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# The Evolution of Truly Preventative Medicine

**The right mix of computational power and informational tools is coming on line in the form of new drugs that can prevent diseases from forming.**

A brand new class of drugs soon to appear on pharmacy shelves could change the practice of medicine as profoundly as the introduction of the first monoclonal antibodies.

Known as *antisense* drugs, they will work unlike any medicine ever created. Instead of directly attacking cancer cells, bacteria, or the viruses that cause diseases, they will disrupt a disease-causing cell's genetic machinery. They won't simply mop up or destroy the harmful proteins that these cells produced—antisense drugs will keep these proteins from ever being created.

Antisense might be a familiar term: like monoclonal antibodies, the research concept has been around for years. Wall Street has been both warm and cool to the idea. And like the first monoclonal antibodies, early iterations of antisense drugs contained fatal flaws that limited their effectiveness. Only recently has a confluence of technological advances enabled a new generation of antisense drugs that will vindicate this paradigm's therapeutic promise.

The first antisense drug, Vitravene, won FDA approval in 1999 against a viral infection that can rapidly blind advanced-stage AIDS patients. Its developer, and the leader in this technology, is **Isis Pharmaceuticals, Inc.** [ISIS] of Carlsbad, California. Isis has a strong intellectual property position and a teaming pipeline that includes about a dozen other antisense drugs in various stages of late preclinical and clinical testing. Two are in phase 3.

Over the next five years, the half-dozen or so other companies that specialize in this new technology could seek FDA permission to market antisense drugs against infectious and inflammatory diseases. The most striking application, however, could be in fighting the approximately 200 diseases we collectively refer to as cancer.

Dr. Scott Gottlieb

"Pharmaceutical companies that previously shunned the field are giving it serious consideration."

## INSIDE:

## Proteins run the show

After water, our bodies are made mostly of proteins. Remove the moisture and protein from a typical adult and what's left won't quite fill a shoebox. Proteins occupy a similarly large place in medicine, because in addition to building bodies, they also regulate body functions.

These versatile molecules consist of strings of different amino acids. Scientists in labs can construct an almost infinite variety of these amino acids, but Nature makes just 20 kinds. All the millions of different proteins on Earth are compounded from that basic amino acid set, just as all 415,000 words in the *Oxford English Dictionary* are compounded from 26 letters.

The task of genes is to make sure that amino acids line up in the right order to produce the right protein. In biology the right protein is everything. Proteins carry and translate the instructions for building new cells. Enzymes, a category of proteins, speed chemical reactions. Hormones such as insulin and epinephrine (which give us our "fight or flight" response when we're threatened) and estrogen are also proteins. Proteins form the pipes and pumps that move raw materials into cells and carry out finished products—mostly other proteins. When bugs or viruses attack our bodies, it's often not the bug doing the dirty work, but the proteins it secretes. Proteins run the show.

If your body produces too little of the protein insulin, you will be diagnosed with diabetes. If you make too much of the protein tumor necrosis factor, all kinds of inflammatory diseases, such as arthritis and Crohn's, are the result. Or if your body produces the wrong protein, one that tells a malignant cell to keep dividing rather than self-destructing (a process termed *apoptosis*), cancer results. In short, the right protein is everything.

Antisense technology is elegant and appealing because it has the potential to treat both a significant number and a wide range of diseases by directly blocking the assembly of the wrong protein. In theory, a disease can be knocked out before it has a chance to get started. Here's how it works:

Protein production is a complex, two-step process. Normally to produce a protein like insulin, our body first scans for the gene that contains the code for manufacturing insulin and then copies it out from the DNA into an intermediate set of instructions called messenger RNA (mRNA). The process of copying the gene into mRNA is called transcription.

Afterward, another set of molecules called ribosomes are brought in to use the mRNA as templates upon which they manufacture proteins. The proteins themselves are built from amino acids floating in the viscous sea of cytoplasm found inside the cell. These amino acid links in the protein chain are coupled to each other in the precise order specified by the mRNA. The finished product is a new protein.

## Antisense Therapeutics

An antisense compound is the mirror image of the messenger RNA. Let's say you know the gene that codes for the production of a protein involved in diabetes. You design an antisense compound to attach to the specific messenger RNA coded for by that gene, thereby preventing the production of proteins involved in the disease. In that way, antisense technology uses synthetic DNA or RNA—called oligonucleotides—to block the production of faulty proteins. These custom-designed compounds are called antisense drugs because their molecular structure is the opposite of the "sense" or pattern of the original mRNA.

The goal of the resulting antisense is to treat disease by blocking the activity of specific genes associated with a given condition. Many drugs, by contrast, are discovered essentially by chance: various chemical configurations are tested until one proves

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effective. The more clearly focused approach of antisense could help speed the development process.

Antisense drugs also have the potential to be far more lethal protein killers than traditional medicines. The small-molecule drugs that fill your medicine cabinet rely on their chemical structure to wedge themselves into crevices on proteins, preventing them from latching onto other proteins and interrupting the chains of biochemical events that experts dub pathways. Pain relievers like aspirin, for instance, work by blocking a protein enzyme called cox-2. This enzyme normally promotes the production of hormone proteins called prostaglandins, which amplify nerve signals related to pain and cause tissue inflammation. Antibody drugs such as Remicade and Enbrel work much the same way, but are far more specific since they can be easily engineered to bind to specific proteins.

Antisense drugs, in comparison, are stretches of DNA designed to silence the genes producing particular proteins—in theory, preventing the proteins from ever being made in the first place.

There are three basic types of antisense therapeutics. Classical antisense compounds are the short, gene-specific sequences of nucleic acids, known as oligonucleotides, typically 15 to 25 amino acid bases in length. These molecules bind to complementary sequences on specific messenger RNAs and prevent them from being properly translated into protein.

The binding of these antisense molecules to the messenger RNA also makes the RNA vulnerable to digestion by naturally occurring enzymes called Rnase. This process may have the added bonus of freeing an intact antisense molecule, while destroying the target mRNA. In effect, the classical antisense drugs kill mRNA via two different mechanisms. And once they're finished, they're free to re-circulate. Most antisense companies are developing at least some classical antisense compounds.

The second type of antisense therapeutic takes advantage of another naturally occurring class of enzymes called ribozymes, comprised of RNA—not protein—that can be used to destroy mRNAs bound to antisense oligonucleotides. **Hybridon, Inc.** [HYBN.OB] of Cambridge, Massachusetts, is pursuing an antisense oligonucleotide with a built-in ribozyme sequence.

Some researchers in the field do not consider the third antisense model, triple-helix DNA, to be antisense at all. Triple-helix oligonucleotides are designed to bind to target sequences in double-stranded DNA in order to block their transcription. Nevertheless, the chemical similarity between these and other antisense compounds means that they face similar challenges on the way to becoming viable drugs, including problems with stability, formulation, delivery, toxicity, and cost-effectiveness. **Gilead Sciences** [GILD] was once the principal developer of triple-helix oligonucleotide therapeutics. Now this technology is mostly used for designing super accurate diagnostics. (A privately held Canadian company called **Genexus** specializes in this approach to molecular diagnostics.)

## Antisense drugs are stretches of DNA designed to prevent the proteins from ever being made in the first place

The antisense drugs being developed by Isis mostly follow the first form: blocking the production of proteins from the mRNA instruction sets, either by physically binding the RNA sequences that the protein translation machinery needs to access, or by marking the RNA molecule for destruction by the naturally occurring enzyme called RNase H. Once the antisense drug is bound to a piece of messenger RNA, this enzyme digests the RNA-antisense hybrid molecules.

The model Isis follows is the most elegant, since the reactions it relies on closely mirror those already taking place naturally in the human body every day, arising most often when viruses infect cells. Indeed, naturally occurring reactions in the human body use antisense-like compounds to protect against viral attack and in some types of gene silencing. So Isis is actually mimicking Mother Nature.

Antisense sounds simple enough, but in medicine elegant and easy usually prove the most difficult to execute. It took 20 years for the theory behind antisense technology to mature into the first commercial product, Isis's drug Vitravene, the only antisense medicine to ever win FDA approval. It's the solitary commercial achievement of an idea reaching back to 1978. Vitravene generates about $150,000 in sales

for Isis Pharmaceuticals and its partner Novartis, a sum that disappointed investors primed for the heralded antisense blockbusters that never appeared.

The problem? Initially, scientists believed that antisense drugs would target cells with such precision that they would cause few side effects. But as tests with animals began, the first antisense agents proved too toxic to be practical. Many of the first biotech firms that grew up around the technology suffered the same fate as their laboratory animals.

## Reversal of fortune

If confidence in antisense technology tumbled during the late 1990s, it hit rock bottom late in 1999, when a phase 3 trial of a drug sponsored by Isis failed. ISIS 2302 was being tested for treatment of Crohn's disease and had been hailed by some observers as a pivotal development in the antisense field.

In a reversal of fortune, Isis presented impressive results from its diabetes research program in June 2000: preclinical data on antisense against two targets, phosphatases p10, a phosphatase that had not been implicated previously in insulin signaling, and phosphatase pdb1b that had long been of interest to the drug industry. The combination of a new target and an apparently successful antisense drug strategy caught the attention of big pharmaceutical companies. **Eli Lilly** [LLY] signed a $200 million deal with Isis in August 2001 (it could be worth as much as $400 million if certain milestones are reached). Other large pharmaceutical and biotechnology companies have followed suit.

## Initially, antisense worked too well, causing significant problems

The comparisons between the evolution of antisense and monoclonal antibodies are crystal clear. Both technologies took years to refine. Both were variously lauded and maligned by investors and scientists. Both went through years of fits and starts. Today, monoclonal antibodies comprise some of the most important new drugs. Antisense will soon do the same.

Monoclonal antibodies, originally made from mouse antibodies, sparked nasty immune reactions in humans, later tamed by making the drugs more human. Antisense development went in the opposite direction, surmounting problems by making the molecules less human. The chemical backbone found in natural DNA, referred to as a phosphodiester backbone, could not withstand attack from enzymes found in the blood called nucleases, meaning antisense drugs were unable to survive long enough to be useful. Today, all of the antisense drugs Isis is developing have new, more durable chemical backbones.

Initially, antisense worked too well, causing significant problems. The first antisense drugs appeared effective against a whole variety of diseases, ranging from viral infections to tumors. However, more careful controls showed that the drugs' effects were primarily due to nonspecific boosting of the immune system by the oligonucleotides, rather than specific inhibition of the targeted gene. In other words, antisense appeared to be a single drug with a broad effect, rather than a technology platform capable of producing an entire class of selective drugs.

## Isis: the antisense leader

One reason antisense technology is only now breaking through as a therapeutic option is that until recently scientists lacked many of the computational tools necessary to develop the right drugs. One key to specific inhibition is to target the correct portion of the RNA sequence you're pursuing. RNA folds back on itself to form complex structures, and not all sites in a given RNA molecule are equally accessible to an antisense inhibitor. The trick is to find exactly the right spot to stick your antisense molecule to.

Today, scientists are using mathematical models that attempt to predict the accessible sites, rather than working strictly by trial and error. The right mix of computational power and informational tools is just now coming on line through a merger of medicine and microchip. These mathematical models are still underpowered, so much of the work is a hit-or-miss process. But it's much better than the Stone Age of antisense science just a decade ago. Finicky molecules—difficult to make and easy to degrade—caused manufacturing problems as well, most of which have been licked.

Isis has developed a second-generation chemistry for its antisense drugs that allows them to last longer in the blood stream. Most experimental antisense drugs are administered intravenously during clinical trials, but with a little tweaking, the Isis drugs can also be delivered orally, giving antisense a major advantage over other

biotechnology-generated therapies.

Isis shares the antisense therapy space principally with Hybridon, **AVI BioPharma, Inc.** [AVII], and **Genta Incorporated** [GNTA]. All are usually identified as the major survivors in the antisense field. But Isis has locked up much of the intellectual property and is clearly the leader.

When antisense became a dirty word on Wall Street, Isis took advantage of rock-bottom prices to add patent rights from other companies, including Gilead and Hybridon to its own important technologies. A thicket of patent claims would make it cheaper to stop and shop at Isis, rather than try to drive around its patent estate.

**ISIS's Development Pipeline Targets a Broad Range of Diseases**

| Product | Target | Lead Indication | Market | Phase |
|---|---|---|---|---|
| ISIS 3521 | PKC-alpha | Cancer: NSCLC | 191,400 | 3 |
| ISIS 2302 | ICAM-1 | Crohn's Disease | 500,000 | 3 |
| ISIS 2302 | ICAM-1 | Psoriasis | 6.4M | 2 |
| ISIS 2302 | ICAM-1 | Ulcerative Colitis | 500,000 | 2 |
| ISIS 14803 | antiviral | Hepatitis C | 4M | 2 |
| ISIS 2503 | H-ras | Cancer: Pancreatic | 23,300 | 2 |
| ISIS 104838 | TNF | Rheumatoid Arthritis | 2M | 2 |
| ISIS 104838 | TNF | Psoriasis | 6.4M | 2 |
| ISIS 113751 | PTP-1B | Diabetes | 18M | preclinical |
| ISIS 13650 | c-raf | Retinopathy, MD | 1.2M | preclinical |
| ISIS 107248 | VLA-4 | MS, Inflammatory | 350,000 | preclinical |
| OGC-011 | Clusterin | Prostate, others | 198,100 | preclinical |

## Functional genomics

While the science of antisense was progressing, some antisense pioneers also discovered a sideline that could pay the rent during the lean years: *functional genomics*.

While genomics is producing all these great potential gene targets, how do you decide what the targets do? Antisense is perfect for that. Isis's proprietary Genetrove drug-target screening program has blossomed in recent years, and the company is now carrying out screening programs for most of the major pharmaceutical companies. Through Genetrove, drug companies can hire Isis to do functional analysis of target genes using antisense. The Genetrove partners get information to use nonexclusively, and in turn Isis keeps the antisense drug rights.

Current cancer treatments rely on surgery, chemotherapy, and radiation to beat masses of renegade cells into submission. By throwing a carefully aimed wrench at malfunctioning genetic machinery, antisense drugs could, in a manner of speaking, stop the cancer before it begins. Since genetic defects that produce harmful mutant proteins are the source of many cancers, antisense technology seems an ideal form of treatment.

Antisense has also found increasing application in models of virally induced cancer. Another anti-cancer application focuses on telomerase enzymes, which are responsible for controlling the length of the human chromosomes and have been implicated in a variety of cancers. For example, the majority of gastric cancers express high levels of the human telomerase template RNA (hTR), which is essential for cellular survival. Antisense hTR (ahTR)—which neutralizes this protein— has been shown to have a growth-inhibitory effect on model gastric cancers.

Recent preclinical and clinical studies have successfully tested antisense compounds against seven cancer-related genes, including p53, bcl-2, c-raf, H-ras, protein kinase C-alpha, and protein kinase A. The development of several of these antisense compounds has proceeded relatively rapidly. Many have shown convincing *in vitro* reduction in target gene expression and promising activity against a wide variety of tumors. Several clinical studies have yielded encouraging results.

As two generations of antisense drugs move through clinical trials, investors and researchers are reminded of the reasons the technology looked good in the first place: low toxicity, low production costs (using traditional oligonucleotide synthesis techniques), and potentially easier drug discovery. Simply knowing the target gene sequence leads directly to the drug. At the same time, ongoing research has defined the limits of antisense with even greater clarity.

At very high doses, antisense drugs activate the

## Upcoming milestones expected in 2002

■ **ISIS 3521 Affinitac (inhibitor of protein kinase C-alpha)**
Treatment of nonsmall cell lung cancer (NSCLC) and non-Hodgkin's lymphoma (NHL)
- complete enrollment of ISIS 3521 phase 3 trial in NSCLC (135,600 U.S. patients)
- report phase 1/2 trial with Gemzar in NSCLC
- report phase 2 trial with taxotere in NSCLC
- report phase 2 results in NHL (56,200 U.S. patients)

■ **ISIS 2302 (inhibitor of ICAM-1)**
Treatment of inflammatory bowel diseases (IBD) and psoriasis
- report phase 2 results in psoriasis (6.4M U.S. patients)
- initiate second phase 2 trial for Crohn's disease (500,000 U.S. patients)
- initiate phase 2 trial for ulcerative colitis (500,000 U.S. patients)

■ **ISIS 2503 (inhibitor of h-ras)**
Treatment of pancreatic cancer and other solid tumors
- report phase 2 interim results for pancreatic cancer (29,200 U.S. patients)
- report phase 2 final results for pancreatic cancer
- complete enrollment for studies in metastatic breast and NSCLC

■ **ISIS 104838 (inhibitor of tumor necrosis factor TNF-a)**
Treatment of inflammatory bowel disease, psoriasis, and rheumatoid arthritis (RA)
- initiate second phase 2 trial in rheumatoid arthritis (2M U.S. patients)
- initiate phase 2 trial in psoriasis
- report results from first (20-patient) phase 2 trial in treatment of RA

■ **ISIS 14803 (inhibitor of hepatitis C mRNA)**
Treatment of hepatitis C infection
- report phase 2 results in hepatitis C (94M U.S. patients)

■ **ISIS 5132 (inhibitor of C-raf kinase)**
Treatment of solid tumors
- report phase 2 results in ovarian cancer (23,400 U.S. patients)

■ **ISIS 13650 (inhibitor of c-raf)**
Treatment of diabetic retinopathy
- file IND for phase 1 trial in diabetic retinopathy and age-related macular degeneration (about 1.7M patients)
- initiate phase 1 trials in diabetic retinopathy and age-related macular degeneration

■ **Other:** establish 2 to 3 GeneTrove database subscribers in 2002.
- initiate phase 1 trials of novel clinical candidate (either ISIS 12650, 107428, or Clusterin). Advance development of oral formulation antisense drugs.

immune system's complement cascade, resulting in potentially serious side effects. However, the more potent drugs now in company pipelines are effective at doses far lower than those capable of triggering the side effects. There may be other concerns surrounding the intravenous administration of antisense drugs, including an increased risk of infections in the delivery lines. It's thought that this effect, which has been seen in some clinical trials, could be caused by negatively charged antisense molecules, resulting in the aggregation of white blood cells near the site of injection. But this problem seems to be manageable as well.

Some other limitations remain. The antisense molecules do not appear to reach skeletal or cardiac muscles from the bloodstream, so they can't target the heart. Antisense compounds currently in development are unable to penetrate the blood–brain barrier, making it unlikely that they will be used to treat diseases of the central nervous system. And antisense will not be useful for treating acute conditions in which a protein must be eliminated rapidly. If an antisense drug is indeed working via an antisense mechanism, the actions of the gene product will not be terminated until the existing protein pool has been degraded by the cell—a process that could take hours, or even days.

However, antisense has delivered some pleasant surprises, including the finding that oligonucleotides can be delivered easily through the skin and by inhalation into the lungs. Inhalation, in fact, may turn out to be an ideal mode of delivery for these drugs. Since the nucleic acids that comprise antisense drugs are large molecules, they cannot diffuse easily across cell membranes. Large doses are required to achieve any results. These large doses, in turn, result in nasty side effects. While a patient injected with antisense molecules may require a dose of

several grams to produce an effect, only a few milligrams are required if he breathes them.

Significant effort is also being devoted to the successful application of antisense as novel antimicrobial agents. For example, antisense inhibition of the lactamase gene in ampicillin-resistant E. coli resulted in the bacterium becoming sensitive to the antibiotic. In the next few years, more antisense drugs will soon join Vitravene on the market. Even ISIS 2302, the drug whose failure nearly wiped out Isis in early 2000, is now in a restructured phase 3 trial for the treatment of Crohn's disease.

If you like antisense, you have to love Isis. The company's strong development pipeline includes eight products undergoing clinical trials, mostly phase 2 and phase 3 studies. So far the company has hit all its key milestones this year and could have at least two new drugs on the market by 2004.

Isis recently announced a second phase 3 clinical trial of alicaforsen (ISIS 2302): an antisense inhibitor of intercellular adhesion molecule-1 (ICAM-1) in people suffering from active Crohn's disease (500,000 U.S. patients). ICAM-1 plays a central role in inflammation as well as autoimmune conditions. A drug that successfully blocks ICAM-1 could be broadly applicable in a range of diseases.

If these two phase 3 trials are successful, the drug could be on the market in the first half of 2004. Aside from being a debilitating disease that's poorly treated by today's current crop of drugs, Crohn's as a therapeutic market is attractive for a small biotech company like Isis. With only 10,000 gastroenterologists in the United States, Crohn's is a lucrative market that can be targeted cheaply, with a small sales force.

Isis is also making significant progress in its cancer portfolio. In two presentations at the recent meeting of the American Society of Clinical Oncology (ASCO), Isis and partner Eli Lilly presented data from their ongoing phase 2 studies of ISIS 3521 (Affinitac) in patients with nonsmall cell lung cancer. Overall, Affinitac demonstrated tumor reduction in patients who were not previously treated with chemotherapy, as well as patients who were unresponsive to two or more previous therapies, with no added toxicities. So far the drug has helped chemotherapy patients survive twice as long as patients on chemo alone. Isis and Eli Lilly have two ongoing 600-patient and 700-patient phase 3 studies with the drug, and could file for approval as early as 2004.

After recently retiring some of its debt, Isis is also in a strong cash position. The company has about $290 million in cash on hand, against a burn rate of $45 million and a market cap of around $500 million. That translates to about $5.40 of cash on its books per share. With its stock trading slightly above that price, Wall Street—which remains singularly focused on the handful of biotech companies that have products on the market—isn't giving Isis's late-stage clinical pipeline or its proprietary intellectual property much value. We believe that's a mistake, but a clear opportunity for investors.

**With only 10,000 gastroenterologists in the U.S., Crohn's is a lucrative market that can be targeted cheaply, with a small sales force**

Isis recently expanded its collaboration with Lilly to include the preclinical development of antisense inhibitors of gene targets associated with cancer. Isis has also leveraged its antisense technology through corporate collaborations with Merck, AstraZeneca, Abbott, Aventis, Elan Pharmaceuticals, and Novartis. Its Genetrove division provides target validation as a service model to industry partners Abbott, Aventis, Celera, and others.

Isis also has a small-molecule therapeutics division called Ibis, which is focused on the development of antibiotic and antiviral therapeutics. Ibis has been paid for by a DARPA grant and has a drug discovery partnership with Pfizer.

The science of antisense has made steady progress toward a better understanding of how gene expression can be regulated artificially. Now, pharmaceutical companies that previously shunned the field are giving it serious consideration. Antisense is a serious route for developing novel drugs. The surviving antisense companies are now poised to reap the benefits, and Isis sits at the pinnacle.

Scott Gottlieb, M.D.
July 9, 2002

# BIOTECH COMPANIES

| Company | Technology Leadership | Reference Date | Reference Price | 6/28/02 Price | 52-Week Range | Market Cap |
|---|---|---|---|---|---|---|
| Cell Genesys (CEGE) | Cancer Therapeutics | 6/10/02 | 13.24 | 13.49 | 11.65 - 25.02 | 480.8M |
| Cogent Neurosciences (none*) | Neurogenomics | 5/2/02 | | | | |
| CuraGen (CRGN) | Cellular Signalling | 3/13/02 | 17.67 | 5.63 | 4.56 - 38.25 | 275.2M |
| Gilead Sciences (GILD) | Rational Drug Design | 12/05/01 | 33.88** | 32.88 | 22.85 - 39.00 | 6.4B |
| Human Genome Sciences (HGSI) | Cellular Signaling | 10/26/01 | 43.97 | 13.40 | 11.75 - 61.20 | 1.7B |
| Isis Pharmaceuticals Inc. (ISIS) | Antisense Therapeutics | 7/9/02 | 7.30 | | 6.76 - 27.15 | 395.4M |
| MDS Proteomics (none*) | Proteomics | 2/05/02 | | | | |
| Nanogen (NGEN) | BioChips | 10/2/01 | 4.95 | 3.50 | 2.49 - 10.13 | 75.8M |
| Quorex (none*) | Rational Drug Design | 12/05/01 | | | | |
| Sequenom (SQNM) | Pharmacogenomics | 1/09/02 | 9.00 | 3.53 | 2.86 - 13.19 | 132.4M |
| Triad Therapeutics (none*) | Rational Drug Design | 4/9/02 | | | | |
| Vertex (VRTX) | Rational Drug Design | 9/17/01 | 28.60 | 16.28 | 15.02 - 49.38 | 1.2B |

* Pre-IPO startup companies. ** Split-adjusted price.

NOTE: This list of Gilder Biotech Report companies is not a model portfolio. It is a list of technologies in the biotech paradigm and of companies that lead in their applications. Companies appear on this list only for their technology leadership, without consideration of their current share price or the appropriate timing of an investment decision. The presence of a company on the list is not a recommendation to buy shares at the current price. Reference Price is the company's closing share price on the Reference Date, the day the company was added to the table, typically the last trading day of the month prior to publication. The author and other Gilder Publishing, LLC staff may hold positions in some or all of the companies listed or discussed in the issue.

**Editor's Comment:**

We are dropping our coverage of Elan Pharmaceuticals over our concern that they cannot shake a past riddled with financial dishonesty. Although its technology is attractive and its shares are now cheap, Elan may never get past the latest corporate setbacks. We want no part of a company that appears to have been serially dishonest with investors.

Last month, Elan announced that it had forward sold royalty rights on some of its key products, in effect, manufacturing earnings with sales that didn't yet exist. This accounting trick was revealed after Elan had given us, as well as Wall Street, assurances that it had put financial finagling well behind it.

In our view, this wasn't a difference over interpretation of accounting rules, but a clear, if legal, deception. As a result of the most recent disclosure, a management shake-up has ensued with the resignation of both the chairman/CEO and the vice chairman.

Liquidity is now a growing concern for the beleaguered company. While the company has $1.4 billion in cash to meet debt obligations throughout 2002, liquidity concerns become a paramount issue in 2003 when the $951 million in outstanding debt becomes due late in the year. This is further compounded by a write-down in the company's investment portfolio, for which a significant impairment charge of about $600 million is expected to be recorded in the company's results.

In view of these uncertainties, we recommend investors join us on the sidelines despite the temptation of investing in a seemingly very low stock price.

-SG

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