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Monthly Market Report

Contents: November 2006

Drug firms hit by development snags

· Trouble in the pipeline for AstraZeneca and GSK
· Investors scared as new products face setbacks

GlaxoSmithKline and AstraZeneca both suffered blows yesterday as the announcement of setbacks in their drugs pipelines scared investors away, wiping more than £7.5bn off the value of Britain's two top pharmaceutical companies.

AstraZeneca shares fell 267p to £32.62 after its stroke drug, NXY-059 - a potential blockbuster that analysts said could have been worth about £1.5bn in annual sales - failed in Phase Three trials, the last stage of clinical development.

It is the third drug that AstraZeneca has had to abandon at a late stage, after Galida for diabetes and Exanta for blood-clot prevention failed to make the cut.

The announcement coincided with an otherwise good set of third-quarter results. Pre-tax profit rose 25% to $2.2bn (£1.2bn), on sales of $6.5bn, compared with $5.8bn at this time last year, and the company raised its forecast for earnings per share for the year.

The group's five main drugs, which include the ulcer treatment Nexium, and Seroquel, a treatment against bipolar depression, performed well.

However, analysts focused on AstraZeneca's late-stage pipeline. The group has only four remaining products in Phase Three development. The next key milestone is in the first quarter of next year, when data on another Phase Three high-risk drug to treat hardening arteries is expected. Mike Ward, an analyst at Nomura Code Securities, said: "People have already got question marks over why these guys are not getting drugs to the market."

The firm said it had always made clear that NXY-059 was a risky project. Jon Symonds, chief financial officer, said: "We're not dependent on every pipeline event being successful and we've been saying for some time that [the drug] was high-risk."

Analysts remained concerned about the group's long-term prospects. Navid Malik, an analyst at Collins Stewart, said: "Whilst AstraZeneca can, of course, maintain short-term momentum by continuing its cost-cutting for the next two years, it desperately needs to bring new products to the market, without which no amount of cost cutting will help the company's future earnings growth."

The company said it would continue to look for development opportunities, both in its own laboratories and externally.

GlaxoSmithKline, meanwhile, also suffered a tumble as it announced that the United States filing of Cervarix, its ground-breaking vaccine against cervical cancer, had been delayed until April. The vaccine will rival Merck's Gardasil, which has already been launched in the US and Europe. Annual sales of both products are expected to exceed £1bn a year each.

Investors were worried that the Cervarix delay would mean GSK losing market share to Gardasil in the US.

However, David Stout, GSK chief operating officer, said: "This is a drug with a 10 to 20-year lifespan and the market for it will grow over time. So a one quarter delay isn't a big concern to me."

Shares in the group closed down 60p at £14.51 despite an otherwise good set of third-quarter results.

GSK posted a 15% rise to £2bn in pre-tax profit for the three months to September 30, announced a £6bn share buy-back over three years, and raised its earnings guidance for the year.

But there was disappointment over the state of the company's pipeline. Redona, the diabetes drug, was put on hold as it entered Phase Three trials, Promacta, a treatment to assist with chemotherapy, produced poor data in Phase Two, and a product to fight sepsis was stopped over safety concerns.

AstraZeneca's Stroke Drug Trial Failure Precipitates Stock Tumble

Astrazeneca reports that it has decided to discontinue development of NXY-059 in acute ischemic stroke based on negative results from its Phase III trial.

"NXY-059's lack of efficacy in the SAINT trial II is disappointing for stroke patients in view of the significant unmet medical need," reports Tomas Odergren, vp, global product director for NXY-059.

The SAINT II (Stroke Acute Ischemic NXY-059 Treatment) trial showed that NXY-059 did not meet its primary outcome of a statistically significant reduction in stroke-related disability compared to placebo. Subgroup analyses, including time to treatment, did not demonstrate a treatment benefit.

In addition, NXY-059 did not cause a statistically significant improvement in neurological status versus placebo on the NIH Stroke Scale; there was no evidence of NXY-059 lowering the incidence of symptomatic intracranial haemorrhage when administered with rt-PA; and mortality, the incidence, and profile of adverse events in patients receiving NXY-059 were similar to placebo.

The company's stock declined more than 7% on the London, Stockholm, and New York exchange.

Scientists at the University of Liverpool have created a new chemical compound that could be developed into a drug treatment for Alzheimer's disease.

The research team has used a family of long chain sugars called Heparan Sulphates (HS), found on nearly every cell of the body, to produce a new compound that can prevent the formation of clumps of small proteins that form in the brain. These clumps or 'plaques' disrupt the normal function of cells leading to progressive memory loss which is characteristic of Alzheimer's disease.

The clumps are formed from a small protein fragment called Amyloid-beta (A-beta) peptide released from its 'parent' protein - amyloid precursor protein (APP). This process requires the action of an enzyme called beta-secetase (BACE), which is critical in clipping up the APP to form the smaller A-beta fragments.

Professor Jerry Turnbull and Dr Ed Yates, from the University's School of Biological Sciences, have discovered that the HS sugars may play a key role in limiting the development of Alzheimer's disease. The sugars stick to the BACE enzyme and reduce its ability to 'clip' the A-beta peptide, thus controlling the amount of A-beta peptide available to form damaging plaques in brain tissue.

Professor Turnbull said: "We have developed a new class of compounds called 'engineered heparins' that could possibly be developed into drugs to stop A-beta peptides in the brain from forming and for the first time treat the underlying cause of Alzheimer's. The compound, based on the blood thinning drug, heparin, has modified chemical structures designed to optimise their desired activities and reduce potential side effects.

"The compounds work by blocking the beta-secretase enzyme, responsible for snipping proteins into smaller fragments. Despite its central importance to the disease, there are currently no drug treatments which target this enzyme because it has proved difficult to find inhibitors using traditional drug discovery approaches. The new compounds, based on the body's natural substances, may provide a novel route to effective treatments for this debilitating disease."

A spin-out company, IntelliHep Ltd, has also been founded to explore the commercial opportunities of developing engineering heparans as new drugs against Alzheimer's and other important medical conditions.

The research, funded by the Medical Research Council and the Biotechnology and Biological Sciences Research Council, is published in the Journal of Medicinal Chemistry.

Hail Russian Pharma!

The major pharmaceutical markets like North America, Europe and Japan are facing a very sluggish growth. This has forced the pharmaceutical market participants to shift their focus towards the regions that offer solid ground for research and development (R&D). Innovation is currently heading towards countries like India, China, Russia, Central & Eastern European countries.

Marked as a communist country, Russia faced various challenges including poor infrastructures, high tax rates, poor wages and low standard of living. The economic slowdown impeded industrialisation in the country. Though it possessed the economic strength to emerge as one of the strong markets in the world, Russia has been faced with substantial challenges to overcome.

The challenges

The Russian pharmaceutical market is overwhelmed by formidable challenges. The poor state of the healthcare system encourages the use of generics. Thus generic pharma market occupies around 80.0per cent of the market. With no proper reimbursement system, the patients have to loosen their purse strings to avail any primary healthcare service. In addition the local drug manufacturers contribute to 70.0 per cent of the pharmaceutical products sold in the market. The lack of proper manufacturing facilities or standards to govern the quality of the drugs being manufactured, the Russian market is flooded with spurious generics and fake drugs. Trading in the Russian soil is impeded by unfriendly import licensing policies and political interferences.

Moreover, the lack of sufficient infrastructure, poor implementation of the intellectual property rights and the unfavourable atmosphere for foreign investments including the widespread corruption act as roadblocks to pharmaceutical companies entering the market.

The opportunities

Amidst all the aforesaid challenges, the Russian pharmaceutical market projects a promising future. The Russian pharmaceutical market has been valued at $3.75 billion in 2005. The pharmaceutical market has witnessed steady growth for the past five years. The market is likely to grow in double digits during the next five years. The markets for branded drugs and over the counter (OTC) drugs are on the rise.

Cambrex Announces Sale of Bioproducts and Biopharma Subsidiaries to Lonza for $460 Million In Cash

Stockholders to Receive Cash Dividend of Approximately $13.50 to $14.50 Per Share

Cambrex to Continue as Streamlined Human Health Business Focused On Value-Added Pharmaceutical Services

Company to Submit Proposal to Declassify Board At 2007 Annual Stockholder Meeting

EAST RUTHERFORD, N.J., Oct. 24 -- Cambrex Corporation ("Cambrex") (NYSE: CBM) today announced that it has entered into a definitive stock purchase agreement with Lonza Group AG ("Lonza") (SWX: LONN) for the sale of the businesses that comprise its Bioproducts and Biopharma segments ("Bio Businesses"), for total cash consideration of $460 million. The Company expects to realize net proceeds, after paying taxes and transaction- related costs, of approximately $450 million which will be used to repay all outstanding debt under the Company's existing credit facility and to help

fund a special dividend to stockholders. The sale of the Bio Businesses, which is subject to Cambrex stockholder approval and customary regulatory approvals, is expected to close in 90 to 120 days.

Following completion of the sale, Cambrex expects to pay a special dividend that will be funded by the net proceeds from the sale plus an additional $125 million to $150 million from new lines of credit that Cambrex expects to secure after closing. Assuming financing can be arranged on favorable terms at the currently anticipated levels, Cambrex expects the special dividend to be approximately $13.50 to $14.50 per share.

Cambrex currently has three business segments -- Bioproducts, Biopharma and Human Health. The Bioproducts business manufactures and markets research, therapeutic and analytical testing products based on cell biology and used in drug discovery and biotherapeutic manufacturing. The Biopharma business offers process development services and contract manufacturing under cGMP conditions for therapeutic proteins, vaccines and other biologic drugs. The Human Health business features a broad portfolio of products and services for process development and manufacturing of approximately 120 active pharmaceutical ingredients, advanced pharmaceutical intermediates and specialty intermediates for animal health, x-ray diagnostic and other applications. Combined 2005 sales from the Bio Businesses accounted for 42% of the Company's total gross sales of $452 million.

James A. Mack, Chairman, President and Chief Executive Officer of Cambrex Corporation, said: "We are pleased to announce the successful completion of this important phase of our strategic review. After a thorough and deliberate process, our Board of Directors determined that the sale of our Bio Businesses to Lonza represents the most compelling means for realizing value for Cambrex stockholders. In addition to receiving a substantial cash dividend, stockholders can look forward to additional benefits from their continuing investment in our strong Human Health business."

"Going forward, Cambrex will focus on growth opportunities in the markets we currently serve through our Human Health business. Our robust portfolio of products and services in value-added niches, coupled with our proven capabilities and first-rate regulatory record, uniquely position Cambrex to support both branded and generic manufacturers throughout the drug development life cycle. We are confident that our strong customer relationships and talented employee base give us a solid foundation for winning new business in the growing healthcare markets," continued Mr. Mack. "Concurrently, we will be working to aggressively reduce our corporate overhead in light of the decrease in both the size and complexity of Cambrex's operations. We expect these cost reductions and the ongoing benefits from the rollout of Lean Six Sigma programs to create additional value for our stockholders. Consistent with our fiduciary duties, we will also continue to evaluate strategic opportunities for the Human Health business as they arise."

Stefan Borgas, Chief Executive Officer of Lonza, said: "For Lonza, this is the largest acquisition in our long company history and represents a significant commitment and leap forward toward achieving our long-time goal of becoming one of the world's leading suppliers to our existing and new customers in the pharmaceutical, healthcare and other life science industries. We are now closer to this goal than ever before."

The Bio Businesses transaction is not subject to any financing conditions and is subject to approval by Cambrex stockholders and customary regulatory reviews. Under the terms of the agreement with Lonza, Cambrex's Board of Directors may consider unsolicited superior acquisition proposals that include these businesses if presented between signing and stockholder approval, subject to a customary break-up fee.

Background on Strategic Alternatives Process

In February 2006, as part of Cambrex's publicly announced evaluation of strategic alternatives, the Cambrex Board of Directors announced the retention of Bear, Stearns & Co. Inc. to advise on options for maximizing stockholder value. Over the course of the following months, Bear Stearns solicited and received indications of interest from numerous potential strategic and financial buyers seeking to acquire all or parts of the Company. The Board of Directors decided that the combined sale of the Bioproducts and Biopharma businesses on the terms proposed by Lonza is the most effective means

of delivering maximum value to stockholders for these businesses, as it represents an opportunity to realize premium value in a highly tax-efficient manner. The Board decided to retain the Human Health business as it believes that more value can be created by continuing to operate this business than through the other alternatives presented in the strategic review process to date. As a further result of the evaluation of strategic alternatives and as part of the drive to improve the profitability of the remaining Human Health business, the Company recently announced the sale of its subsidiaries based in Cork, Ireland and Landen, Belgium.

Upon completion of the Bio Businesses transaction, Cambrex will concentrate on deploying its resources to maximize the potential of the Human Health business through reducing overhead by approximately $8 million per year and refocusing and streamlining the business. The Human Health business has consistently delivered industry-leading sales growth and EBITDA margins, even in periods of industry overcapacity and reduced market demand. We believe we are uniquely well positioned to capitalize on the expected growth in global consumption of active pharmaceutical ingredients, Human Health's primary business. The Company plans to accelerate the rebalancing of its product line and enhance its position in high-value, fast-growing niche markets through internal development programs and selective acquisitions in order to drive future growth.

Merck & Co. Pays $1.1B for Sirna

Merck & Co. will acquire Sirna Therapeutics for a cash value of approximately $1.1 billion. At $13 per share, this amount is more than double Sirna's closing price of $6.45 on October 30, 2006. Sirna is currently trading at $12.7 per share.
"This is another example of Merck delivering on its strategy of aggressively pursuing biotechnology companies that complement our considerable internal research capabilities," remarks Richard N. Kender, vp of business development and corporate licensing.

Sirna creates RNAi-based therapeutics. Its lead clinical development candidate, Sirna-027, is a chemically optimized, siRNA currently moving into Phase II development for the treatment of the wet-form of age-related macular degeneration as part of a broad collaboration with Allergan. The company also has an alliance with GlaxoSmithKline for the development of siRNA compounds for the treatment of respiratory diseases. In addition, Sirna has several programs covering a range of therapeutic areas, including infectious diseases, metabolism, CNS, and dermatology.

Merck and Sirna expect to complete the acquisition in the first quarter of 2007. Sirna stockholders who own approximately 36% of the company's outstanding shares have said they will support the transaction and have entered into voting agreements.

Merck's risky bet on a little biotech

Purchase of Sirna could lead to profitable cancer drugs, or nothing at all.

NEW YORK (CNNMoney.com) -- Merck's billion-dollar deal for Sirna could lead to profitable new drugs for treating cancer but the acquisition is a risky bet on a biotech with no proven products on the market, industry analysts said.

Merck & Co., (down $0.17 to $45.47, Charts) the No. 4 U.S. drugmaker, agreed late Monday to buy Sirna Therapeutics (up $6.18 to $12.63, Charts), a San Francisco-based biotech, for $1.1 billion in cash.

The price was about double the market value of Sirna, whose stock soared Tuesday. The deal is expected to close in the first quarter of 2007.

Barbara Ryan, who tracks the drug industry for Deutsche Bank North America, said the purchase price reflects potential future earnings at Sirna had it remained independent. In a published note, Ryan called the deal a "smart move" because it demonstrates that Merck is "forward-looking and continues to make substantial and aggressive investments to fuel longer-term progress."

But some analysts said that while buying biotechs with promising pipelines is key for big drugmakers that want to keep growing, the acquisition of Sirna comes with considerable risks.

Merck and Pfizer (down $0.56 to $26.64, Charts), the world's largest drug company, have been buying up biotechs and licensing their experimental products, because their in-house research isn't enough to ensure sales growth. Big Pharma is under growing pressure to buy, discover or license new products to make up for patent losses on some of their top-selling products.

So why exactly did Merck buy Sirna? Because the biotech specializes in RNA interference technology, also known as RNAi, which could conceivably be used to control gene activity to destroy cancer cells without harming healthy cells. In 2001, Merck bought another biotech, Rosetta Inpharmatics, which specializes in this "targeted" type of RNAi technology.

Sirna has no products on the market. The most advanced experimental product in the biotech's pipeline, a potential treatment for a type of eye disease that can cause blindness, is years away from market approval, assuming its tests are successful. But that experimental product, called Sirna-072, is not the big draw for Merck, according to Ding Ding, analyst for Maxim Group.

"I think Merck paid $1.1 billion in cash really to buy the technology platform," said Ding. "I'm not convinced that Merck is going to continue the current pipeline that Sirna has. The key pipeline that interests Merck is oncology."

Merck could now find itself competing with Alnylam (up $3.06 to $19.66, Charts), another biotech that specializes in RNAi technology, said Ding. She added that Alnylam is an unlikely takeover target for Merck because it's already about 20 percent owned by the Swiss drug giant Novartis (up $0.41 to $60.81, Charts).

Though the cancer industry has great potential, trying to develop profitable drugs with RNAi is risky. Jonathan Aschoff, analyst for Brean Murray, Carret & Co., said one of the biggest challenges in developing RNAi-based drugs is figuring out how to successfully deliver them to diseased parts of the body.

"The delivery of these drugs is the Achilles' tendon of the RNAi industry," said Aschoff, who said they were being sent in what amounted to "unaddressed envelopes." But if Merck can overcome this hurdle, the company could have cancer drugs in the early stages of testing within two years, said Aschoff.

But Les Funtleyder, analyst for Miller Tabak, said he was "skeptical" of Merck's acquisition, because its purchase of Rosetta had failed to produce tangible results in the last five years.

"I still like Merck as a company and I think they're going to be fine, but I'm skeptical of the return potential of the deal," said Funtleyder.

Achillion Pharmaceuticals Announces Pricing of Its Initial Public Offering

New Haven, Conn., Oct 26, 2006 -- Achillion Pharmaceuticals, Inc. (Nasdaq: ACHN) today announced the pricing of its initial public offering of 4,500,000 shares of its common stock at $11.50 per share, before underwriting discounts and commissions. All of the common stock is being offered by Achillion. In addition, Achillion has granted the underwriters an option to purchase up to an additional 675,000 shares to cover over-allotments, if any. Cowen and Company, LLC is acting as the sole book- running manager, CIBC World Markets Corp. is acting as co-lead manager and JMP Securities LLC is co-manager. The shares will trade on the NASDAQ Global Market under the symbol "ACHN."

Net proceeds from the offering are expected to be approximately $46.2 million, or $53.4 million if the underwriters exercise their over-allotment option in full, after deducting the underwriting discounts and commissions and the estimated offering expenses.

The public offering is being made by means of a written prospectus. Copies of the final prospectus relating to the offering may be obtained from: Cowen and Company, LLC, Prospectus Department at ADP, 1155 Long Island Avenue, Edgewood, NY 11717, (631) 254-7106. A registration statement

relating to these securities was declared effective by the Securities and Exchange Commission on October 25, 2006.

This press release shall not constitute an offer to sell or a solicitation of an offer to buy, nor will there be any sale of these securities in any state or jurisdiction in which such an offer, solicitation, or sale would be unlawful prior to registration or qualification under the securities laws of any such state or jurisdiction.

About Achillion

Achillion is a biopharmaceutical company focused on the discovery, development and commercialization of innovative treatments for infectious diseases. Achillion is currently developing treatments for HIV infection, chronic hepatitis C infection and serious hospital-based bacterial infections.

Cellzome Announces further Extension of Molecular Pathway Collaboration

Boston, 25th October 2006 - Cellzome Inc. announced today that its research collaboration with Novartis has been extended until 30 June 2008.

Cellzome will continue to apply its proprietary technology to identify tractable therapeutic targets in several disease-relevant pathways, and to the identification of pharmacological targets, and potential off-target effects, of active Novartis compounds. Novel drug discovery projects have resulted from this work.

Tim Edwards, Cellzome's CEO, said: "Our two teams have been working very well together and continue to make progress and create novel intellectual property. I look forward to further progress with Novartis, as Cellzome continues to integrate its technology into the drug discovery process."

About the Collaboration
In 2004, Cellzome and Novartis entered into a collaboration that combines Cellzome's experience in chemical proteomics and pathway mapping with Novartis' insights into particular disease pathways and its expertise in sensitized cellular screens. The companies are charting the physical and functional protein maps of key cellular pathways of a variety of diseases, with the potential to select the best protein targets within these pathways for the development of new drug candidates.

Cellzome's chemical proteomics expertise is also helping identify the role of active Novartis compounds in disease and their potential side effects. The work is being conducted between Cellzome's Heidelberg operations and Novartis' Developmental and Molecular Pathways group based in Cambridge MA. Novartis has made an equity investment in Cellzome Inc. and contributes research funding. There are also lead compound development options for both companies in exchange for licenses, milestone payments and royalties.

About Cellzome Inc.
Cellzome is a privately-owned drug discovery company applying its world-class proteomics technology to the discovery of novel small molecule therapeutics. Cellzome is commercializing its assets and technology by developing its own pipeline of small molecule kinase inhibitors for inflammatory disease, and by collaborating with leading pharmaceutical companies. Cellzome's emerging pipeline includes a small molecule Histamine H4 receptor antagonist, initially for asthma and allergic rhinitis, which is on track to begin clinical studies in Q4 2007. In addition, Cellzome is applying its distinctive *Kinobeads* technology to the discovery and development of novel, selective, kinase inhibitors targeting key inflammatory mediators in immune receptor signaling and chemotaxis, including Itk, PI3Kγ and Zap-70.

The Company is also collaborating with Ortho-McNeil Pharmaceutical and Johnson & Johnson PRD, focusing on developing a series of small-molecule gamma-secretase modulators for the treatment of Alzheimer's Disease.

Cellzome is intent on developing both organically and through merger or acquisition. Its holding company is domiciled in the USA and it employs about 80 people at its two operating subsidiaries in Cambridge, UK and Heidelberg, Germany. To learn more about Cellzome, please visit the website: www.cellzome.com

Market Outlook for Protein Therapeutics

The protein therapeutics industry got its start in early 1980s with the launch of recombinant insulin. Since then, the sector has undergone a rapid metamorphosis with the introduction of innovative new therapies like interferons and interleukins in the 1990s and monoclonal antibodies in the 2000s. Indeed, the market for therapeutic proteins is arguably the most exciting sector in the pharmaceutical industry .

The success of the sector is truly a triumph of good science. These treatments have revolutionized the treatment paradigms in areas of high unmet need. Driven by strong innovation, the market has experienced handsome double-digit growth since the early 2000s and should continue to see strong growth for the foreseeable future.

According to **Kalorama Information's**(www.kaloramainformation.com) research, the protein therapeutics market totaled $51 billion in 2005 and is expected to reach more than $87 billion by 2010. Though the protein therapeutics market is substantially smaller than the pharmaceutical market—about $660 billion in 2005—the relative growth of protein therapeutics market at 19% is substantially higher than overall pharmaceutical market growth, which was closer to 7% in 2005. The genesis of this market explosion can be traced back to the last 20 years of building a knowledgebase and research base in proteomics and genomics and a broader understanding of the molecular basis of disease.

In addition to the strength of the science, there are several other reasons the protein therapeutics sector is outpacing traditional pharma. The biopharmaceutical sector has fared much better than the pharma industry as a whole in terms of receiving regulatory approvals for its products. The biotech sector gained about 40 new chemical entity (NCE) approvals in 2005 as compared with the pharma sector that gained a meager 11 NCE approvals in 2005.

The sector also enjoys a much lower threat from generic erosion. Despite the fears of an onslaught of biosimilars, or biogenerics, the protein therapeutics market remains relatively immune to a threat from generic products. The primary reason is that protein products require specialized manufacturing cell lines and strong process controls. So, generic products may not be able to offer similar or equivalent efficacy and safety at their lower prices.

The biotech industry has been the fortunate beneficiary of capital investment in recent years. The success of recent company launches in the protein therapeutics market area has led to a significantly upbeat investor mood. Overall, the protein therapeutics sector raised nearly $35 billion through both public and private sources in 2005, which is up from $18 billion in 2002.

The pricing environment has also been favorable for protein therapeutic products, which generally target diseases with high unmet needs and potentially life-threatening consequences. In such situations, the bargaining power of HMOs, private and public payors, and patients is limited. Several products have targeted such niche markets and have such strong IP behind them, such that they are virtual monopolies.

There are challenges ahead for the sector. Manufacturing these products is difficult and expensive, and despite new potential approaches, such as transgenics, alternatives to cell culture processes are not around the corner. Manufacturing capacity and supply chain issues will continue to be challenges for the biopharma sector. Pricing issues, too, while currently a net plus for the sector, may in the future become onerous.

These challenges aside, the protein therapeutics industry is currently in the growth phase of its life cycle. Considering its robust biotech pipeline, the growing acceptance of protein therapeutics in the market, and the expected emergence of strong enabling technologies in

drug delivery and pharmacogenomics, the industry is expected to continue in a growth phase for a protracted period of time. By our assessment, the protein therapeutics market has an immensely attractive future.

Maximizing the Value of Biotech Patents

Biotechnology and pharmaceutical patents often reach their maximum value toward the end of their term when the inventions described in the patents have matured from the laboratory through product development, clinical trials, and regulatory approval and are on the market earning revenue.

While it is obvious to most companies that their bottom lines would be well-served by keeping competitors out of the market for as long as possible, many are not aware of the opportunities to extend the term of their patents beyond the standard 20 years. This article provides an overview of several mechanisms for maximizing patent term, with an emphasis on the opportunities and pitfalls of the U.S. Patent Office's Patent Term Adjustment rules.

Since the 1984 enactment of the Drug Price Competition and Patent Term Extension Act, patent-term extensions have been available for patents directed to a product (or method of manufacturing or using a product) that was subject to a regulatory review period (such as FDA review) prior to commercial marketing. The relevant statute (35 U.S.C. § 156) places significant limits on this type of patent term extension.

For example, the regulatory approval must be the first regulatory approval for the product (e.g., the first approval of the active ingredient). Thus, patents directed to new formulations or extended-release versions of existing drugs usually are not eligible for this type of extension. Additionally, the statute only permits one patent extension per approved product. Thus, if there is a family of patents directed to the product, the patent owner must select a single patent for extension. Also, a given patent only can be extended one time, even if it covers several different products.

The length of extension available depends on the length of the regulatory review process and may be reduced if the patent owner did not act with due diligence during the regulatory approval process. The maximum extension available under this statute is five years, and the patent term may not be extended beyond fourteen years from the date of regulatory approval. This type of extension can prove extremely valuable, but its limited applicability makes it available to only a small number of patents.Knowledgeable Patent Owners Can Take Advantage of Patent-term Extension Provisions

URAA

The Uruguay Round Agre-ements Act of 1994 (URAA, effective June 8, 1995) created another mechanism for patent term extension, which also has limited applicability. The URAA was intended to harmonize certain U.S. patent laws with those of other countries, and brought the 20-year patent term to the U.S. patent system.

Recognizing the significant delays and loss of effective patent term that could arise from certain Patent Office proceedings, Congress provided for patent-term extensions in cases where the patent application was subject to a secrecy order, an interference proceeding, or an appeal (including an appeal in federal court) that resulted in the reversal of an adverse determination of patentability (i.e., a decision favorable to the patent applicant). The relevant statute (effective from June 8, 1995 to May 28, 2000) provided for one day of extension for each day the secrecy order, interference proceeding, or appeal was pending, up to a maximum of five years.

Although the URAA extension provisions addressed the loss of patent term due to specific proceedings that delay the issuance of a patent, the 20-year term provisions of the URAA drove home the adverse consequences of other delays in the patent examination process.

Prior to the URAA, U.S. patent term was measured from the patent's issue date. Thus, patent examination delays did not affect patent term and in some cases even benefited patent owners, for example, by providing more time to ready a product for market before the patent term started running

. With the 20-year term, however, any delay in the patent examination process limits the effective patent term because the 20-year clock starts running with the patent's earliest effective U.S. filing date.

PTA Provisions

The Patent Term Adjustment (PTA) provisions (codified in 35 U.S.C. § 154, effective May 29, 2000) were enacted to limit the loss of patent term due to Patent Office delays. The PTA statute includes the URAA extension provisions outlined above, and also grants patent term extensions if the Patent Office fails to meet certain internal timelines during the examination process.

For example, if the Patent Office takes more than fourteen months to issue a first Office Action, more than four months to issue a subsequent Office Action, or more than four months to grant a patent after the Issue Fee is paid, PTA begins to accrue in the patent applicant's favor. Importantly, the statute also requires deductions from any extension period to account for times when the patent applicant "failed to engage in reasonable efforts to conclude prosecution."

Examples of common PTA pitfalls and strategies for avoiding them are outlined below. By becoming familiar with these rules and adopting strategies for avoiding PTA deductions, patent owners can enjoy the full benefits of the PTA provisions, thereby maximizing the life of their patents and, hence, maximizing patent value.

PTA Pitfall

Filing a Preliminary Amendment within one month of an Office Action/Notice of Allowance will result in PTA deduction if the Examiner has to issue a supplemental Action/Notice of Allowance.

PTA Strategy: File Preliminary Amendments as soon as possible after an application is filed. Consider calling the Examiner to make sure an Action is not about to issue, and see if the Action can wait.

PTA Pitfall

Filing a response more than three months after the relevant Notice or Action will result in PTA deduction, even if the response period is properly extended. PTA also is reduced if a deadline falls on a weekend or federal holiday, and the response is not filed until the next business day.

PTA Strategy: File responses at the three-month deadline whenever possible. If a response deadline falls on a weekend or holiday, file it on the preceding business day, even though the Patent Office rules permit filing on the next business day.

PTA Pitfall

Filing a supplemental response will result in PTA deduction.

PTA Strategy: Minimize the number of supplemental responses filed. Consider calling the Examiner to determine whether the issue can be addressed in response to the next Action or resolved by an Examiner's Amendment. If an Examiner suggests an amendment to allow the application, ask him/her to issue an Examiner's Amendment.

PTA Pitfall

Filing an Information Disclosure Statement (IDS) after the first Office Action will result in PTA deduction, unless the IDS is filed with a response or the submitted information was cited by a foreign patent office less than 30 days previously.

PTA Strategy: File IDSs well before the first Office Action. If an Office Action is pending, wait to file the

IDS with the response. Advise foreign patent attorneys of the 30-day deadline, to ensure that foreign-cited references can be submitted within that time frame.

PTA Pitfall

Filing an Amendment after a Notice of Allowance has issued will result in PTA deduction.

PTA Strategy: Ask the Examiner to make the correction by an Examiner's Amendment. If the correction is a minor one that is supported by the prosecution file history, consider making the correction by a Certificate of Correction after the patent has issued.

Patent owners who are aware of the different types of patent-term extension provisions can implement strategies to take advantage of these provisions and maximize the terms of their patents.

Such strategies are particularly important to biotechnology and pharmaceutical companies whose patents often continue to demonstrate significant value at the end of their terms.

Trial to see how stem cells can mend heart attack damage

A major trial of stem cells to repair heart attack damage will take part on 100 patients in London within weeks, scientists said yesterday.

The £1.2 million trial of stem cells isolated from the cardiac patients' own bone marrow is to be backed by £500,000 from philanthropists and will investigate earlier small studies which suggested that prompt action could cut deaths and suffering.

The trial is the first to be announced by the UK Stem Cell Foundation and aims to enrich stem cells from the bone marrow and then inject them into the previously blocked coronary artery within a critical five hours of the heart attack to see if stem cells can improve quality of life and delay or prevent the onset of heart failure.

The randomised control blinded trial, which will see half the patients injected with blood serum for comparison, will be conducted by Prof John Martin, British Heart Foundation chair in cardiovascular sciences, and Dr Anthony Mathur, senior lecturer and consultant cardiologist; at University College London NHS Trust and Barts and the London NHS Trust respectively.

The study begins after Christmas and will follow up findings from trials in Germany on small groups of patients, though there is much dispute about how the transplants work, whether they seed the growth of new muscle, new blood vessels or whether they exude factors or hormones that aid self repair. Results are expected in two years.

"We don't know exactly what happens in the heart. We know it is safe and we know it works in animals," said Prof Martin, who added that this was an unusual treatment in that it came from doctors, rather than the pharmaceutical industry, since the use of a patient's own cells cannot be patented.

David Macauley, chief executive of the UK Stem Cell Foundation, said that animal tests had shown that the earlier the treatment, the better.

"This is the first project of its type in the UK to combine stem cell delivery to the heart with primary angioplasty – where the blocked arteries in heart attack patients are opened as quickly as possible," he said. "It addresses one of the biggest killers in the UK – 108,000 people die every year from heart attack."

Over the last decade, a shift has occurred from people dying during the acute phase of a heart attack to those eventually dying from long- term effects, including heart failure, when the heart does not pump enough blood to meet the needs of the body.

Prof John Martin, who is also chairman of a European stem cell task force, said: "Previous studies have shown that stem cell delivery to the heart is safe. We will show whether it works in acute heart attack. Our study combines the two new ways of treating heart attack victims for the first time."

The London Development Agency has provided 50 per cent of the funds required to support the project and private funding of £500,000 has been donated by the financiers William Bollinger, and his wife, Judith.

One of the first Britons in the German trials was Ian Rosenberg, who had heart failure and was given two months to live. Three years ago he had his own stem cells injected into his heart to renew damaged tissue. He received a new lease of life but died a few months ago.

"Stem cell therapy transformed Ian's life " said his wife, Jennifer. "It gave him three years he would never otherwise have had."

Stem-cell transfer breakthrough raises hopes for blindness cure

A breakthrough in restoring sight to the blind has been made with a study showing that a damaged eye can be repaired by transplanting light-sensitive cells. The results of an experiment on laboratory mice have been so successful, scientists believe clinical trials on blind people could start within 10 years.

If the breakthrough can be developed further it could lead to new forms of treatment for the 300,000 visually impaired people in Britain who suffer from age-related macular degeneration and the thousands of blind children with inherited diseases such as retinitis pigmentosa.

Mice that were born blind because of a genetic condition were able to see light for the first time after a revolutionary transplant operation involving stem cells the key cells that develop into the light-sensitive tissue of the eye's retina.

The scientists behind the research believe that it is the first time that nerve cells at the back of eye have been successfully transplanted to restore vision, a development that promises to help millions of blind people throughout the world. "The most important thing is the principle that it can be done," said Robert MacLaren, a consultant surgeon at Moorfields Eye Hospital in London, who was part of the Anglo-American research team.

"We've discovered a biological principle, a healing mechanism that we can take advantage of, but it's still a long way to go before we can apply this to people. We are now confident that this is the avenue to pursue to uncover ways of restoring vision to thousands who have lost their sight."

The study, published in the journal Nature, involved blind mice that were born without light-sensitive "photoreceptors", which detect light when it reaches the retina and send the appropriate signals to the brain via the optic nerve.

Stem cells from the eyes of normal mouse foetuses were cultured in the laboratory before being transplanted to the eyes of the blind mice. Tests showed the stem cells developed into mature photoreceptors of the retina and could transmit signals to the brain.

Previous attempts at transplanting stem cells to a damaged retina had failed, it is believed, because the cells were too immature. The key difference with the latest research is that stem cells were transplanted after they had already developed along the route to becoming photoreceptors, Mr MacLaren said.

"We got them at the point of no return. It is the first time anyone has shown that it is possible to transfer photoreceptors successfully and timing was crucial," he said.

The 100 million photoreceptors of the human retina are like the pixels of a 100-megapixel digital camera and they come in two forms cone cells for seeing colour in daylight and rod cells for seeing black and white in low light.

The study on the mouse only transferred rods which are more common in mice, a nocturnal animal so the scientists have yet to demonstrate that the technique will work with cones, the most important cells for discerning images at the centre of the human retina. It is hoped that to help people with age-related macular degeneration it may only be necessary to transplant the relatively small number of cones in the central part of the retina that are important for good daylight vision.

In the mouse experiment, the scientists knew that the mice could see some light because their pupils contracted and dilated in response to differences in light intensity, showing that the brain was actively processing information from the eyes.

"Remarkably we found that the mature retina, previously believed to have no capacity for repair, is in fact able to support the development of new functional photoreceptors," said Jane Sowden of the Institute of Ophthalmology at University College London (UCL).

Professor Robin Ali of UCL said that in future human clinical trials it may be possible to use embryonic stem cells, or even adult stem cells from within a patient's own eye, for the first transplant operations.

Mr MacLaren said that one obvious advantage of using a patient's own stem cells for the operation was that it would avoid the complication of tissue rejection.

Professor Anand Awaroop of the University of Michigan at Ann Arbor, who collaborated on the study, said the findings may lead to new ways of treating other diseases of the central nervous system.

"Rather than focusing on stem cells, we believed that if we could understand how cells develop and become photoreceptors or any other specific neuron our transplantation efforts would meet with greater success," Professor Awaroop said. "This technique gives us new insights in repairing damage to the retina and possibly other parts of the central nervous system," he said.

How sight is lost

* Macular degeneration affects about 500,000 people in the UK.

* The macula is at the centre of the retina, where the light is focused, and is essential for reading and writing and seeing colour.

* In affected individuals, delicate cells at the centre of the macula stop working for unknown reasons.

* Most cases are of the slow-progressing dry kind; there is no treatment.

* Wet macular degeneration is faster and affects 27,000 new patients a year.

* Most of these patients can now be helped by laser treatment, photodynamic therapy or drugs.

* Most patients pay for drugs because the National Institute for Clinical Excellence is not due to issue guidance on their NHS use until autumn next year.

Abbott Pays $3.7B to Step-Up Presence in Cholesterol Management Market

Abbott has acquired Kos Pharmaceuticals for $3.7 billion in cash to strengthen its position in the $20-billion cholesterol management market. The transaction is valued at $78 per share, a 56% premium over Kos' closing price Friday of $50.09. "This acquisition expands Abbott's presence in the lipid management market and will provide several on-market and late-stage pipeline products," points out Miles D. White, chairman and CEO, Abbott.

Kos' two lead products are Niaspan®, an extended-release niacin product that raises HDL levels and Advicor®, a Niaspan/lovastatin combination product that treats patients with multiple lipid disorders. A new Niaspan caplet formulation with a range of dosages is currently under review. Kos predicts that it will submit Simcor®, a fixed-dose combination of Niaspan and simvastatin (generic Zocor®) to treat lipid disorders, for review in the first half of 2007.

Abbott reports that these on-market cholesterol products and development opportunities will join its own lipid management portfolio, which includes on-market TriCor® and a TriCor/Crestor® development program with AstraZeneca.

Abbott expects the transaction to be $0.02 to $0.03 dilutive to ongoing earnings per share in 2007, neutral to accretive in 2008, and building to significant accretion thereafter. Following the closing, the transaction is expected to result in one-time charges, primarily for in-process R&D and integration expenses.

Kos opened Monday at $76.95, a 53.62% climb from its Friday close.

Agreement Potentially Worth $100M Inked Between Takeda and Xoma

Xoma and Takeda Pharmaceutical entered into an agreement for therapeutic Mab discovery and development. Using its extensive collection of phage display libraries and antibody optimization technologies, Xoma will discover therapeutic antibodies against multiple targets selected by Takeda.

The agreement calls for Takeda to make upfront and milestone payments to Xoma, fund the company's R&D activities, including manufacturing of the antibodies for preclinical and early clinical supplies, and pay royalties on sales of products resulting from the collaboration. Payments to Xoma could exceed $100 million before royalties in the course of the collaboration.

Xoma will also undertake preclinical studies to support regulatory filings, cell line and process development, and production of antibodies for initial clinical trials. Takeda will be then responsible for clinical trials and commercialization of drugs after IND submission and is granted the right to manufacture once the product enters into Phase II trials.

Niche work, if you can get it

"The blockbuster is dead." "I have come to bury the blockbuster, not to praise it." For more than a decade, market analysts and media specialists (me included) have cried out to the wilderness about the death of the blockbuster model on which the pharmaceutical industry has relied for its livelihood. The marketplace has loosely defined a blockbuster as any drug that generates more than $1 billion in revenue annually.

The arguments against the blockbuster model suggest that it stifles basic R&D by shifting funds from discovery to sales and marketing and thereby forcing discovery scientists to only work on drugs or drug indications with potentially huge markets. And by trying to target the widest patient population,

companies are forced to cease development of compounds that might help a smaller population but have negative indications for the larger population, thereby increasing the cost of drug development because of late-stage attrition. And finally, because of these high development costs, drug companies are forced to charge prices that will allow them to recoup their costs and allow for the tidy profit that investors demand.

And so the negative feedback loop continues; a loop that cannot possibly be sustainable in the long term. (Oops, did I just say the sky is falling?)

The advent of technologies that will allow researchers to better target specific drug candidates to specific patient populations is supposed to help us break out of the blockbuster model. Call it pharmacogenomics. Call it biomarker analysis. Call it the personalized medicine paradigm. The bottom line is that many of the drug candidates that would have once been thrown in the trash bin for wide-scale negative indications might now be resuscitated for use in smaller patient populations. Lemons into lemonade.

Recently, however, I came across a sign that while our technologies are advancing to the next stage of drug discovery and development, our collective mindset may be just as stuck in the blockbuster mode as ever. The sign? The development of a new term—nichebuster—used to describe drugs that target very specific conditions experienced by very limited patient populations yet still have the capacity for large payoffs.

The poster-child nichebuster, as described in a recent Datamonitor report, is Novartis's cancer drug Gleevec. As market analyst Dr. Mark Belsey explained, the drug was initially approved in 2001 for the treatment chronic myeloid leukemia, making it a classic niche player. This would be perfectly fine, except in the next breath, Belsey derails his own argument.

"Despite the fact that this was a niche indication with a small patient population, it generated $2.2 billion in annual global sales by 2005," he says in announcing the report. "Part of its success is that it has since been approved for other oncological diseases as well, even though these are also niche indications."

First, by the simplistic revenue-based definition of a blockbuster, Gleevec is a blockbuster. Second, if the drug has been approved for use against a variety of cancers, can we not just call it an anti-cancer drug and move it into the therapeutic blockbuster category? If not, perhaps we should call aspirin a nichebuster because it treats headaches (a niche), toothaches (a niche), joint pain (a niche), and limits the impact of cardiac arrest (a niche), to name a few.

We are apparently still looking for that game-winning home-run ball. To set Gleevec as the standard for niche-targeted drugs is to doom the concept from the outset. Now, we're looking to turn lemonade into caviar.

The very concept of being a niche player is predicated on the idea that a drug will only be a "buster" to the people seeing benefit from the drug, which is why it has been such a difficult (and typically unpopular) business proposition to date. As such, until we can remove "buster" from our pharmaceutical vocabulary, we will be doomed to repeat the business models of the past.

In future editorials, we'll revisit this challenge and see if we can't come up with ways around the dilemma…reader input is very welcomed.

In the meantime: The blockbuster is not dead, it just has a new public relations firm.

Biotech cos. gaining on upbeat outlook

OCT. 26 4:51 P.M. ET Biotechnology companies are riding a positive wave of investor sentiment that has been rising steadily since August and could continue at least through year's end. The steady rise helped push several industry indexes higher, and in some cases, they showed faster growth than the overall market. The Dow Jones U.S.

Biotechnology Index has been on the rise since August and is now approaching its 52-week high of 487.1. The Nasdaq Biotechnology index has shown a similar gain and breached 800 Thursday. The American Stock Exchange Biotechnology index, meanwhile, is approaching its 52-week high of 758. The driving factors behind the trend include an upswing in investor confidence that has raised the Dow Jones industrial average on a similar path, pushing it to recordbreaking levels. But there's more to the peaked interest in biotechnology, several analysts have said, and it grows out of a shift to positive drug development news and a boost in merger and acquisition activity that is shining a light on how valuable some of the players in the sector are. A large part of the movement is being driven by large-cap biotech companies like Genentech Inc. and Amgen Inc. Citigroup analyst Yaron Werber, in a September report, said the large-cap section of the sector was due for a rally, citing stock values and potential for strong earnings. And the earnings have been coming in strong, with Genentech opening the season with a 58 percent jump in third-quarter profit with Amgen following soon after with a 14 percent increase. It's not uncommon to see a rally in the typically volatile sector during the second half of the year, said Citigroup analyst Elise Wang. But this year, the really started a bit later than expected. "We've had the opportunity to see the upside because earnings have been better," she said.

Genentech made a strong showing on its Rituxan and Avastin cancer drugs while Amgen's anemia drug Arenesp pushed its revenue higher. While the outlook on the drugs remains solid, it's the possible expanded use of medications already on the market that is helping many of the larger companies' stocks. For example, analysts expect Avastin, used to treat colon cancer, will gain approval for several other types of cancer; earlier this month, the Food and Drug Administration approved its use for lung cancer. Smaller players are contributing to the positive momentum also. Millennium Pharmaceuticals posted a strong quarter on sales of its multiple myeloma treatment Velcade, and analysts see the drug as a key driver for the company. The industry upswing is also being driven by a positive outlook on development pipelines and that in turn has spurred an increase in merger and acquisition activity.

"There's been this persistent viewpoint that the pharmaceutical sector has some challenges around their pipelines and need to fill the coffers there," Wang said. And while big pharma is on the lookout for the next biotech buyout, biotechnology companies themselves are looking to expand pipelines through acquisitions. Millennium and Genzyme Corp. tried to do just that in a bidding war for AnorMed Inc. Gilead Sciences Inc. is in the midst of buying Myogen Inc. for $2.5 billion. Performance during the fourth quarter for biotech companies is likely to hinge on additional acquisition activity on top of clinical trial news, Morningstar analyst Karen Andersen said.

Biotech's Beef

Companies say grad schools aren't stressing what students require in the real world

The U.S. is the mecca of biotech. Most top companies in the field are based here. Government research budgets in biology are immense and growing. Universities compete to attract great professors. Students flock to their courses. And once they're armed with graduate degrees, they can count on landing a job in the industry.

Or can they? In recent months biotech outfits have begun to complain that job applicants coming out of U.S. universities lack the knowhow companies seek. Left unresolved, the troubles could stifle growth in this booming sector, valued at $48 billion last year by consultant Ernst & Young. The knowledge deficiencies could also force biotech companies to move more of their operations overseas, say executives and recruiters.

The problem is a disconnect between what universities are teaching and what biotech wants. "The focus of academia is getting basic and theoretical knowledge in place," says E. Dale Sevier, a director at the California State University Program for Education & Research in Biotechnology. "The skills needed to be successful in the industry are just not taught in universities."

There are several weaknesses. First, recent grads lack the technical knowledge to carry out applied research in areas that straddle engineering, math, and computers. Second, job candidates have little awareness of what the Food & Drug Administration is looking for when it considers whether or not to approve a drug. Recent grads simply aren't familiar with issues such as quality control and regulatory affairs. Academic programs "don't train students to function in today's small-R, large-D environment,"

says Stephen Dahms, president and CEO of the Alfred E. Mann Foundation for Biomedical Engineering.

The California State University biotech program tried to identify what companies want from new hires in a 2000 report. Close to the top of the list are familiarity with FDA compliance, experience in clinical trial design, and quality control. All require knowledge of computing, statistics, and database management--pretty low priorities for most academic biotech programs.

As it happens, these are common credentials for foreign researchers in the U.S. who hold temporary work papers known as H-1B visas. U.S. Citizenship & Immigration Services reports that 3.6% of all H-1B visas for 2003, a total of 7,119, went to employees in scientific research and development. Some 80% of them have graduate degrees from U.S. universities, Dahms says, but "there's something special about the prior exposure of foreign nationals. They have a more applied R&D perspective." Of course, there are smart U.S.-born candidates with good math and computer skills. But they're rarely fluent in both math and life sciences.

Invitrogen Corp. (**IVGN**), a biotech company in Carlsbad, Calif., currently employs about 75 H-1B visa holders in a workforce of 5,000, and it needs more. The company hired 1,000 people last year and will raise that to 1,400 this year. But with H-1B quotas filling up earlier every year, Invitrogen has chosen to do more drug development in Japan, China, and India. It may also open facilities in Korea and Singapore, says Rodney Moses, Invitrogen's vice-president of talent acquisition. Compensation in China and India is lower than in the U.S., but that's not what motivates the move offshore, says Moses. "If the talent is located in Singapore, it's just easier for us to go there."

U.S. colleges take the problem seriously. State university systems in California, Wisconsin, and elsewhere are adding more industry-oriented classes. California State has crafted a curriculum that includes chemistry, engineering, and computer science. A new biotech program at the University of Wisconsin's Stout campus offers statistics and technical writing. Students must also work full-time at a biotech company during the summer or for a semester.

Industry buys into this idea. Invitrogen is sponsoring occupational summer camps for high school students, hoping to nudge them into taking more science and math courses. Many other companies are setting up intern and apprentice programs to identify promising students and prepare them for a post-academic career. After all, the goal in industry isn't just to raise interesting questions, as in academia. It's to find the answers.

US Biotechs strong, but face challenges

OCT. 17 10:57 A.M. ET The U.S. biotechnology industry is verging on profitability and outperforming pharmaceutical companies in some areas but faces tough challenges, biotech industry experts said Monday. The number of U.S. approvals of new drugs last year hit 18 for biotech companies, versus only 11 for traditional drug companies, consultants told about 800 attendees at the sixth annual joint conference of the New Jersey and Pennsylvania biotech trade groups. Two of the top 10 medicine makers in the world by revenue now are biotech companies, Genentech and Amgen. Revenues of U.S. biotech firms topped $50 billion last year, up almost 16 percent - - double the 8 percent growth rate of their big brother drug makers. And biotech firms are getting a bigger share of venture capital in the life sciences field: 17 percent last year, about four times the percentage in 1999. U.S. biotech companies are still in the red, but their combined net loss dropped 40 percent to about $4 billion in 2005. "The sector is closer to profitability than at any point in the past," said Keith Brownlie, a life science industry expert at consultant Ernst & Young. He noted the biotech industry this year marked its 30th anniversary, with its birth considered to be the April 1976 founding of Genentech Inc. of South San Francisco. In New Jersey, the 29 publicly traded biotech companies had a combined $1.45 billion in revenues last year, up 11 percent from 2004, and their market capitalization jumped 38 percent to nearly $17 billion. Their combined net loss was down 16 percent to $494 million. In eastern Pennsylvania, 11 publicly traded companies saw their combined revenues climb 18 percent to $1.42 billion, and their market capitalization rose 11 percent to $6.9 billion. Their combined net loss was rose 20 percent to $488 million.

Most biotech companies in the neighboring states are privately owned, and figures on their performance were not available. While venture capital has generally been difficult to raise as investors seek safe options, Brownlie said New Jersey and Pennsylvania biotechs pulled in $506 million last year, up from $161 million in 2004. Despite that, about two-thirds of investment in U.S. biotech companies now comes from mergers and acquisitions. "Companies are saying that M&A is their exit strategy," Brownlie said. That's because if a company survives to get a drug on the market, the pressure to then turn a profit each quarter limits investment in developing another drug to an unworkable level, said C. Boyd Clarke, a general partner at Five Lakes Venture Partners and former chief executive of Neose Technologies of Horsham. Unless you can afford to buy rights to a product in late-stage development from another company, Clarke said, "you're going to look for someone to buy you." The experts said this is one reason the industry now has some Fortune 500 companies and many small startups, but fewer mid-size companies. Other looming challenges for biotechs include increasing pressure from both government and managed care insurers to hold down prices of genetically engineered drugs, which are more expensive to make than chemically synthesized pills, normal ups and downs in business cycles and, in this region, creating a more entrepreneurial culture, a panel of experts said. Brownlie said pending changes in U.S. patent law could hamstring small biotech firms.

Report: Calif. leads world in biotech

California remained biotechnology's favorite place of business last year as other states unsuccessfully tried to woo a disease-fighting industry that has yet to turn a profit, according to a report issued Thursday by an industry booster.

The California Healthcare Institute found that biotech, broadly defined to include diagnostic companies and makers of medical equipment and devices, accounted for $62 billion in revenue in the state last year. The report didn't say how much the industry lost in that time.

Nearly half of the $5.9 billion in venture capital invested in the industry nationwide flowed to California companies. Many of the companies are developing so-called biological drugs to combat such diseases as cancer, diabetes and arthritis. These biological drugs are often derived from genetically engineered microbes, rather than chemicals used in traditional pharmaceuticals

California scientists also landed $3.6 billion in National Institutes of Health grants in fiscal year 2004, the report found. "California's biomedical industry is a vital and growing component of our state's high-tech economy," Gov. Arnold Schwarzenegger said in a foreword to the report. With the average salary rising to $70,400 from $60,000 a decade ago, Florida, Arizona and other states have put biotechnology atop their economic development lists. Yet, for all its prestige, biotechnology remains an unprofitable, niche industry that analysts said can't single-handedly boost a sagging economy. Despite being home to 2,700 companies, most employ fewer than 100 workers. With 260,000 of California's 15 million workers, it's a bigger employer than the aerospace, movie and computer industries individually but smaller than the labor force in government, manufacturing and services.

"It's an industry not growing very rapidly in terms of the number of jobs it's adding," said Joseph Cortright, a Portland, Ore.-based economist. "It's a relatively small component of the metropolitan economy." Biotechnology companies are clustered around just a few cities, the three biggest being San Francisco, San Diego and Boston. To a smaller extent, Austin, Texas, Seattle and North Carolina's Research Triangle are home to other companies, but Cortright doesn't see biotechnology clusters sprouting in new places. In the California Healthcare Institute report, compiled by PriceWaterhouseCoopers, there was scant mention of profitability -- something that has eluded a large majority of the state and country's biotechnology companies. Since the industry's inception 30 years ago, U.S. biotechnology companies have lost a combined $52 billion.

The losses continued to mount last year when the sector finished another $2.1 billion in the red, according to a report issued earlier this year by Ernst & Young. The Ernst report did note that the rate of loss was slowing compared with losses of $4.9 billion in 2004 and $6.4 billion in 2003. That report

didn't break out losses by state. "From a profit standpoint, these companies have very long gestation periods until they actually start selling products," said Ernst & Young partner Tracy Lefteroff, the report's author. He predicted the industry as a whole will break even within five years and begin showing an overall profit within 10 years as smaller companies begin receiving regulatory approvals for their drugs. A handful of biotechnology companies, such as Genentech Inc. of San Francisco and Amgen Inc. of Thousand Oaks, have hit it big after modest beginnings, making their initial investors wealthy.

But they remain an exception. What's more, the high prices of their drugs, especially to treat cancer, are coming under political pressure and several patents on pioneering drugs are set to expire, opening the industry to generic competition for the first time. "Though the biomedical industry is a solid, significant and growing component of the state's economy, California's life science leadership is fragile," David Gollaher, the institute's chief executive said in statement. In the report, Gollaher said that "there are storm clouds in the California and national political environment that could dampen the industry's prospects." Gollaher said several drugs and medical devices recalled last year could prompt the Food and Drug Administration to demand more and costlier data to ensure that products are safe and effective.

European IPO activity 'slows'

The number of initial public offerings (IPOs) in Europe slowed during the third quarter of this year, new figures show.

IPO activity among European venture-backed companies slowed to just 14 over the three months to September 2006. The number of IPOs over the quarter was two higher than the same period of 2005, but the total raised fell by two thirds (68 per cent) to 116.7 million euros (£78.5 million).

The Dow Jones VentureOne report indicates that merger and acquisition exits declined during the period in question, from 52 to 31, with the majority of IPOs now serving as capital raising opportunities for small start-ups.

The average amount raised by European IPOs in the third quarter of 2006 fell over the year from 11.6 million euros to 4.6 million euros.

Stephen Harmston, VentureOne director of global research, commented: "While European companies are achieving IPOs at a brisk clip this year-with 56 occurring to date-these public offerings are occurring on mostly entrepreneurially focused smaller exchanges such as Alternext and Deutsche Bourse and are thus not raising the sums we saw in years past."

According to the European Liquidity Report, four of the IPOs over the three months were IT companies, five were in the healthcare industry, and three were business, retail and consumer firms. The companies were based in Germany, Sweden, France, Norway, Belgium, the UK and Poland.

In the UK, credit fund manager BlueBay Asset Management is planning to float on the London Stock Exchange, while homewares retailer Dunelm started conditional dealing this week, having placed 60.3 million shares, representing around 30.2 per cent of its issued share capital.

Study reveals secrets to faster drug development

Effective and efficient decision-making is still a major roadblock in companies

For a business in which ultimate success — the approval of new drugs — is achieved over a time frame of years and decades, it might seem odd to look at ways in which companies can shave mere days off the development process.

But bringing a new drug to market involves a vast array of disciplines, and minor delays within individual disciplines soon add up and increase development costs for companies, not to mention losing valuable patent exclusivity time. With the average blockbuster drug bringing in around US$1 million a day in revenues, wasted days really can hit companies' pockets hard. So a great deal of effort is spent trying to identify where time improvements can be made without sacrificing quality. The latest contribution, a report from the Tufts Center for the Study of Drug Development, names the fastest drug development companies, and proposes the secret to their success. Over the development and regulatory period for drugs approved by the FDA between 1994–2005, Bayer, AstraZeneca, Allergan, Boehringer Ingelheim and Merck were the fastest development companies, or, as the study authors call them, 'speed demons' (*Tufts CSDD Impact Report* Sept/Oct 2006). These five companies, according to the report "deliver as much as a 17-month speed advantage over average performers".

It is always difficult to apply these data across the board because of the development and regulatory nuances within individual therapeutic areas. But interviews with clinical development executives at the speed-demon companies showed there were several factors that set them apart from slower drug developers. "There is no single way to be the fastest; it is all about the commitment to consistently apply strategies and practices across the portfolio," says Kenneth Getz, senior research fellow at the Tufts Center, and lead author of the study.

Executives at the speed-demon companies cited four main areas that made them efficient. Three areas point to external influences: the enterprise-wide adoption of e-clinical technology solutions; the high usage of contract clinical service providers; and active interaction with regulatory agencies. The fourth area, though, is one that strikes at the very heart of a company's make-up: effective management and prioritization of resources, including the termination of poor projects sooner. And making efficient and effective decisions between phases is still one of the major impasses in developing a drug, say analysts.

Companies have worked hard to make project phases more efficient, but they still need to improve on the so-called 'frictional' times and costs incurred by delaying decisions to move from one phase to another. "Somebody has to declare that the trial is stopped, somebody has to make a decision about that trial, and somebody has to get the process going for the next set of trials," says Navjot Singh, Associate Principal at McKinsey and Company. "All of that takes weeks, if not months, and the question is how can you save on that?" Part of the problem lies with the decision making structure in pharmaceutical companies. Decisions still tend to be made at the highest possible level, which means decision-makers have less insight into what people are working on. Project teams go to the decision-makers fighting for their compounds as much as possible, and are reluctant to give up on their project, in the hope that a project will succeed through perseverance. This makes it easy for projects to run beyond the point where the team knows they are not going to work. One major consequence of ineffective management is illustrated in the Tufts report.

The fastest companies terminated 56% of discontinued projects in Phase I, compared with 36% for slowest companies, and the situation is almost reversed for Phase II (FIG. 1). Another problem is that decisions to go forward on projects often lay stagnant within the layers of middle management. Efficient companies are more likely to have leaner and meaner decision-making structures, and a greater focus of competencies, says Nipon Das, President & Managing Director of Billinge Group, LLC. These companies have built strong competencies and incorporate their experience and talent to make quick decisions. Larger companies can become inefficient by trying to manage too many portfolios. "I am always concerned with companies spread across too many therapeutic areas,' says Das. With the exception of AstraZeneca, the five named companies in the report have grown via a culture of organic growth (although AstraZeneca has been integrated for many years). "I have seen the after-effects of sequential merger and acquisition growth: the loss of good people with experience and decision-making skills," says Das. "You cannot put too high a premium on the people that helped get an acquired product to market in the first place."

Singh agrees that more knowledge input is needed from people closer to the bench. "These people often know whether something is working or not," he says. "If you can distribute the ownership of

Resource management effectively at lower levels of management, and with the right incentives, these people have experience and information that can help you make a decision."

ERC Scientific Council agrees 2007 work programme

The Scientific Council of the European Research Council (ERC) has finalised the first draft of its work programme for 2007, outlining who will be eligible to apply for funding from the ERC, and how proposals will be evaluated.

The ERC is a new initiative, and is due to begin operating in 2007 as part of the Seventh Framework Programme (FP7). As the work programme explains, 'The fundamental principle for all ERC activities is that of stimulating investigator-initiated frontier research across all fields of research, on the basis of excellence.'

Two types of grant will be available, the Advanced Investigator Grant and the Starting Independent Researcher Grant. The first call for proposals will address the latter. It will be open to excellent researchers of any nationality who are in the EU or an associated country, or moving to the region, who are establishing and leading their first research team or programme. The budget for the first call will be around €300 million.

The grant will be awarded to the host institution, which will be asked to commit to allowing the Principal Investigator the independence to manage the research funding for the duration of the project.

'Independence' is spelled out in the work programme as allowing the principal investigator to:

- apply for funding independently of senior colleagues;
- manage the research funding for the project and make appropriate resource allocation decisions;
- publish as senior authors and invite as co-authors only those who have contributed substantially to the reported work;
- supervise team members, including research students or others;
- have access to reasonable space and facilities for conducting the research.

Grants will amount to between €100,000 and €400,000 per year for a period of up to five years, depending on the peer review evaluation and the needs of the project.

The Scientific Council emphasises that 'Proposals of an interdisciplinary nature which cross the boundaries between different panels, proposals in new and emerging fields and 'high-risk, high-gain' proposals are encouraged.' The proposals will be evaluated twice, with only those that pass the first stage being invited to submit a more detailed proposal.

As explained in the work programme, the Starting Grant is intended to encourage more young researchers to embark upon an independent career in science: 'Europe offers insufficient opportunities for young investigators to develop independent careers and make the transition from working under a supervisor to being independent research leaders in their own right. This structural problem leads to a dramatic waste of research talent in Europe. It limits or delays the emergence of the next-generation of researchers, who bring new ideas and energy, and it encourages highly talented researchers at an early stage of their career to seek advancement elsewhere.'

The work programme is subject to change before the first call for proposals is published, and will be revised in 2007 to include the ERC Advanced Grant scheme.

Oxford University spin-out wins grant from French charity

VASTox plc has won a grant from the Association Française contre les Myopathies (AFM), a neuromuscular disease charity, to support to the company's spinal muscular atrophy drug discovery programme.

VASTox has developed an in vivo screen that models spinal muscular atrophy in fruitfly (Drosophila melanogaster) larvae. It is using the screen to identify small molecule hits from its proprietary compound library. The money from AFM will allow the company to accelerate preclinical screening and candidate identification

Spinal Muscular Atrophy, an inherited disease that affects 50,000 people in the developed world, causes loss of motor neurons in the spinal cord, causing muscle to atrophy. In its severest form life expectancy is often less than two years.

AFM is one of the largest charities in the world focusing on neuromuscular diseases, and has raised over €1.2 billion since 1987, mostly for R&D into the causes of and treatments for these diseases.

VASTox's most advanced drug programme is developing a treatment for Duchenne muscular dystrophy based on the up-regulation of production of the muscle protein utrophin. The company has four additional programmes in osteoarthritis, cancer, tuberculosis and stem cell therapies.

These are based on VASTox's chemical genomics technology platform. This uses transgenic zebrafish and fruitflies as the basis of in vivo screening that can predict the efficacy and toxicity of potential drug compounds in humans.

Swiss-German biotech completes listing on Swiss Exchange

Santhera Pharmaceuticals has completed its IPO and listing on the Swiss Exchange, raising CHF 98.4 million (€61.7 million) at CHF 90 per share, the lower end of the indicative price range of CHF 85 to 100 per share.

The company, based in Liestal, Switzerland, sold all of the 983,859 new shares on offer, and said the IPO attracted a good geographic spread of institutional investors from the UK and elsewhere in Europe, as well as qualified institutional buyers in the US.

The money will be used for the company's four ongoing clinical development programmes, to start new clinical programmes and to build a US sales and marketing capability.

Santhera was formed in September 2004 by the all-paper merger of Graffinity Pharmaceuticals AG of Heidelberg, Germany and MyoContract AG, based in Leistal.

The ordinary share capital of Santhera now consists of 2,951,577 shares corresponding to a market capitalisation at the offer price of approximately CHF 265.6 million. The new shares constitute 33.3 per cent of the total equity.

Of Santhera's four clinical-stage development programs, three are investigating its lead compound, SNT-MC17, in the treatment of Friedreich's ataxia, Duchenne muscular dystrophy and Leber's hereditary optic neuropathy. The fourth clinical programme is developing JP-1730 for the treatment of dyskinesia in Parkinson's disease

The most advanced programme, SNT-MC17 in FRDA, has entered pivotal Phase III clinical development; the others are in Phase II.

Innate Pharma raises €30M in Euronext Paris IPO

Innate Pharma SA, a Marseilles-based biopharma company, said it raised €30 million in an initial public offering and listing on Euronext Paris.

The successful flotation, at a price of €4.50 a share, was in the mid-range of its target of its €4.10 to €4.80 a share. The offering, which valued Innate Pharma at €108 million, was 2.5 times over-subscribed, the company said.

The company had initially announced plans to float in June, but then held off on the flotation - saying it was waiting until the market picked up before going ahead.

Innate is developing drugs that target the innate immune system. The main focus is on cancer, where its lead product IPH 1101 is in Phase II trials in renal cell carcinoma, but the technology is relevant to autoimmune and infectious diseases also.

The company has collaborations with a number of Inserm (Institut National de la Santé et de Recherche Médicale) laboratories in France and with the universities of Perugia and Genoa in Italy.

In addition, Innate is partnered with Novo Nordisk in the area of natural killer cells. The Danish pharmaceutical company owns 20 per cent of Innate and has said it will take part in the IPO. As expected, Novo Nordisk invested €5 million in a private placement, buying 1.1 million shares at the IPO price.

The stock began trading on Wednesday 1 November.

Cambridge Consultants, Esprit launch £10M spin-out fund

Cambridge Consultants, a leading technology-based design and development company, announces that it has created a new venture fund of up to £10 million jointly with Esprit Capital Partners. The creation of the fund supports Cambridge Consultants' move to restart its spin-out activities after a four year gap and will be used to invest exclusively in its own technology ventures. Cambridge Consultants has a track-record of creating and developing successful start-up companies that is second to none, with just four of its spin-outs creating a value in excess of £1 billion in the last 7 years.

According to the British Venture Capital Association survey of 2004, the upper quartile performance of early stage funds between 1999 and 2004 returned a net IRR (internal rate of return) of 9.6%. During the same period Cambridge Consultants' spin-out investments produced an IRR in excess of 50%. Not surprisingly, this performance led to extremely strong competition to partner with the company in the creation of the new venture fund, one that will see one new start up company created every two years on average.

Esprit Capital Partners, formed by the recent merger of Cazenove Private Equity and Prelude Ventures, won the tender process due to its strength in both investing in, and supporting, early stage technology ventures, as well as its ability to provide funding for later stage growth. The team at Esprit Capital Partners also brings to bear significant experience in investing in technology start ups, including several from Cambridge Consultants. These include Cambridge Silicon Radio (CSR) whose market cap is approximately £1.1 billion, and Alphamosaic, which was sold to Broadcom for $120 million just three years after start-up. The new investment will be made by Prelude Trust plc, the investment trust that specialises in early stage technology-based businesses, now managed by Esprit Capital Partners.

Ray Edgson, Ventures Director at Cambridge Consultants commented, "To make a truly successful venture you need three key ingredients – the right people, the right technologies and the right market conditions. With confidence now restored in the global technology markets, we believe that it is people that make the essential difference between average and truly great new ventures. Our track record of success in this area, and an IRR in excess of 50%, shows that our unique culture allows us to develop just such people."

Edgson continued, "We are able to recruit some of the best engineers in the world because of the stimulating and creative environment we provide as they develop throughout their careers. However, whilst there is a structured career path within the company, our venturing model allows those who want to exploit their entrepreneurial skills to go on and start their own businesses, whilst being supported by our established networks and systems. It's an approach that has made us central to the

creation of today's vibrant technology cluster in the Cambridge area, as well as making quite a few millionaires."

The aim of the new fund is to invest exclusively in Cambridge Consultants' own new ventures, following the company's success in this arena. The first new venture is expected to appear in 2007. Candidates for the next batch of ventures are expected to come from a range of Cambridge Consultants' core markets, including wireless technologies, drug delivery, diagnostics, radar and electronics.

Spin-outs from Cambridge Consultants collectively employ almost 3,000 people, many of whom are headquartered in the Cambridge area. It is this pool of successful technologists in one area that has created what is often referred to as the 'Cambridge Phenomenon' or 'Silicon Fen'.

Simon Cook, CEO of Esprit Capital Partners commented, "Naturally, we are delighted to partner with Cambridge Consultants to create this fund, which reflects our core strategy of working with, and investing in, early stage hi-tech companies with global ambitions. By combining both partners' venture expertise, our aim is to deliver a clutch of spin-outs over the next few years that will carry on the tradition of generating both employment and wealth-creation for many in the region."

Novartis in China: East Meets West in R&D

Lower costs, top talent, and access to the huge mainland market drive the Swiss drugmaker's plans for a $100 million research center in Shanghai

On Nov. 6, Swiss drugmaker Novartis (NVS) unveiled plans to build a $100 million research and development center in Shanghai. The new facility will focus initially on the infectious causes of cancer endemic in China and Asia. It will also work to combine Western technology and drug-discovery approaches with those of traditional Chinese medicine.

This is Novartis' eighth and largest investment in China—underscoring how important the surging Asian giant is becoming for drugmakers. It's also the latest sign that China's efforts to transform itself from a low-cost manufacturing base into a global center of innovation are starting to reap dividends. With an estimated 1,000 small and midsize biotech firms, China has now seen the creation of 20 biotech parks around the country and continues to increase the government funds allocated to R&D.

"The Chinese government has made a concerted effort to promote life sciences," says Daniel Vasella, chairman and CEO of Novartis. "And the caliber of the science is extremely good and improving all the time."

Bountiful Market

China's emergence as a source of inexpensive yet topflight scientific talent isn't the only attraction. With a population of more than 1.3 billion, it's also one of the world's largest and fastest-growing markets for prescription drugs. China's domestic pharmaceutical market has grown more than 20% a year for the last three years, according to IMS Health, a market research firm in Fairfield, Conn. So although the country is not now among Novartis' top 10 markets, it is expected to be by 2010. By that time, China's annual drug sales are expected to nearly double, to $25 billion, according to Boston Consultancy, an independent consulting group.

As the Chinese become more affluent, spending on prescription drugs is set to rise. So too will the incidence of chronic disease, however. Increased wealth often leads to lifestyle changes—for instance, less healthy diets and reduced exercise—and a consequent rise in chronic illnesses such as diabetes, cancer, and heart disease. By 2025, China will have 38 million diabetes patients, almost double the number projected in the U.S., and about 13% of the global diabetic population, according to PricewaterhouseCoopers.

No wonder that in recent years Western pharmaceutical players have rushed to gain a foothold in China. All the major drugmakers have some sort of marketing or manufacturing presence in the country. One immediate advantage is lower costs. While the average expense of bringing a new drug to market in the U.S. is estimated to be $800 million, in China it's just $6.5 million, says PricewaterhouseCoopers. Moreover, the average salaries for Chinese scientists are just one-tenth those of their American counterparts.

Drugmakers Put Down Stakes

Lately, China's appeal to foreign investors is about much more than just cheap labor. The country's entry into the World Trade Organization in 2001 and the government's promise to expand intellectual-property rights have helped reassure foreign investors. So, too, has the establishment of a regulatory system similar to the U.S. Food & Drug Administration. China's regulator is called the State Food & Drug Administration (SFDA).

These changes have led Big Pharma to move beyond manufacturing into conducting clinical trials in China, where they cost roughly two-thirds less than in the U.S. Novartis, which began conducting clinical evaluations in China several years ago, now has 4,700 Chinese patients enrolled in a dozen trials.

It's only recently that foreign drugmakers have felt comfortable enough to expand into R&D. In May, Britain's AstraZeneca (AZN) announced its own $100 million R&D investment in the country. Switzerland's Roche also has an R&D center on the outskirts of Shanghai, and Pfizer (PFE), which set up a regional headquarters in Shanghai, is considering establishing its own R&D center in China.

"Shanghai is clearly emerging as a new epicenter of science globally, and is a magnet for the best and the brightest investigators," says Mark Fishman, who heads the Novartis Institutes for BioMedical Research in Cambridge, Mass. Novartis also hopes to capitalize on the increasing number of Chinese returning home from abroad. The new center's head of research was born in Shanghai but has spent time at MIT, Harvard, and, most recently, at Novartis' global research headquarters in Cambridge.

R&D's Twofold Path

A provisional R&D facility in Shanghai's Zhangjiang Hi-Tech Park is set to open in May, 2007, and by July, 2007, Novartis plans to have completed a permanent 38,000-square-meter facility for an estimated 400 scientists, mainly of Chinese background. The company also aims to continue mining its long-term collaborations with Chinese partners such as the Shanghai Institute of Materia Medica (SIMM), WuXi PharmaTech, Chinese University of Hong Kong National Institutes of Biological Sciences (NIBS), and Kunming Institute of Botany.

The partnership with SIMM to isolate and deliver natural products from Chinese medicine gave rise to 1,800 potential new drug targets, of which 10% have been validated and entered into preclinical development. Novartis already had success with Chinese development partners in using Chinese medicine to produce the antimalaria treatment Coartem, which is made from sweet wormwood plants grown in China.

At the new R&D center, Novartis aims to follow two paths—traditional Chinese medicine and Western drug discovery—in parallel. Initially, the focus will be on infectious causes of cancer such as the hepatitis viruses that cause liver cancer. Some one-third of the 400 million people infected with the hepatitis-B virus are in China, with experts estimating that the virus kills 300,000 people in mainland China each year.

Vasella believes China has the potential to become a global center for biomedical innovation. "As we build up our scientific expertise and capability, we will add additional research activities, and there's no reason that research we conduct in China cannot be used globally," he says.

Is Cell Therapeutics In Remission?

The battered biotech's controversial CEO has won over Novartis, but investors are wary

On a tense August day in 2005, Cell Therapeutics' (**CTIC**) chief executive sat in a conference room while the company's board of directors met next door and debated whether or not to fire him. The Seattle biotech's lead drug candidate, a lung cancer treatment called Xyotax, had failed a key clinical trial. To make matters worse, the CEO, Dr. James A. Bianco, had decided to sell off Cell Therapeutics Inc.'s only moneymaking drug. Throughout that gut-wrenching day, he was introspective but resolute. "I didn't question my vision and values," says Bianco, an oncologist who left clinical practice 15 years ago to develop cancer treatments that would be less punishing than chemotherapy and radiation.

Bianco survived the coup attempt and has been struggling ever since to regain his stride. Some days are pretty good. This year he persuaded the U.S. Food & Drug Administration to consider Xyotax as a drug just for treating women. Several studies, including four released on Nov. 8, show that Xyotax interacts with the female hormone estrogen to slow the growth of some tumors. If it's approved, Xyotax--a reengineered form of the chemo drug paclitaxel--could usher in a new treatment paradigm. The approval would bolster the idea that certain tumors behave differently in men and in women and give doctors a new weapon in the fight.

DOGGED BY SHORT SELLERS

FDA approval would be a victory for Bianco, a controversial character whose reputation for scientific ingenuity is offset at times by his excessive enthusiasm. For example, Bianco estimates that Xyotax could be worth $500 million a year, and he even won the confidence of Novartis, which signed a co-development deal that could bring $285 million in much needed capital to CTI. But Bianco has a long history of making similar grand claims for the drug. Xyotax is still years away from the market--and short sellers who bet on CTI's continuing disappointments have made a killing.

Bianco hasn't shaken the black cloud that has hovered over him since he co-founded CTI in 1992. Xyotax, which was initially tested in both men and women, logged so many research disappointments that investors pounded the stock from 70 in 2000 to a recent 1.50. Clearly, the market is wary of Bianco's perennially sunny predictions. "He's not everybody's favorite CEO," notes CTI Chairman Phillip M. Nudelman. Even the Novartis milestone seems to have set pessimists sniffing for blood. Short interest in CTI's stock jumped 44% from August to September. Bianco is unlikely to regain investors' confidence until the FDA weighs in on the lung cancer approval in 2008.

Nonetheless, when the board considered who might make a worthy successor to Bianco, they couldn't think of anyone who matched his prowess in both medicine and finance, Nudelman says. Bianco has engineered 20 financing rounds, raising a cumulative $1 billion for CTI--a feat he lists on his résumé alongside his medical training and his penchant for collecting electric guitars and 16th century ceramics. "He always has more than one ball in the air," says George Bickerstaff, managing director of CRT Capital Group, a Stamford (Conn.) investment bank that has worked with CTI. "He's extraordinarily flexible in dealing with almost insurmountable challenges."

Bianco's toughest decisions were rooted in two acquisitions. In 2000, CTI bought a New York biotech and succeeded in getting its leukemia drug on the market. But by 2005 the product was generating just $22 million a year in sales while costing CTI $53 million a year. The company needed cash to support trials of Xyotax and another cancer drug, Pixantrone, which it picked up in its 2004 acquisition of Italian biotech Novuspharma. So Bianco sold the leukemia drug for $68.8 million and announced plans to cut staff in the U.S. and Italy by more than half. For the dissenting board members, recalls Bianco, "it was very emotional that I had the chutzpah to take this company back to a development-stage organization." (The four dissenters have left the company. Three didn't return calls; the fourth declined to comment.)

CTI has dodged so many bullets on Wall Street that it seems miraculous the company is still standing. Once, one of the physicians managing a trial of Xyotax was asked to participate in a conference call for investors, most of whom managed hedge funds. The call was supposed to be about two other cancer drugs, but the analyst threw in a question about Xyotax. The physician answered by expressing concern that some of the clinical trials were being done in Eastern Europe. "Boom! Our

stock went down," Bianco recalls. More recently, investors blanched when NASDAQ threatened to delist CTI's shares. Regulators told Bianco that CTI's stock offering in September violated NASD rules. So he quickly bought back $3 million in shares and warrants from investors and escaped delisting.

Just when Bianco thought it was safe to crow about Xyotax again, more trouble arrived. On Nov. 3 the company announced it was suspending enrollment in Xyotax trials for six months so it could analyze patient mortality patterns. CTI also redesigned the study to focus on women with normal estrogen levels, including post-menopausal women who take hormone supplements. The changes were made based on guidance from the FDA. While the company does not believe the deaths signal safety issues, the suspension will push potential approval back by as much as six months.

Meanwhile, competitors have beaten Bianco to his goal of developing less toxic chemo drugs. An archrival, Los Angeles-based Abraxis Oncology, had its reengineered paclitaxel approved to treat breast cancer in 2005.

Bianco rarely gets rattled--a trait he honed while attending Mount Sinai School of Medicine in New York. While still in his third year, the faculty invited him to be chief resident. "He was very thorough and compulsive, which are qualities that made for an excellent role model," recalls Dr. Richard M. Stein, who directed the residency program at the time. Bianco put himself through college by managing three discount retail drugstores, so the administrative part of the job didn't faze him. His biggest challenge was soothing the psyches of residents who cracked under pressure. Diagnosing disease, Bianco says, "is about learning to connect the dots real fast. I loved it. I counseled them on how to get there."

Bianco hopes Cell Therapeutics is finally entering the last leg of its excruciating Xyotax marathon. Initial trials show that 40% of women on the drug survive for a year, vs. 25% of patients in control groups. And the Xyotax patients suffer fewer side effects, such as hair loss and anemia. CTI's other lead drug, Pixantrone, which is designed to be a safer version of a chemo treatment that causes heart trouble, has proven so promising in trials that Novartis optioned the rights to develop it as well.

CTI isn't out of the woods, yet Bianco permits himself to feel vindicated. At least on good days.

Genentech to buy Tanox for $919M

Deal would boost No. 2 biotech's income from anti-asthma collaboration; Tanox shares surge.

SAN FRANCISCO (Reuters) -- Genentech Inc., the world's second largest biotechnology company, said Thursday it plans to buy Tanox Inc. for about $919 million to boost income from an anti-asthma treatment jointly developed by the two companies.

Genentech (Charts) said it plans to pay $20 per share in the cash transaction, which Genentech expects to be completed by the end of the first quarter of 2007.

Shares of Tanox (Charts) jumped 43 percent after the deal was announced following the close of active trading on Nasdaq. Tanox stock finished regular trading down 5.9 percent at $13.64.

Shares of Genentech were little changed in extended trading.

Genentech of South San Francisco, Calif., said that by acquiring Tanox, it will eliminate royalties it pays to Tanox in connection with Xolair, a treatment for moderate to severe allergic asthma. Genentech said it and Tanox have been working together with Swiss drug maker Novartis AG (Charts) since 1996 to develop and market Xolair.

Genentech said it also will get Novartis' profit share and royalty payments to Tanox, which is based in Houston, as well as Tanox's product pipeline. Genentech competes with Amgen Inc. (Charts), the world's largest biotechnology company.

Boards of both companies have approved terms of the transaction, which is subject to approval by Tanox's shareholders, Genentech said.

Merck wipes Serono off Swiss biotech map

Merck KGaA's surprise 10.6bn acquisition of Serono has surprised many in the industry.

On the average report card a test score of three out of five would usually draw the comment 'could do better'. The admonishment to try harder was also given by some observers to Darmstadt-based Merck

KGaA's surprise 10.6- ($13.2)-billion acquisition of Serono on September 21. Although the price tag, roughly 5.l times 2005 sales, looked reasonable—albeit in excess of the 3.2 times paid by Bayer for Schering and the 4.4 times UCB paid for the Schwarz Pharma—serious doubts remain about the rationale of lashing the two companies together.

By picking up Geneva-based Serono, Merck KGaA boasts that it has achieved three of the five objectives it set itself to foster growth and remain independent. These are: achieving competitive scale

in R&D (now up to about 1.1 billion), adding new therapeutic treatments in specialist areas and expanding its geographical reach into to the US.

Michael Roemer, Merck chief executive appears to have struck the deal personally with Ernesto Bertarelli for his family's 64.5% stake in Serono, surprising the rest of Serono's executives. Despite the gloss put on the deal by Roemer, the two outstanding objectives on its list—the strengthening of the oncology franchise and gaining an entry into Japan—make the deal look like one struck not from a position of strength but one of weakness, says analyst Mike Booth of investment bank Canaccord Adams in London. "Most people would agree that Merck needed to do something," he says. "They missed out on Schering and they had a lot of cash that they needed to be seen doing something with."

Alongside needing scale to compete with the deep research pockets of big pharma and big biotech, Merck has also been looking for a way to alleviate its dependence on its highly cyclical liquid crystal display business, prompting the bid for Schering to beef up its ethical drug making business. But well-publicized problems inside Serono have also given the deal an air of two less-than-fit companies trying to prop each other up. Most recently Serono has been grappling with the fallout of its very public failure to find a buyer after it put itself up for sale last November (*Nat. Biotechnol.* **24**, 5, 2006).

Questions were also hanging over its pipeline given the slowdown in its mature reproductive health business and increasing challenges to Rebif (interferon -1a), its top-selling multiple sclerosis drug, which, with sales of about 1 ($1.3) billion in 2005, contributed more than half of group turnover. However, the paucity of late-stage products available from the combined groups' 28 compounds (5 in phase 3) has left Andy Smith, investment manager at venture capital firm SV Life Sciences in London questioning what the deal will ultimately deliver. "What it adds for Merck in the next five years is going to be difficult to work out," he says.

As such the acquisition has drawn unflattering comparisons to Altana's decision to sell its pharmaceuticals business to Danish company Nycomed in Roskilde for 4.5 ($5.7) billion. Konstanz, Germany-based Altana, which has been looking for a buyer since August 2005, also cited the need for scale. But others have pointed out the generic threat to Protonix (pantoprazole), the group's blockbuster ulcer drug and the decision by New York-based Pfizer to hand back the rights to Altana's next generation of ulcer treatments as more compelling reasons to cozy up to Nycomed.

One company that has managed to convince the market that its recent merger was about adding value is Brussels-based UCB. Its 4.4- ($5.6)-billion deal to acquire the family-controlled Schwarz, headquartered in Monheim, Germany, was greeted with almost universal approval, given the nine late-stage products it added to the pipeline. UCB is now expecting to launch three products over the next three years, including Cimzia (certolizumab) to treat Crohn disease. This helped the shares, which have hovered around the 42 mark this year, hit a record high of 50.

Peter Fellner, former chief executive of Celltech and present UCB director, argues that although some of the recent mergers may have been done from positions of weakness, the take-home lesson is that pharma and biotech need scale to keep driving the innovation. "To be in the game you have to be able to place some big bets, and if you don't have the financial clout to place these bets then you will be out of the game," he says. And although the once great white hope of European biotech, Serono, might be out of the game, many believe its disappearance will do little to alter the rest of the continent's much smaller market cap biotech companies, still wrestling with funding, signing licensing deals and bringing products to market.

One of the consequences, however, says Booth, could be the sparking of interest in previously neglected companies. "Analysts could start to look at covering some of the less liquid companies in the sector in the hope of a deal," he argues.

Smith is equally pragmatic about the demise of Serono, but believes that it will shift investment to the next layer of biotech companies. "Money usually finds other places to go and the bigger market cap European biotech groups like Speedel, Actelion and Genmab could take up the slack."

Robin Campbell, biotech analyst at investment bank Jeffries, in London, however, argues that Serono, as part of Merck, could continue to drive consolidation in the industry in its attempt to score five out of five in its strategic objectives. "When Merck gets its act together and is recapitalized, that will determine how much flexibility they will have in terms of in-licensing new products, in addition to what Serono brings."

Amgen acquires Avidia for $290 million

THOUSAND OAKS, Calif.—Marking the third time in three years that it has acquired a Bay Area-based biotech, Amgen announced in late September that it had entered into a definitive merger agreement to acquire Avidia, a privately held biopharmaceutical company that discovers and develops a new class of human therapeutic known as Avimer proteins.

Company spokesperson David Polk confirms that the transaction did indeed get antitrust approval and was completed on October 24, though he was not able to comment on any other details of the future of the 37-employee company other than the fact it is now a wholly owned subsidiary of Amgen. Amgen has facilities both Fremont, Calif., and South San Francisco, employing approximately 370 workers and 600 workers in those locations, respectively.

Under terms of the agreement, Amgen paid $290 million cash, net of existing cash balances and Amgen’s existing equity stake in Avidia, and will pay up to $90 million upon the achievement of certain milestones.

The transaction provides Amgen with Avidia’s lead product candidate, an inhibitor of interleukin-6 for the treatment of inflammation and autoimmune diseases, which is in Phase I clinical trials.

Avidia, which was founded in 2003 as a spin-off from Maxygen with venture capital money from Amgen and others, focuses on using proteins to develop drugs to treat inflammation, autoimmune diseases and other ailments. The company’s biotherapeutics consist of single protein chains composed of modular binding domains, like beads on a string. Each bead is designed to bind to a particular target site, thus increasing the relative amount of the drug where it is most needed and decreasing the amount of the drug where it isn’t desired, creating more favorable safety profiles. Avidia’s method has been described by some as a “LEGO approach” because it can hit multiple epitopes on a target and multiple targets.

“The Avimer technology is among the most attractive protein-based technologies currently under development,” says Dr. Roger M. Perlmutter, Amgen’s executive vice president for research and development. “Avimers may have several advantages as therapeutic products in terms of biological activity, tissue distribution, reduced immunogenicity and improved manufacturing efficiencies.”

The proteins Avidia uses work in a manner similar to monoclonal antibodies but the company’s technology isn’t encumbered by hefty royalty payments that are often associated with monoclonal anti-

bodies, adding to the value proposition for Amgen in the acquisition deal, according to Morgenthaler Ventures of Menlo Park, Calif., one of Avidia's early venture backers.

In addition to Amgen Ventures and Morgenthaler, other venture backers of Avidia included Skyline Ventures of Palo Alto, Calif.; Alloy Ventures of Palo Alto; HealthCare Ventures of Cambridge, Mass.; MedImmune Ventures Inc. of Gaithersberg, Md.; and TPG Ventures of Menlo Park, Calif.

Cardiovascular collaboration

BERKELEY, Calif.—Early last month, independent French pharmaceutical company Servier announced it would collaborate with Plexxikon Inc. whereby Plexxikon would work to discover non-peptidic inhibitors of rennin, an enzyme that is known to play role in hypertension, renal failure and vascular disease.

Under the terms of the deal, Plexxikon will receive an upfront payment, research funding and potential milestone payments that could total more than $100 million over the life of the collaboration.

The target of the collaboration is the population of people who have high blood pressure, but don't respond to existing hypertension medication. According to Plexxikon CEO Dr. K. Peter Hirth, that amounts to roughly half of the people who seek treatment for high blood pressure.

"Cardiovascular disease is a focus for Servier and that makes them an ideal partner to develop therapeutics for this significant unmet need," says Hirth.

But beyond the potential to help Servier bring new hypertension therapies to market is the added benefit of Plexxikon broadening its research scope and expertise. Founded in 2001, the company has thus far focused its proprietary Scaffold-Based Drug Discovery platform in three areas: kinases, nuclear receptors and phosphodiesterases.

"What is really significant here is that we have opened another protein family using our approach," says Hirth. "Our work with Servier is only focused on rennin, but it will also validate our approach to this protease family and that represents a great opportunity for us to develop additional compounds in addition those we have already in development.

For Servier, working with Plexxikon should provide it with novel compound leads in a relatively short time-frame as it looks to build on its expertise in cardiovascular therapies.

"Servier is entering into this collaboration with Plexxikon as a key step in our strategy to expand our efforts in the development of new drugs for cardiovascular diseases," says Dr. Emmanuel Canet, vice president Servier research and development. "This partnership will expedite the development of novel rennin inhibitors with potential use in therapeutic indications with high unmet medical need."

Successful and quick development of rennin-inhibitors could also have strong implications to both companies' bottom lines. According market research firm Datamonitor, the global market for hypertensive drug sales should top $50 billion by 2009, so bringing to market a therapeutic that has the potential to effectively treat the high percentage of patients who don't respond well to current therapies could grab a significant share of that market.

While the agreement between the two companies has the potential to earn royalties for Plexxikon, Servier will be responsible for the development and commercialization of products and will receive an exclusive worldwide license for any rennin inhibitors developed in the field of cardiovascular disease.

$20 million gift to establish cancer stem cell research center at Stanford

STANFORD, Calif. — The Stanford University School of Medicine has received a $20 million gift to establish a new world-class research enterprise to study cancer stem cells, which are believed to be at the heart of most cancers.

The New York-based Virginia and D.K. Ludwig Fund announced Nov. 14that the money was part of a $120 million commitment—one of the largest gifts ever by a private foundation for cancer research—for Stanford and five other academic centers nationwide.

At Stanford, the funding will be used to launch the Ludwig Center for Cancer Stem Cell Research and Medicine, and build upon the distinguished discoveries that Stanford researchers have made in this field. The goal of the center is to identify and better understand the role of these elusive cells in common cancers and then use this knowledge to develop more effective treatments. Most of the initial grant will be used to create a permanent endowment for the Ludwig Center.

“These funds will enable us not only to advance our initiatives on human cancer stem cells, but also to strengthen other unique aspects of Stanford’s cancer activities—from genomics to clinical care,” said Irving Weissman, MD, who in 2005 assumed a professorship at Stanford endowed by the fund—the Virginia and D.K. Ludwig Professor for Clinical Investigation in Cancer Research. (Another Ludwig chair was endowed in 1998 and is held by Lucy Shapiro, PhD.)

Weissman, who first identified blood-forming stem cells in humans and mice, will direct the new enterprise. Michael Clarke, MD, professor of medicine (oncology) and the first scientist to identify cancer stem cells in breast cancer, will serve as its deputy director.

In addition to promoting cancer stem cell research at Stanford, Weissman said he hoped Stanford researchers would, through the Ludwig network, interact with other groups that are complementary to their work. For instance, Weissman noted that scientists with the Ludwig Center at Memorial Sloan-Kettering are focused on the immunology of cancer; Stanford researchers will collaborate with them in examining the immune responses to cancer stem cells, he said.

The opening of a new field

Cancer stem cells were first found in acute myeloid leukemia in 1994 and have since been found in solid tumors, including brain, breast and prostate tumors. These stem cells have the exclusive ability to generate new cancer cells and cause the disease to spread. Thus, it appears that any treatment that leaves cancer stem cells behind will inevitably cause a patient to relapse.

The ultimate goal of cancer stem cell research at Stanford will be to develop therapies that target and destroy these critical cells. Researchers will begin by working to identify and characterize the stem cells in various tumor types.

Stanford scientists already are collaborating in efforts to isolate stem cells in a wide range of solid tumors, including brain, ovarian, head and neck, lung, bladder, prostate, colon, breast and melanoma. The next step will be to trace the biological pathways that enable them to self-renew and ultimately to develop and test new treatments to stop them from proliferating.

“ The Ludwig Fund is synonymous with excellence in cancer research and we are honored to have been designated a Ludwig Center,” said Philip Pizzo, MD, dean of the School of Medicine. “In addition to helping to support important cancer research being carried out at Stanford, the six new Ludwig Centers offer an unparalleled opportunity to foster interactions and collaborations among some of our nation’s most distinguished institutions and leading investigators. As a consequence our understanding of cancer will be enhanced and will help improve the diagnosis and treatment of patients with cancer.”

The new Ludwig Center, which will include more than 30 faculty members in 10 departments, builds on Stanford’s wide-ranging expertise in cancer and stem cells. Faculty at the new center will collaborate with their counterparts at Stanford’s Comprehensive Cancer Center and Stanford’s Institute for Stem Cell Biology and Regenerative Medicine.

An emphasis on collaboration

The center also will capitalize on Stanford’s expertise in genomic analysis through collaborations such as the one between Clarke and Patrick Brown, PhD, professor of biochemistry. Together, the two have worked to identify genetic signatures of individual breast tumors. This type of analysis ultimately will enable doctors to predict the severity of a patient’s disease and help them plan individualized treatments.

Andrew Shelton, MD, assistant professor of surgery, and his colleagues are also applying a similar approach in their study of colon cancer. By using genetic analysis to identify which malignancies in the colon are likely to be aggressive, Shelton hopes to spare some patients unnecessary colostomies.

Another key player in the Ludwig Center is Roeland Nusse, PhD, professor of developmental biology and a Howard Hughes Medical Institute investigator. Nusse, a leading scientist in the area of signaling pathways, is directing efforts to understand the molecular pathways that regulate stem cell renewal

and differentiation. He will be joined in the Ludwig Center by a new recruit, Philip Beachy, PhD, professor of developmental biology, who has investigated another signaling pathway that leads to a dread childhood brain cancer, medulloblastoma. Beachy already has found lead compounds that block the pathway and block tumor growth in animal models.

The Ludwig Fund was created by American billionaire businessman Daniel K. Ludwig, who died in 1992, leaving much of his fortune for cancer research. He established a trust, the Virginia and D.K. Ludwig Fund for Cancer Research, which has provided $50 million for endowed chairs at the six beneficiary institutions, including the chairs held by Weissman and Shapiro. The five other institutions are Memorial Sloan-Kettering Cancer Center, Johns Hopkins University, Massachusetts Institute of Technology , Dana Farber Cancer Institute and the University of Chicago.

Daniel Ludwig also established the Ludwig Institute for Cancer Research, the world's largest institute of its kind, which has disbursed more than $1.1 billion since 1971.

Overview of the Global Pharmaceutical Market

Last year saw the global pharmaceutical market grow to $602 billion, up 7.7% from 2004. North America contributed 44.1% of global pharmaceutical sales in 2005. The three major pharmaceutical regionsNorth America, Europe, and Japanaccounted for 82.3% of the world market.

Global pharmaceutical sales growth of 7.7% in 2005 was primarily driven by a 10.8% growth in European markets. However, sales growth in all major markets slowed in 2005, with the Japanese pharmaceutical market growth falling from 10.7% in 2004 to just 4.6% in 2005.

The U.S. pharmaceutical market grew by 7.0% in 2005 to $252 billion. The U.S. retail pharmaceutical market grew to $183 billion and was dominated by sales in the central nervous system, cardiovascular, and alimentary/metabolism therapy areas.

The European pharmaceutical market grew by 10.8% to $170 billion in 2005. Germany, France, and the U.K. together accounted for almost 50% of all European pharmaceutical sales in 2005. The Japanese pharmaceutical market grew by 4.6% in 2005 to $60.3 billion.

Main Companies

Sixty four companies generate pharmaceutical sales in excess of $1 billion and these account for 72.6% of the global pharmaceutical market. The top-10 companies, ranked by pharmaceutical sales, generated total sales of $252 billion in 2005, with a year-on-year increase of 5.1%. Total pharmaceutical sales from the top-10 companies accounted for more than 40% of the total market. **Pfizer** was the leading company in 2005 with a market share of 7.4%. **Sanofi-Aventis** and **GlaxoSmithKline** both had market shares of 5.6%, **AstraZeneca** 4.0%, and Johnson and Johnson 3.7%.

The top 10 biotechnology companies by revenue all generated revenues in excess of $1 billion in 2005. The leading biotechnology company was Amgen **with total revenues of $12.4 billion. Next was** Genentech **with revenues of $6.6 billion, and third was** Genzyme **with $2.7 billion. The top 10 biotechnology companies all increased revenues in 2005, with** Gilead Sciences **achieving the greatest increase of 53.1%. For the top 10 pharmaceutical companies there is a strong relationship between sales and value. Current market share and future growth expectations are important factors in determining company value. Sales levels and year-on-year growth rates are critical components in building shareholder value for pharma firms. Sales levels also influence R&D levels, which as a result, help to sustain future sales growth.**

Key Trends and Opportunities

The global pharmaceutical market is forecast to grow to $842 billion in 2010, an equivalent CAGR of 6.9% over the next five years. U.S. market growth has slowed over the last three years and is set to remain moderate over the next five years. Sales growth will be limited by high prescription drug co-pays for insured consumers, the growing availability of generic drugs, and a lack of new blockbuster drugs coming through the pipeline. Strong growth in the 10 European markets that joined the E.U. in 2004 will help boost European sales over the next five years. Continued double-digit growth in China will result in it becoming the seventh-ranked market by pharmaceutical sales in 2010.