldwide over a 12 month period with improved survival as the primary clinical endpoint. The trial randomized ≈ 200 patients to receive the current standard of care (surgery+radiation) ± Gliadel.

In November 2000, the Company reported the results from testing in 240 patients and found that Gliadel increased survival from 11.6 to 13.9 months ($p < 0.03$). Approximately 27 percent of the enrolled patients required a second surgery. Including these patients, Gliadel use increased overall survival by four months over placebo ($p < 0.004$). However, a rigorous reading of the primary clinical endpoint showed that survival *at twelve months* increased with Gliadel by only 23 percent; i.e., 59 percent of patients receiving Gliadel were alive twelve months later versus 48 percent receiving placebo and this difference was not statistically significant.

In December 2001, FDA's outside Panel voted in favor (8-5) of Gliadel for use in first line primary brain cancer. In March 2002, the FDA contradicted the Panel and rejected the Company's supplemental NDA (sNDA). Gliadel sales, which averaged $6.2 million over each of the prior three quarters, fell 45 percent in Q2/'02 to $3.5 million and ended the year at $14.5 million, off 29 percent from $20.4 million in FY'01.

In September 2002, Guilford presented additional data to the FDA from an open-label extension study of the 239 patients, some now three to four years since their first surgery. The results were still modest, but a "kinder" FDA agreed that Gliadel provided some benefit and, this past February, expanded Gliadel's approval to include first line surgery for brain cancer. This approval (reimbursement remains a bit uncertain), should expand the Gliadel market potential almost four-fold and sales in the second quarter were relatively robust at a $20 million annualized run rate.

Footnote: In June 1996, Rhone-Poulenc-Rorer, now Aventis, acquired exclusive, worldwide (except Japan and Scandinavia) marketing and distribution rights to Gliadel. Including milestones plus royalties on sales, Guilford had received approximately $25 million before October 2000, when it reacquired all rights to Gliadel, paying Aventis $8 million in stock.

Current manufacturing capacity from one of Guilford's two cGMP manufacturing facilities is about 20,000 Gliadel "doses" (≈ 150,000 wafers) per year. This capacity should prove adequate to meet demand. However, one potential risk to Gliadel manufacture is the limited availability of raw BCNU drug. Guilford has identified two suppliers, Aerojet and Johnson-Mathey. Bristol-Myers Squibb obtains its BCNU (injectable), on an exclusive basis, from Ben Venue Labs, a subsidiary of Boehringer Ingelheim.

Gliadel may have been Guilford's early claim to fame, but no longer is. The drug addresses a small market with potential sales unlikely to exceed $60 million per year.

Neurological Disease:

Neurons are among the most highly specialized of the 250 cell types found in humans. For this reason, they seem to lack the regenerative properties observed in other tissues, such as liver or fat cells. Rejuvenating damaged nerve cells remains one of medicine's greatest challenges. The number one neurodegenerative disease in the U.S. is Alzheimer's disease, affecting four million people. Number two is Parkinson's.

Parkinson's disease was first described in 1817. It is characterized by uncontrollable tremors and stiffness and its cause is unknown. Flare-ups of the disease are random, so the placebo effect observed during clinical testing is high. The disease is thought to affect approximately one million people in the U.S. Standard treatment is with L-DOPA, but its usefulness dwindles over time. Other drugs include Roche's Tolcapone, Novartis' Parlodel and Somerset Pharmaceutical's Eldepryl. Also, there is an experimental surgical procedure called pallidotomy, ablation of either or both pallida in the brain, which has had promising results.

Immunophilins: NIL-A

In the mid-90s, a class of proteins were discovered to which immunosuppressive drugs (e.g., Novartis's cyclosporin A; Fujisawa's Tacrolimus, originally called FK-506; American Home Products' Rapamune) preferentially bound. Subsequently identified as peptidyl-prolyl isomerases, the proteins were serendipitously found (by Dr. Solomon Snyder at Johns Hopkins) to be elevated in brain tissue by ten- to forty-fold. Even more intriguing was the discovery that variations of these immunosuppressive molecules exhibited extremely potent neurotrophic activity; that is, they caused nerve cells to regenerate. Subsequent research has demonstrated that the immunosuppressive activity of these protein-binding ligands was chemically distinct from the neurotrophic activity. Proteins which bind to FK-506 (*FKBP*s, FK-binding proteins) and those that bind cyclosporin (cyclophilins) have been lumped together into the class called immunophilins. Guilford refers to the class as *neuro*immunophilins.

In August 1997, biotechnology behemoth Amgen inked a $392 million biobuck deal with Guilford ($35 million up-front plus $4.5 million per year in R&D support over three years plus milestones plus royalties) for the worldwide rights to FKBP-neuroimmunophilin drugs. Specifically, Amgen acquired the rights for drugs to treat seven neurological indications (Parkinson's, Alzheimer's, stroke, peripheral neuropathies, traumatic brain and spinal cord injury and multiple sclerosis) and three unidentified indications.

Unlike protein-based (therefore, injectable) nerve growth factors in development at other biotechnology companies, the immunophilin molecules are small and orally active. Several molecules have been identified by Guilford and they showed promising results in animal models of certain neurological diseases, including Parkinson's.

In August 1999, Guilford and Amgen announced the initiation of a Phase I safety and dose-ranging clinical trial for GPI-1485 ("*'1485*") in healthy volunteers in Europe. With Amgen controlling all information on the clinical development program, investors became increasingly frustrated with Guilford's lack of "guidance." In July 2001, the companies announced disappointing Phase 2 results for *'1485* in Parkinson's. The double-blind, placebo controlled, dose-ranging study (200- or 1,000 mg, dosed four times daily) enrolled 300 patients at 42 sites. After 24 weeks of treatment, there was no difference in motor symptoms (using the standard UPDRS tests) for patients on drug or placebo. In September 2001, Amgen dissolved the partnership.

In November 2002, Guilford began a second Phase 2 clinical trial of *'1485* in Parkinson's. The Company plans to enroll $\approx$ 200 patients in this double-blind, placebo-controlled study. The test dosage(s) were not disclosed. This differs from the prior trial in its use of a *surrogate* (not clinical) endpoint which will be a $\geq$ 50 percent reduction in the loss of dopamine transporters based on Dopascan imaging. In the previous trial, no improvement in this parameter was observed. A secondary endpoint will be that of drug sparing by *'1485*, measured as the time to initiation of L-Dopa therapy. Guilford's rationale for conducting this clinical trial remains a mystery. *At this stage of development, there is no future financial value assignable to this project.*

Aquavan Anesthetic

In October 1989, the FDA approved (Astra)Zeneca's Diprivan (propofol), as the first injectable general anesthetic. All previous drugs, since ether's first use in 1846, were inhalational gases requiring sophisticated delivery devices. With its rapid onset, easy depth-of-anesthesia control, rapid recovery and a ten-fold lower incidence of post-operative nausea and vomiting (≈ 2 percent), Diprivan is now used in roughly half of all surgeries worldwide. The drug's major problem is that it dissolves only in oil, not water. Thus, it has to be formulated as an emulsion (like an oil-and-water salad dressing) containing soybean oil and egg lecithin (a common emulsifier). The emulsion formulation leads to several problems.

First, unlike Aquavan, Diprivan emulsion lacks a preservative, so there is a higher risk of contamination and possibly, infection. Second, injecting the emulsion is painful. According to Diprivan's Package Insert, 15-20 percent of patients reported burning, stinging and pain at the injection site. In Aquavan's European Phase 1 trial in 24 patients, none of the patients had any pain with an Aquavan injection while ten of the same 24 patients (40 percent) experienced injection site pain with Diprivan. Diprivan is often used as a sedative/analgesic to treat post-surgical pain and, as such, is delivered as an intravenous drip over a period of days. Thus, pain at the infusion site is a problem that should not occur with Aquavan. Finally, oil-in-water emulsions are unstable. If the two phases have separated, for example during shipping, the drug must be discarded. The Aquavan molecule easily dissolves in water, resulting in a far more stable preparation.

In March 2000, Guilford acquired exclusive worldwide rights to a water-soluble propofol pro-drug. The Company paid privately-held Kansas-based ProQuest Pharmaceuticals $1 million up-front with milestone and royalty obligations downstream. Proquest's PQ-1002 (renamed Aquavan by Guilford) is a phosphorylated derivative of propofol which is enzymatically activated to propofol in the body. A search of the US Patent Records reveals some 50 patents related to propofol formulations, confirming active interest in this drug. Curiously, no patents assigned to Proquest were identified.

Guilford initiated clinical trials in December 2000, in Europe, to study Aquavan's safety and efficacy profile. Twenty-four volunteers, all at one investigator's site in Ghent, Belgium, were treated with Aquavan at one of four dosages and asked to return one week later to be treated with Diprivan for comparison. In April 2002, Guilford released top line data from the study showing rough equivalence at the two higher dosages of Aquavan to Diprivan. Specifically, the time to loss of consciousness was 157 seconds at the 20 milligram Aquavan dosage compared to 184 seconds for the same volunteers treated with Diprivan. Similarly, at 25 milligrams of Aquavan, the values were 162 seconds compared to 208 seconds. One significant difference was reported. The time to return to consciousness for Aquavan, at 48 minutes, was three times that of Diprivan's 16 minutes. This delayed awakening could hinder market acceptance in the surgical anesthesia (ICU) arena, where rapid recovery and post-operative step-down are important clinico-economic considerations.

The US Phase 1 *safety* trial for Aquavan began in June 2002. That July, Guilford began a Phase 2 *efficacy* trial comparing Aquavan to Diprivan in 24 coronary artery bypass graft (CABG) patients in Europe. This past February the Company initiated a US Phase 2 study of Aquavan in the setting of *conscious sedation*. After a small, exploratory dose-ranging study (so-called Phase 2a) in colonoscopy patients of Aquavan ± fentanyl or Celebrex, the Company plans to initiate a full, Phase 2b efficacy trial in 110 patients, randomized to receive either Aquavan or Roche's Versed (midazolam) which is an anxiolytic (like Valium), not a true anesthetic. The primary clinical endpoint will be "time to full recovery," although how this endpoint is to be objectively quantified has not been disclosed.

The design of the Phase 2b clinical trial is a little curious. Comparing a sedative with an anxiolytic may confound the interpretation of efficacy. However, without the clarification of other design parameters, it would be premature to discount Guilford's stratagem. Also, although midazolam and Aquavan are both injectable drugs, an oral formulation of midazolam (typically used in the pediatric setting) is available. If oral midazolam were adopted in the adult colonoscopy setting, Aquavan might be at a disadvantage. Guilford deserves credit for targeting the large and growing market opportunity of more than five million colonoscopies per year in the US.

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Other pro-drugs include Roche's Xeloda (pro-drug to 5-fluorouracil used in cancer), Pfizer's Cerebyx (pro-drug to Parke-Davis' phenytoin, aka Dilantin, for epilepsy) and Salix Pharmaceuticals' Colazal (pro-drug to mesalamine, Procter and Gamble's Asacol, for colitis). Overall, the history of pro-drugs' successes augur well for Aquavan's eventual approval, possibly by 2007. *This drug is Guilford's brightest opportunity on a risk/reward basis with revenue potential of greater than $250 million per year at comparatively modest development risk.*

*** NOTE: At the time of this report, some of the following information regarding Aggrastat was obtained by the author under a CDA, which has expired, as part of this contracted project. ***

Cardiovascular Disease

Since 1912 when the first heart attack was diagnosed in a live patient in the US, cardiovascular disease has been the top cause of mortality every year of the 20th Century except 1919 (Spanish flu epidemic). More than 2,500 Americans die of cardiovascular disease every day. Drug expenditures alone topped $19.8 billion in the US last year. The two most common surgical procedures are (1) percutaneous coronary intervention (PCI, e.g., balloon angioplasty plus stenting, "Roto-Rooter"-like atherectomy) and (2) coronary artery bypass grafts (CABG). In 2002, there were roughly 900,000 PCI procedures (growing 4-6 percent a year) and about 300,000 CABG procedures (shrinking one percent a year). Competition in the cardiovascular disease market, therefore, is intense.

One of the earliest steps in the formation of a blood clot is the aggregation of platelets. Platelets are clear microscopic enucleated cells that are formed in the bone marrow and circulate in the blood. When activated, platelets express a receptor on their surface making them sticky. The receptor, called "glycoprotein 2-B-3-A," abbreviated as GP IIb/IIIa, is one member of a class of proteins called integrins. Blocking this receptor inhibits platelet aggregation, which is one way, among several, to inhibit undesired clot formation. A tiny blood clot can prove fatal, simply by clogging a coronary artery, thereby starving the heart muscle of oxygen and nutrients. Such clots occur often during PCI procedures.

Guilford plans to acquire Merck's Aggrastat (tirofiban), one of three FDA-approved GP IIb/IIIa inhibitors. Aggrastat, like its competitors, Johnson & Johnson's ReoPro (abciximab) and Millennium's Integrilin (eptifibatide), is FDA approved to treat acute coronary syndrome (*ACS*, comprising unstable angina and non-ST elevating myocardial infarction, i.e., mild heart attacks). However, Aggrastat is not approved for use in *PCI*, where the two other drugs dominate. The Company plans to conduct Phase 4 clinical trials designed to obtain the PCI use label. These trials will be (1) expensive due to the large number of patients required and (2) high risk due to Merck's previous report of Aggrastat's inferiority to ReoPro. According to Merck's filings with the FDA, the first Aggrastat patent expires in September 2010, the last in January 2019.

Aggrastat

Merck internally developed Aggrastat as a non-proteinaceous, non-peptidic inhibitor of the GP IIb/IIIa receptor. The other two inhibitors originated outside of their current owners' labs. ReoPro originated at Centocor, which Johnson & Johnson acquired and Integrilin was developed by Cor Therapeutics, acquired by Millennium. All three drugs are delivered intravenously (at least five oral analogs to Aggrastat have failed in clinical testing), are approved in Europe (though adoption has lagged the US) and are not yet approved in Japan.

ReoPro is made from a chimeric human-mouse monoclonal antibody (expensive to manufacture) and was the first drug on the US market, approved in late 1994. That approval was for use in patients undergoing PCI. In November 1997, this indication was expanded to include patients with ACS when PCI is planned within 24 hours. Finally, the label was expanded again in February 1998 noting that the drug's clinical benefits lasted at least three years.

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Based on a huge repertory of academic publications and deep clinical experience, ReoPro remains the gold standard of GP IIb/IIIa inhibitors and, until recently, commanded the highest dollar sales volume; however, growing experience with Integrilin, cost containment pressure from third-party payors and continued clinical investigation have enabled Integrilin to overtake ReoPro. Integrilin now commands a ≈ 60 percent market share based on prescriptions and may surpass ReoPro in dollar volume (US) this year.

Integrilin is a cyclic heptapeptide whose synthesis is far less expensive than ReoPro's. As used in PCI patients, ReoPro currently sells for $1,350 per patient compared to $650 for Integrilin. By comparison, Aggrastat sells for $550.

Despite an initial, unanimous rejection by an FDA advisory panel in 1997, Cor returned to the FDA with compelling clinical data for Integrilin, which was then approved (*for ACS*) on May 18, 1998, four days after Aggrastat was approved (*for ACS*). However, the pivotal change in Integrilin's future came in February 2000 when Cor's ESPRIT clinical trial (**E**nhanced **S**uppression of **P**latelet **R**eceptor GP IIb-IIIa using **I**ntegrilin **T**herapy) was halted early due to a 37 percent drop in major adverse clinical events (MACE, e.g., death, heart attack), compared to the then standard-of-care regimen. This dramatic benefit was observed within both clinically meaningful windows, 48 hours and 30 days after PCI. Integrilin's use exploded.

Just as February 2000 was pivotal to Integrilin's future upside, so was November 2000 pivotal to Aggrastat's demise. At the American Heart Association meeting that year, Merck released the results from its TARGET clinical trial, a head-to-head comparison of Aggrastat to ReoPro in the PCI setting. TARGET (Do **T**irofiban **a**nd **R**eoPro **G**ive similar **E**fficacy outcomes **T**rial) was designed as a non-inferiority trial, meaning Aggrastat did not have to demonstrate results superior to ReoPro. Surprisingly, ReoPro had a 21 percent lower incidence (6.0 percent versus 7.6 percent) of MACE compared to Aggrastat within 30 days after PCI. Although no statistically significant difference in mortality between the two drugs was observed at one year after PCI, the damage was done and Aggrastat's "inferiority" reputation never recovered.

While arguments in favor of Aggrastat's potential abound (use a higher dosage, test sicker patients), the drug does not appear to meet an unmet need for the PCI indication or in treating ACS. Specifically, alternative drugs to block platelet aggregation include aspirin (daily, low dose), two ADP receptor inhibitors (thienopyridines) including Sanofi's Ticlid and Bristol-Myers' Plavix and one cyclic AMP phosphodiesterase inhibitor, Otsuka's Pletal.

Guilford can not win by simply demonstrating Aggrastat's non-inferiority to either of the other two drugs in the PCI indication. Aggrastat must demonstrate superiority to win back the hearts and minds of interventional cardiologists. Presumably, Merck reached a similar conclusion last year. There is scant evidence that Guilford will be able to succeed.

Guilford's low risk strategy would be to recover Aggrastat's sales lost from 2002 to 2003 by actively promoting the drug's benefits for indications where it is already approved. Additional clinical trials will be expensive and high risk. Guilford may even have a problem convincing hospitals and physicians to enroll patients at all. Of course, the higher risk strategy carries the potential for greater reward.

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Financial Overview
(GLFD - NASDAQ)

Recent Price[1]	$6.66	Market Cap ($ Million)	198
52-week Range	$2.65 - $6.78		
Shares Outstanding	29.8 million	Cash/Share	$4.45
Institutional Ownership (March 03)	≈ 63 percent	Technology value/share	$2.21
Shares in Float	22.6 (78 percent)	Analysts:	CIBC, Raymond James, UBS Warburg
Average daily volume (90-day)	595,000		HOLD
Shares short (Aug)/Short ratio (days)	3.9 million/7.0	Technology value/LTM Revenues:	3.4
LTM Revenues ($ Million)	19.0	P/E	N.A.
FY'02A EPS	($1.99)	Fiscal Year End	December
FY'03E EPS[1]	($1.25)	Founded	July 1993
IPO price/date	$8.00/June 1994		Since:
		COB/CEO: Craig Smith, M.D.	August 1993
		CFO: Andrew Jordan	September 1993

[1] *Source: Guilford SEC filings, Multex at September 12, 2003*

Financial Snapshot
($ million)

	6/30/03	6/30/02	2002	2001
Cash & ST Investments	133	124	102	155
LT Debt 82.2	5.2	6.9	5.1	
Revenues	10.6	3.6	14.7	20.5
Gliadel	5.0	3.5	14.5	20.4
R&D Expense	7.4	12.6	46.6	54.3
SG&A Expense	8.1	8.0	30.1	30.1
Net Loss	(5.36)	(16.8)	(59.3)	(60.3)

Since its layoff of ≈ 60 employees (21 percent) in July 2002, Guilford has controlled its headcount growth and, due to some attrition, has been stable over the past year at about 200 FTEs. Since inception, the Company has recorded $350 million of paid-in capital and, at June 30, 2003, had an accumulated deficit of $266 million.

Investment Merits:

- Management: Craig Smith, M.D. has been with Guilford since its inception. His 13 years on the faculty at Johns Hopkins resulted in a strong reputation in the clinical research community. A subsequent five years at Centocor as both VP Clinical Research and Senior VP Business Development built a similarly strong reputation in the business community. Along with CFO Andy Jordan, Guilford's leadership has remained scientifically focused, financially conservative and judicious in its corporate partnering. Guilford's partnering strength has benefitted, in part, from its always having had a strong balance sheet.

- Development Record: The Company has already demonstrated it can bring a new product to the market, but needs to do it again. Aquavan is Guilford's next best opportunity to get to market. If handled correctly, Aggrastat, though outside the Company's focus areas of oncology and neurology, could provide a substantial financial bridge until Aquavan is approved.

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- Corporate Partners: Pfizer provides modest financial support either directly in funded R&D or indirectly by partially funding clinical trials. At least as significant is the strategic validation afforded by having a sophisticated partner. The risk in taking on a partner becomes manifest when that partner leaves, as was observed with Amgen in September 2001.

- R&D pipeline: Little value has been assigned to Guilford's deep and rich research pipeline. Unfortunately, only by signing on a new corporate partner (analogous to the Pfizer deal) can the Company expect to capture any of this hidden value from Wall Street, which is increasingly focused on products, not platforms. A European marketing partner for Aquavan would play well on Wall Street.

- Acquisition Candidate: Big pharma has become increasingly aggressive about acquiring biotechnology companies as evidenced by J&J's recent acquisition of Scios, Merck's acquisition of Rosetta, and Warner-Lambert's acquisition of Agouron, among others. The ideal target has product(s) and pipeline. Guilford must be viewed as a potential acquisition target, especially if Aquavan shows signs of success in the clinic.

Investment Risks:

- Early-stage clinical trials: Even relatively straightforward clinical development plans can stumble. Gliadel was quickly approved for primary brain cancer, but only in second surgeries, 25 percent of the GBM market. It was six-and-a-half years before the supplemental NDA was cleared granting first line use. Parkinson's is a notoriously difficult disease to study and *'1485*'s history has borne that out. Animal models notwithstanding, clinical research is always risky. At least 80 percent of all drugs entering human clinical trials never reach the market.

- Reimbursement: Third party payors (insurance, Medicare) resist covering off-label usage of drugs, especially when cost-effective, efficacious alternatives exist. Even Gliadel, for which no alternative exists, has faced significant push-back due to its high cost and very modest efficacy. "Who will pay and why?" is a question every drug development program must answer *before* embarking on the development path.

- Poor visibility: Small biotechnology companies need to trumpet their progress (at the price of also announcing their stumbles) in order to command some "signal above the noise." Big pharma (like Pfizer, Amgen) need say nothing. This silence is leaden, not golden, and hurts small firms like Guilford.