BioWorld®

The Future of Biotech

The 2010 Guide to Emerging Markets and Technology

From the publishers of *BioWorld® Today*

The Future of Biotech: The 2010 Guide to Emerging Markets and Technology

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About BioWorld®

BioWorld Today, the newspaper of record for the biotechnology industry, is read by biotechnology professionals worldwide for its hard-hitting, objective news reporting. *BioWorld Today* is delivered by e-mail and fax every business morning, and is also found exclusively online at www.bioworld.com. The BioWorld Online website has been internationally recognized as the most comprehensive resource for strategic biotechnology news and information available today.

In addition to original daily news reporting, BioWorld offers an extensive searchable database with more than 18 years of biotechnology archives. This site is not only a great source for insightful, up-to-the-minute news coverage, but a veritable library of information on the developments of the industry as well. With a quick search, BioWorld subscribers have instant access to a wealth of biotechnology market intelligence from every biotech hotspot around the globe.

BioWorld does not post press releases, but rather uses information that is researched and written by the top business and science reporters in the industry. With nearly 20 writers spread throughout eight countries, BioWorld covers news on public companies and hard-to-find information on private companies. Our seasoned reporters get the inside scoop on what's happening within the corporate walls, on regulatory issues in Washington and elsewhere, and on scientific breakthroughs worldwide. This news coverage of the biotechnology industry is 100 percent original and available only at BioWorld.

All of the BioWorld resources are available for easy online searching, including:

- *BioWorld Today* – The daily biotechnology newspaper.
- *BioWorld International* – The weekly monitor of global biotechnology developments.
- *BioWorld Financial Watch* – The weekly report on all market data and business trends in biotechnology.
- *BioScan: The Worldwide Biotech Industry Reporting Service* – The most comprehensive directory of biotechnology companies available.
- *The BioWorld Biotechnology State of the Industry Report* – A must-have annual report reviewing financial trends in the biotechnology industry.
- *The BioWorld Executive Compensation Report* – An annual report revealing executive compensation data at biotechnology companies in the U.S.
- *The BioWorld Phase III Report* – A quarterly compilation of biotechnology products in late-stage clinical trials.
- *BioWorld Perspectives* – A free weekly e-zine that brings you unique perspectives on the trends and issues that are shaping the industry. Sign up for free at www.bioworld.com.

• *The BioWorld and BioAbility Biotechnology and Medical Device VC Directory 2009: U.S., Canadian, European, and Asia Pacific Venture Capital Firms and Contacts* – The only directory that connects you with VC firms investing in biotechnology and device companies. This report gives you access to each VC's portfolio and contact information, making it perfect for anyone looking for financing.

• *The BioWorld BioPartnering Report 2009: Strategies and Paradigms of the Deal* – A report that provides strategies to identify partners, negotiate transactions and navigate the biopartnering landscape.

• *The BioWorld Diabetes Report: Developments and Opportunities in Drugs and Devices* – An in-depth overview of the therapeutic and venture landscapes for the diabetes drug and device markets.

• *The BioWorld Biofuels Report 2008: Economics of a Driven Market* – An in-depth report on the emerging biofuels industry, which has quickly placed itself at the forefront of many government initiatives and spans across many vertical markets: biotechnology, auto, oil and energy.

• *The BioWorld Genomics Technologies Report: Advances and Challenges in RNAi, Stem Cells and Synthetic Biology* – This market report appraises the state and potential of the genomics technologies market allowing you to see where the trends are taking us for 2009.

• *BioWorld Industry Snapshots* – An exclusive online product updated daily with market data, such as collaborations, mergers, acquisitions, financings, market cap rankings and more.

• *Medical Device Daily* – Relied upon by thousands of industry insiders every business morning, this is the only daily medical technology newspaper. With new product developments, company news, regulatory activity, legislative actions, strategic alliances, sales and mergers, market updates, and much more — you are alerted to targeted news. That's why this has been a trusted source for the latest developments since 1997.

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Table of Contents

Foreword

Dear Colleague,

Thank you for downloading our free report, **The Future of Biotech: The 2010 Guide to Emerging Markets and Technology**. This thought-provoking collection includes articles and essays written by many top biotech writers and reporters. It was edited and is published by ***BioWorld Today***, the newspaper of record for the biotechnology industry. **The Future of Biotech** offers insights into current trends and successful strategies in biotechnology and provides a glimpse of what you can expect through 2010.

As you'll quickly see as you scroll through this report, having information like this is invaluable in today's turbulent industry. That's why being a subscriber to ***BioWorld Today*** is so important — you get a steady stream of analysis, news and insight just like this every business morning. Thousands of today's leading biotech executives and investors turn to ***BioWorld Today*** because each daily briefing provides need-to-know information on all of the key developments in the industry:

• **What your competitors have planned** — Our industry experts keep you up-to-date on what companies are doing and why, and how you can anticipate their next move.

• **Where the money is going** — Now you'll know how sources of funding are changing, and where smart investors are making strategic bets.

• **The impact of technological innovations and discoveries** — Our writers are seasoned business and science reporters who know the ins-and-outs of the industry. Their insider reports explain and interpret the latest clinical developments across the industry in detail that no other news source can approach.

• **Who's working with whom** — You'll discover which mergers and licensing deals are in the works and identify opportunities to jump ahead of your competition.

• **What the FDA and Congress are up to** — Do you know what's being said behind closed doors about rule changes and federal legislation? Now you will, with breaking news updates from ***BioWorld Today's*** Washington news bureau. Now you can be prepared to act before the new administration catches you off guard.

Accompanying this free report will be a 30-day free trial to ***BioWorld Today***. I hope you will enjoy this month-long sample of what our terrific news staff can do. You'll have an opportunity at the end of your trial to begin a new subscription to ***BioWorld Today***. I urge you to please act quickly. You'll never play catch-up again! The future of biotech is taking shape now — and ***BioWorld Today*** can help you stay ahead of the curve.

Best Regards,

Donald R. Johnston
Senior Vice President/Group Publisher

chapter 1:

Defining the Biotech Industry

We Need Uniforms to Tell Who Is Who in the Changing Biotech World

At BioWorld's daily news meetings, as we peruse the latest developments in the life sciences field, from new financings to clinical results to regulatory developments, a common question our staff raises about these companies is, "Are they one of ours?"

By Glen Harris
BioWorld Today Managing Editor

There was a time not long ago when the players in the life sciences game didn't need uniforms. We all knew that big pharma wore the suits and went to work in giant towers of steel and glass, or massive campuses with lawns manicured nicer than the elite golf courses to which they belonged.

And we instantly recognized the biotechnology bunch. They didn't dress as well, and their offices were down a rung or two, maybe just down the street from a great little Thai restaurant, and not too far from one of those dry cleaner/Nails 'R' Us/Dollar Store shopping centers. Or maybe they worked in the far corner of a 1950s university lab with old double-hung windows and a creaky ceiling fan.

At least that was our romantic view of the biotechnology industry. Despite the popular image of journalists as a hardened, cynical lot, we all have a romantic streak running through us.

So many in the bio business have hung onto the romantic notion that biotech, for the most part, is made up of the little guys with the Avis complex — they're smaller, but they try harder. They're the ones with the brains who take the gambles, splicing and dicing molecules and proteins on their way to discovering things that heal and save lives. Even their failures can be applauded because they advance the overall cause, often leading to success down the road.

Biotechs Still 'Our' People

Here at BioWorld, they were, and still are, "our" people. Not that we have anything against pharmaceutical companies. If you browse through our archives you'll find thousands of articles where they've been mentioned, quoted, and even featured. But to us, biotech is our first true love.

At our daily news meetings, as we peruse the latest developments in the life sciences field, from new financings to clinical results to regulatory developments, a common question our staff raises about these companies is, "Are they one of ours?"

Sometimes the debate centers around whether a company is a biotech or a specialty pharma or a tools company carving out a market niche and influencing the field. The verdict from our news crew usually leans toward inclusion, but perhaps not with the enthusiasm we might display for a true bio company that actually does the splicing and dicing. In honesty, we have the same discussions about tools companies. Are they biotech, pharma, or do they cross that divide?

Obviously, this is because we've carved out our own niche in the biotech space. But we've also grown up with the industry. As BioWorld neared its 1990 launch date, Amgen Inc. had product revenues of $400 million — not an unimpressive accomplishment, even today. But for just the third quarter of 2008 it reported product sales of $3.78 billion.

As biotech has grown up quickly, and continues to grow, our internal discussion of what's important to our readers gets more complicated. Dried up pipelines of pharmaceutical companies have naturally led them to the doorstep of biotech compa-

nies. Checkbook in hand, they're paying tremendous prices for compounds that might deliver to them the next Lipitor. As the low-hanging fruit gets picked first, the interest spreads to less advanced products.

Gradually, some of our old bio favorites, both products and entire companies, are being swallowed by big pharma.

The pharmaceutical industry also is catching onto the fact that biologics don't face the same generics problems as the Lipitors of the world. The off-patent generics threat — which may cause Pfizer Inc. annualized losses of more than $19 billion by 2014 —apparently isn't nearly as scary, even with a Democratic Congress nudging the FDA in the direction of bioequivalents.

Blurring Biotech and Pharma

Thus, the line between biotech and big pharma blurs. Aside from mergers and acquisitions, pharmaceutical companies are starting their own initiatives. Pfizer pledged to spend $50 million for a San Diego incubator; Lilly spent $560 million to expand its biotech operation; and Roche in late 2007 announced it would plow $255 million into expanding its biotech research and development (noting proudly that already 45 percent of revenues of its pharma division come from bio drugs).

In the interest of advancing the cause of biotechnology, that's wonderful. The cash infusion is something the field obviously needs. But the problem is, how does anyone with an interest in the biotech field keep track of what's becoming an overwhelming array of development efforts? The Biotechnology Industry Organization counted more than 1,400 biotech companies as of 2005. Add in the pharmaceutical companies that are making moves in biotech and the total grows exponentially. "Our" companies are now becoming "their" companies.

Defining Who Is Who in Biotech

In a *BioWorld Perspectives* column in early 2008, we asked the real experts — readers like you — how you would define biotech and if there is a difference between the biotech and big pharma sectors. You answered, and provided some great responses.

In a survey that accompanied the article, we queried you about how you define biotechnology today, and the differences between biotech and the pharmaceutical industry. Your input mostly fell into four areas that we'll call "Science," "Size Matters," "Difference, What Difference?" and "Culture."

Many of the "Science" answers were wonderful textbook material, seemingly from those well rooted in science. They were clear, to the point, objective, and unencumbered by emotion. I envision these as coming from the R&D crowd. Some examples from this group on how to define biotechnology today:

- "The discovery and application of innovations to problems involving biology."
- "Engineering biologically active molecules that are not obtainable by standard organic chemistry (e.g., small chemical molecules)."
- "Work at the genomic level, i.e., DNA, protein."
- "The use of the tools of molecular biology to develop a view of the molecular basis of disease as well as to create therapeutic or diagnostic products to aid in the diagnosis or amelioration of disease."
- "The use of molecular techniques to understand biologic processes to discover and develop new pharmaceutical agents."

Size Matters

So it's pure science, a matter of small molecules vs. large molecules? It's big vs. small alright, said the "Size Matters" group, but they're talking about company size. Here are some of their thoughts:

- "I think it's no longer a technology distinction. People seem to think of smaller, more entrepreneurial companies as 'biotech' whether they're actually biotech or pharma, and vice versa."

• "Still a size difference. Will I ever consider Genentech or Amgen [as] a pharma? Probably not. But more because of their history than true differences from pharma (which are getting smaller all the time as both sides move towards each other)."

• "The bulk of biotech [companies] are smaller and devote more effort to novel solutions — and they make less money."

• "[The difference is] as much a function of a company's size, management structure and how it is funded. 'Biotechnology' is often short-hand for either VC or small post-IPO loss, making R&D companies that have no revenues or rely on a big pharma partner to market their product(s)."

But there also was a substantial contingent who saw little if any difference between big pharma and biotech. Witness comments from the "Difference, What Difference?" group:

• "Excepting the fact that some biotech companies are still looking for mergers and money, the differences disappear and it seems that only a few original biotech companies remain on the market. Many of them will just disappear without leaving a fingerprint and many others will be acquired by the big pharma players where biotech is 'only' a division."

• "Biotechnology still to me means 'biologically derived drugs' rather than what it mainly encompasses — start-up or 'small' pharma companies, using 'biology' to get small molecules or develop platform technologies, etc. I think the descriptor became blurred about 15 years ago, driven by financiers. Many (most) companies bridge all areas; e.g., you can have a drug discovery company which uses RNA biological assays to discover small molecules! So at one end biotech is just biologicals (or applications of it), at the other biotech is just another word for small pharma."

Nimble, Less Risk Averse

And finally come the "Culturalists," those who despite the realities of modern business needs hold on to the idea that biotech is different, and in some important ways better. Their comments:

• "Even though both parties practice the other's game (Pfizer funds Goodman's biotech institute; Genentech or Amgen compete in the large pharma world), biotech connotes a nimble, data-driven and perhaps less risk averse organization than pharma — often because biotech is carrying less 'fixed costs and baggage.'"

• "I think that too many people in pharma don't understand the biological, physiological and medical implications of most disorders. Pharma is populated by medicinal chemists. They can beat a problem to death, but don't know what the problems are. Most management positions are medicinal chemists."

• "Pharma companies have too many managerial levels, no entrepreneur spirit and biotech companies are just the opposite: innovative and productive."

• "Biotech companies take more calculated risks and develop more novel therapies or drug delivery systems than most pharmaceutical companies."

• "Biotech companies retain a spirit which allows them to work on the more complex problems of molecular medicine."

Differences or not, I suppose both sides can agree with one writer: "Eventually they serve the same purpose — improve human life with artificial designs."

Emerging Markets for Biotech

BioWorld readers also provided insight into which countries and regions outside the U.S. will most affect the biotech industry in the next five years. India was the winner, followed closely by China. Other notables getting votes included Brazil, Singapore, South Korea and Japan. The reasons? Most readers said the booms would be due to the lower costs in those countries.

Trends Driving the Market

We also asked you to provide input on what trends will drive the biotech market through the next 10

years. The front-runner was, hands-down, personalized medicine, including combination diagnostic-therapeutic products. The next biggest trend was expected to be consolidation, in particular, more mergers between biotechs and big pharma.

Affordable health care and making biopharmaceuticals competitive so that health insurance companies can afford them also are on readers' radars. Rounding up the most important issues were: protein therapeutics, biosimilars, stem cells, aging, biofuels and bioplastics.

What You Asked for

The last question on the survey asked about the types of biotech news you would find most useful. You said you were looking for more coverage of Europe and Asia-Pacific, science news, biofuels, deals and financial information, and weekly summaries of key news. We are taking those requests to heart when discussing new product ideas and ways to expand *BioWorld Today* and our other newspapers and products. Until then, check out these BioWorld products for more of the news and information you're looking for. And visit www.bioworld.com for a free trial of the entire BioWorld website to look at more of these publications in-depth.

• *BioWorld International* – a weekly newspaper (delivered every Wednesday) that brings you news about international strategic deals, worldwide investment opportunities, country-by-country regulatory issues, product development and insight on emerging biotech companies.

• Email updates – At the beginning of 2008, *BioWorld Today* started a new service for subscribers, called the *BioWorld Today Midday Report*. It's a daily e-mail sent to *BioWorld Today* subscribers every afternoon featuring a preview of the articles currently being worked on by our business and science reporters worldwide, focusing on the companies — including your partners and competitors — making headlines today. It's the perfect "tip-off" identifying which news is about to break big and what you should pay attention to ASAP.

• Biofuels – BioWorld recently published its second report on the biofuels industry, *Biofuels Report 2008: Economics of a Driven Market*. This report provides you with an in-depth understanding of the emerging biofuels industry which has quickly placed itself at the forefront of many government initiatives and spans across many vertical markets: biotechnology, auto, oil and energy.

• *BioWorld Financial Watch* – Delivered every Monday morning, this e-newspaper provides details on collaborations, public and private financings, clinical trials and FDA submissions, stock market activity, and underwriter and venture capital portfolio performances, with an analysis by BioWorld writers.

• Weekly summaries of key news are available in *BioWorld Week*, the chronicle of biotech news as reported in *BioWorld Today*. This abridged intelligence service comes out every Monday morning and includes news summaries of the biggest stories, News from the Lab, and Market Watch, a three-month overview of industry averages from the CBOE and AMEX biotech indices.

chapter 2:

Financing: Biotech and Funding Models

When Did Biotech Investors Get so Sophisticated?

How Hedge Funds and New Research Models Are Changing the Rules

There's a fundamental shift underway in the biotechnology investment world, particularly for highly specialized fields such as pharmaceuticals and genetic research. Investors, it seems, are getting educated.

By Will Febbo
BioWorld Contributing Writer

On a recent earnings call, the CEO of a mid-size pharmaceutical company was fielding all the usual questions about the firm: earnings projections, R&D spending, sales efforts, etc. Then came a question about an experimental drug that was moving through the FDA approval process. The question was based on one of the more esoteric assumptions about the new drug's efficacy. The CEO was stumped. He had heard some murmurings about recent research on the topic, but he hadn't prepared for the question and was clearly rattled.

It's easy to understand how this happened. CEOs are paid to handle such matters without flinching, but this CEO had never — in years of investor calls — gotten a question like this. In the past, a quick briefing with his direct reports was more than enough preparation for an investor call.

There's a fundamental shift underway in the biotechnology investment world, particularly for highly specialized fields such as pharmaceuticals and genetic research. The MDs and PhDs who run biotech companies are no longer de facto more informed than their investors, nor do they have a monopoly on access to information. Investors, it seems, are getting educated.

Why Is This Shift Taking Place Now?

There are several factors prompting these changes, but overall it's about a fairly simple idea: As competition increases among investors to discover and invest in high-potential companies and sectors, those investors respond by getting smarter. This is the classic story of investors searching for an edge. In this case, hedge funds are changing the game by tapping directly into the industry's experts, either by hiring them outright to join their investment teams or — more cost-effectively — by using primary research firms to assemble expert panels.

To better understand this shift, it's helpful to consider how hedge funds are changing the biotech investment landscape. Looking back just 10 or 15 years, most holders of large-cap biotech companies were mutual funds — relatively passive investment vehicles that buy and hold stocks over a long time horizon and typically track to an index. Mutual funds are usually characterized by low fee structures and modestly paid investment managers (relatively speaking) who work within fairly narrow investment parameters.

Over the past several years, however, hedge funds have become more and more of a force in biotech, as well as in several other sectors. McKinsey estimated in October 2007 that total hedge fund assets under management were around $1.7 trillion, more than triple the total in 2000.[1] (Although not a perfect apples-to-apples comparison, the Investment Company Institute estimated net assets in stock-based mutual funds to be about $6.7 trillion as of the beginning of 2007.[2]) Unlike mutual funds, hedge funds aggressively reward their managers for outperformance. Hedge funds typically use some permutation of

the "2 and 20" formula in which the fund pockets 2 percent of all assets under management, then an additional 20 percent of any profits.

To get a sense of how this plays out, consider the case of a mutual fund and a hedge fund that each take a $100 million stake in a biotech company. The mutual fund might book fees of 1 percent of total assets under management, or $1 million; if the stock price appreciates by 5 percent, investors do not owe a cut of their earnings back to the fund. The hedge fund, on the other hand, with a "2 and 20" structure, would get a $2 million management fee as well as another $1 million for the 5 percent appreciation. Both funds made the same bet, but the hedge fund manager gets three times the take. Investors are willing to pay that premium with the assumption that the hedge fund will consistently make better investments.

Hedge Funds' Competitive Edge

Hedge funds, in turn, use that extra fee income to maintain a competitive edge over the competition. These days they're accomplishing that primarily in two ways, both of which directly tap the expertise of the biotech industry.

First, no longer content with having the best MBAs money can buy, hedge funds are filling out their research teams with PhDs and MDs from leading schools and medical institutions. As a result, the analysts covering biotech companies now often have the same level of understanding and sophistication as the scientists at the companies, raising the bar of investor understanding. In fact, hedge funds and biotech companies now compete for talent.

Second, hedge funds are investing in expert-panel primary research as a more efficient means of getting direct access to top opinion leaders. As an example, consider a hedge fund that is analyzing a pharmaceutical company with a drug in FDA testing; the hedge fund would need a great deal of diverse expert information to make a true evaluation of whether the company's shares are underpriced, overpriced or properly valued. The investor would need the insight of a research scientist capable of interpreting the test results, a regulator who understands the hurdles the treatment might face, an investment analyst who understands the sector and perhaps an economist to give insight into the near- and mid-term outlook for companies that require continuous cash infusions for R&D. It's very rare that any individual would be able to provide that level of perspective, and most investors would not have the necessary contacts to assemble this knowledge. With primary research, hedge funds are assembling these types of panels and getting deeper insights through multiple expert perspectives.

The drive for an edge in research is ultimately about hedge funds' fiduciary responsibilities to their limited partners. It's an arms race of sorts among biotech investors: If a hedge fund is losing money to other funds that are quicker to the punch because they understand the science better, then it is incumbent on that hedge fund to step up its own level of expertise by hiring more industry-savvy people and using better tools.

How Should Biotech Companies React to These Changes?

Biotech executives who want to stay in step with their investors need to rethink how to monitor and then effectively communicate with the investment community. Those who are able to do both will be best able to understand what information investors are looking for and then answer that call.

The first part of this equation, monitoring the investment community, is a classic exercise in gathering strategic intelligence, and it forms the foundation of any good investor relations program. All firms participate in this exercise, with varying levels of formality — sometimes the executive team just knows the investment community; other times it hires outside firms to help it understand what investors are looking for. Nowadays, as institutional investors are turning the due-diligence process on its head by using biotech tools to research biotech companies, those same compa-

nies should consider similar moves. A panel of experts can provide invaluable information to an investor, and — similarly — an expert panel can help companies understand where they meet, and where they fall short on, investor expectations.

Once these firms understand how their investors perceive them, they can then start working to fill in gaps, recast messages, better explain strategy, and so forth. The process could even result in changing business practices, as expert panels can bring a fresh perspective to companies that aren't realizing their full potential.

On top of this, basic investor relations assumptions need to be reconsidered. As the knowledge gap between investors and biotech firms continues to narrow, companies need to begin stepping up their level of discourse. This doesn't involve scrapping current IR approaches and starting fresh. Indeed, many non-science-trained analysts will still be out there reviewing companies, and thus will still want the science simplified. But, alongside of those analysts are new investors with a more sophisticated understanding of the science. Any information that is pushed out to investors will need to accommodate both audiences, and any forum in which company executives interact with the investment community will also be reshaped.

These changes, considered all at once, are likely fear-inducing for biotech executives and their IR officers, but they are ultimately positive developments for the industry. As the knowledge gap between investor and executive narrows, strong companies with complex products and services will be better understood, valued and funded.

Notes:

1. McKinsey Global Institute. *The New Power Brokers: How Oil, Asia, Hedge Funds, and Private Equity Are Shaping Global Capital Markets.* October 2007.

2. Investment Company Institute. *Trends in Mutual Fund Investing.*

Published in *BioWorld Perspectives*

Will Febbo is the CEO of Panel Intelligence LLC

Are Biotechs Built to Prosper or Are They Built to be Sold?

The NVCA data shows a pretty interesting picture going back over the past 17 years. M&As have pretty steadily gained ground as the exit of choice over the past two decades.

By Karl Thiel
BioWorld Today Columnist

It was a difficult year for the biotech industry in 2008, and end-of-the-year economic news did little to relax furrowed brows. Just think: With Roche trying buying out the rest of Genentech, the industry's push to become profitable in aggregate — a milestone it missed by just a scant couple hundred million dollars in 2007 — was dealt a serious setback.

And the list of woes continues: The FDA is missing more PDUFA dates and threatening to make everything from diabetes drugs to cancer treatments harder to green light. Legislators are hauling drug executives up to Capitol Hill to receive public abuse. Support for follow-on biologics is gaining steam. Yikes!

You may have noted one other troubling bit of recent news: The National Venture Capital Association (NVCA) declared nothing less than a "capital markets crisis." After 2008's extremely slow first quarter, in which only five venture-backed companies in any industry went public, the second quarter had zero venture-backed IPOs. That's the first time such a thing has happened since the grim days of 1978, according to NVCA.

If attendance counts, medical/biotech represented pretty well in what was a lousy year. Of those five IPOs, four — CardioNet, IPC The Hospitalist Company, MAKO Surgical, and Bioheart — are involved in the life sciences. (The other, ArcSight, makes security software).

But that's still a concerning trend. After all, if companies are denied money on one end and find it harder to reach commercialization on the other, what hope does the industry really have? The first steps to dealing with a crisis are to determine what has happened, why, and how to improve things.

First of all, let's note that there were quite a few non-venture-backed IPOs in 2008. The most noteworthy one of the year, Visa, produced some pretty handsome returns, even in a very tough market. And more IPOs, both venture-backed and otherwise, are stacked up in the wings, judging the public mood with a finger in the air. So the crisis is most acute for desperate VCs looking for an exit on their investments.

How about the quality of their product? Four of those five venture-backed IPOs — all but IPC — were in early July among the worst performers of the year. Things have improved dramatically, but these companies didn't put forth the kind of performance that gets investors excited about further new issues. Bioheart, which originally filed for a $35 million IPO, was shoved out of the nest at a pathetic $5.8 million.

Indeed, one has to wonder: Were these companies built to prosper, or were they built to be sold? A less widely disseminated statistic from NVCA's survey shows that the venture-backed M&A market, though slow, is still steadily churning out deals — 120 in the first half, which if taken as a run rate would put this year about 32 percent below a very active 2007. That's a big drop — hardly surprising in the current tight-credit climate — but certainly a lot better than approximately 88 percent decline in IPOs in the first half.

In fact, the NVCA data shows a pretty interesting picture going back over the past 17 years. In

1991, M&As accounted for just under 10 percent of venture-backed exit events. The vast majority were IPOs. By 2007, a pretty healthy year with 86 IPOs, M&As nevertheless accounted for 80 percent of the exit events. In the first half of 2008, M&As represent 96 percent of exit events. M&As have pretty steadily gained ground as the exit of choice over the past two decades.

Looking back at the IPO class of 2006-2007, at least in the life sciences, it's easy to conclude that VCs were building companies without independence or the long haul in mind. Even the companies that took the traditional IPO route skewed toward specialty pharma companies with little or no internal research capabilities, all competing with one another over scarce in-licensing opportunities.

Little wonder that companies like Jazz Pharmaceuticals, Cadence Pharmaceuticals, Novacea, and Vanda Pharmaceuticals have disappointed investors. It is notable that some of the most successful companies to follow this strategy — like Speedel, Pharmion and Aspreva — were acquired, which maybe was the better model all along.

Or look at the bloodbath that other members of the class of 2006 handed to investors: Achillion Pharmaceuticals, Artes Medical, Trubion Pharmaceuticals, Altus Pharmaceuticals, Northstar Neuroscience, Catalyst Pharmaceutical Partners, Replidyne and Threshold Pharmaceuticals. Many were victims of failed Hail Mary attempts to reach commercialization quickly with too little to fall back on.

How do investors value them now? Replidyne, as of March 31, 2008, had $78 million in cash and investments, no debt, yet a market cap of only $37 million. That's an enterprise value of negative $41 million. Investors see even this company's money in the bank as a bad risk, since in this environment it will be near impossible to replace after it's spent. Indeed, a similar situation with another lousy 2006 IPO, SGX Pharma, led to an opportunistic buyout by Eli Lilly and Co.

Even the most successful IPO of 2006, Acorda Therapeutics, was nevertheless an extremely risky company at its debut that, unlike the vast majority of its colleagues, had the dice roll its way. This doesn't exactly inspire investors.

But where do VCs point the finger? According to NVCA, 77 percent blame the current IPO drought on "skittish investors." This is a tautological explanation, like blaming high prices on the fact that things cost so much. Of course investors are skittish — just look at what's happened over the past three years! Sixty-four percent of VCs blame the credit crunch. And — I love this — 57 percent blame Sarbannes-Oxley. That implies companies simply don't want to go public because of onerous regulations, which does little to explain why so many companies have withdrawn IPOs due to adverse market conditions. Just 15 percent thought "poor IPO candidates" even ranked in the top three reasons for the IPO drought.

Wake up and read the stock charts. Yes, some of these companies will bounce back as the market turns. Yes, any group of IPOs is going to have its failures. But at the risk of getting downright crotchety, just look back a decade to the class of 1996, which included Affymetrix, Alexion, Cubist Pharmaceuticals, Millennium Pharmaceuticals, Neurocrine Biosciences, Onyx Pharmaceuticals, Transkaryotic Therapies (acquired by Shire for $1.6 billion in 2005), Sirna Therapeutics (originally Ribozyme, acquired by Merck for $1.1 billion in 2006) and many others. It's tough to imagine the recent crop of IPOs producing so many prominent names a decade hence.

The IPO drought will end, as it always does, and improvements in the banking industry will have a lot to do with the timing. But the most important ingredient for a healthy IPO market is vibrant companies that offer a long-term growth at a compelling risk-reward ratio. VCs looking to broker more than M&As should keep that in mind.

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How Biotech Can Make Even Cash Look Bad

CEOs who throw up their hands and wonder how the markets could put such low valuations on their companies should take note: Investors' memories are not that short. There's reason to think that some companies willing to let themselves be acquired near cash value did their shareholders a favor in the long run.

By Karl Thiel
BioWorld Today Columnist

Is your company on life support?

On Oct. 15, 2008, Eun Yang, an analyst with the investment bank Jeffries & Co., put out a report titled "Cash Is King: Where Biotech Stands." It consists primarily of what might be termed death-watch lists — charts tracking where more than 300 public biotech companies stand in terms of cash reserves, debt, burn rate and of course the product of those figures, time left until lights out.

It's not a terribly encouraging report. Out of 248 non-profitable biotechs examined, about half have less than a year's worth of cash remaining.

Needless to say, this isn't a great time to be on the prowl for capital. Stock prices are depressed, public markets aren't terribly interested in secondaries, and even private investors don't want to part with their cash.

About $3.2 billion was raised in 2008, as of November, in any form — secondaries, PIPEs, credit facilities. This is down about 62 percent from the prior year, according to Yang's data.

Yet one of the most interesting bits of information in the report is that 55 percent of public biotech companies with market caps under $200 million are trading beneath their cash value.

That might be expected to prick up the ears of savvy investors. After all, these are companies that theoretically could liquidate their assets and distribute a dividend higher than the stock price. In an industry like biotech, where so much value is wrapped up in intangible assets like patents, know-how and personnel, one hardly expects a company to be worth less than its cash in the bank.

But if you're wondering how we got to such a place, just remember that we've been here before . . . and not even all that long ago.

Look today at Vanda Pharmaceuticals, with $63 million in cash as of the end of the second quarter 2008, no debt and a market cap of $22 million. That sounds like a two-thirds-off sale on cash, right? Surely investors should pile in, knowing that the company must be worth at least its cash balance to an acquirer, even if all other assets are deemed worthless. It's free money, right?!

History would say, no. Why? Because it's a biotech company, and the management of most biotechs will never throw in the towel if they can help it. They're far more likely to throw good money after bad and slowly drive the company into the ground.

Vanda and companies in similar situations like QLT Inc., Adolor Corp., SuperGen Inc. and YM Biosciences Inc. follow in a grim tradition established earlier this century by one-time industry stalwarts such as Human Genome Sciences, Celera, Incyte and CuraGen Corp. Human Genome Sciences, for instance, trades at more than its cash value today, certainly. But those investors who saw it as worth less than its cash five years ago? They were absolutely right.

Let's step down memory lane, shall we?

Human Genome Sciences ended 2003 with cash and short-term, long-term and restricted investments of $1.29 billion, against $503 million in debt. In the five intervening years, total debt (long-term debt and its capital leases) climbed to $755 million. Its cash and investments — even granting the company full value of long-term and restricted assets that may be fairly illiquid — has sunk to $542.7 million. Book value was almost $7 per share at the end of 2003; now it is negative.

The company stock is near an all-time low (only a brief period in 1995 saw lower levels). Human Genome Sciences, it turns out, was worth less than its cash in 2003, because it just continued to spend. Those investments, in the eyes of the market, have produced little of value.

Celera, another company that once traded under its cash balance (shortly after trading at roughly the GDP of Iceland), had $802 million in cash and short-term investments in June 2003. As of June 2008, that was down to just $352 million. The stock price remains virtually unchanged since then, which means the enterprise value of Celera has actually risen substantially over the past half decade. It just hasn't done a thing for shareholders.

The company can at least brag that investors now see more in Celera than its declining book value. But you also can say that every dollar management has invested in the business over the past five years has produced zero return. It's hardly an argument that Celera at under cash levels was a bargain.

And those were big, well-capitalized companies. Other companies that went for less than their cash several years ago — CuraGen, for instance — still go for less than their cash value. It's just that there's a lot less cash now, so the stock price has declined steadily.

Or there's Caliper Life Sciences, which in 2003 angrily turned down repeated offers from Little Bear Capital to buy out the company for just under its cash balance, which was then at $154 million. In late 2008 Caliper had $10.6 million (with $14.9 million in debt from a credit facility due next year). Little Bear's February 2003 offer of $4.50 per share probably looks pretty sweet to Caliper investors now.

To be fair, there have been exceptions. Transkaryotic Technologies, acquired by Shire Pharmaceuticals in 2005 for $1.6 billion, turned out to be a fantastic bargain when it traded under cash value. Those bold enough to gamble on SGX Pharma earlier this year got a nice payoff when Lilly stepped in as a white knight to take over the distressed company. But as an investor, I find a lot more to fear in biotechs trading under cash value than I do to lick my chops over.

So CEOs who throw up their hands and wonder how the markets could put such low valuations on their companies should take note: Investors' memories are not that short. And though we can't know for sure, there's reason to think that some companies that were willing to let themselves be acquired near cash value — Corvas going to Dendreon or Genomica to Exelixis back in 2003, for instance — did their shareholders a favor in the long run.

Certainly we're going to be entering a tumultuous and interesting period in the industry.

Just as 2003 saw some mergers and acquisitions at fire sale prices, we're likely to see a new round of takeovers, desperate financings and outright failures. It's going to be disruptive. It's going to be upsetting. But it is probably going to strengthen some companies in the industry that can selectively shop for distressed assets. And that's a good thing.

Those companies on the short end of the stick, however, shouldn't expect their cash in the bank to prop up valuations.

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Investments in Biofuels Take Dive in 2007, Greentech Grows

"There's a higher profit potential, frankly, in industrial chemicals than in biofuels, but the biofuels are, of course, the big market that captures people's attention . . ." Draper Fisher Jurvetson Managing Director Steve Jurvetson told *BioWorld Today*. "Every consumer understands the price of gas."

By Amanda Lyle
BioWorld Perspectives Managing Editor

Investment in biofuels declined in 2007, but the market is growing rapidly.

In 2006, biofuels was the highest funded cleantech sector, receiving $462 million, according to the *MoneyTree Report* from PricewaterhouseCoopers and the National Venture Capital Association (NVCA). In 2007, however, several firms report that VC investment in biofuels dropped to about $295 million. The amount of VC investment is still an improvement, however, when compared to the less than $1 million in 2004 and $20.5 million in 2005 that went into biofuels. Most VC funding went to second-generation fuel technologies rather than ethanol, according to "Global Trends in Sustainable Energy Investment," a report prepared by New Energy Finance for the United Nations Environmental Programme (UNEP).

Combined private equity and VC investment in biofuels worldwide fell nearly one-third, to $2.1 billion in 2007 from $2.9 billion in 2006, according to the UNEP report. According to the report, much of the decline was due to the end of the push to build ethanol facilities. In addition, "private equity expansion capital investment in US biofuels did not dry up altogether, but its focus switched from ethanol to biodiesel."

"There's a higher profit potential, frankly, in industrial chemicals than in biofuels, but the biofuels are, of course, the big market that captures people's attention because we all can understand the size of those markets," Draper Fisher Jurvetson Managing Director Steve Jurvetson told *BioWorld Today*. "Every consumer understands the price of gas."

Interest Grows in Other Renewable Energy Fields

After the biofuels boom in 2006, much of the attention started to be showered upon other segments of renewable energy. In 2007, solar took the lead, receiving $600 million in investments. Wind energy came in with $115 million, a significant increase over $10 million the previous year. The pollution and recycling sector (including waste treatment) increased from $137 million in investment in 2006 to $203 million in 2007, according to the *MoneyTree Report*.

"A mixture of solar, wind, biofuels, conservation and a series of other technologies coming together as a package are going to be required" for the energy solution, Juan Enriquez, chairman and CEO of Boston-based Biotechonomy LLC, a life sciences research and investment firm that has invested in Synthetic Genomics Inc., told *BioWorld Today*. "But I think biofuels are a part of that package."

Venture capital investments in cleantech in 2007 jumped to $2.2 billion in the U.S., an increase of 45 percent over the previous year, according to the *MoneyTree Report*. In fact, the 7.4 percent of venture investment that cleantech captured in 2007 put the industrial/energy sector in fourth place among industry sectors (coming in behind software, biotech and medical devices). PWC and the NVCA call cleantech the fastest-growing VC investment sector.

Clean Edge puts the number even higher. According to the research firm, more than 9 percent of VC activity in the U.S. was in the clean-energy sector ($2.7 billion). This is an increase of more than 70 percent over 2006. In 2000, U.S. VC investments in energy technologies were just under $600 million.

Globally, the numbers are much higher. Funding for the sustainable energy sector was up 60 percent in 2007, to $148 billion globally, according to the UNEP report. Most of that investment went to Europe, followed by the U.S., China, India and Brazil.

"In a way the planet is really benefitting by the high oil prices we're suffering through day-to-day, by the fact that entrepreneurs everywhere have a huge price umbrella under which they can bring new products to market," said Jurvetson. "It's much easier to cost-justify a project when oil is at the current prices than when oil was where it was a couple years ago."

Firms Starting Green Funds, Stepping up Renewable Investments

Over the past five years, numerous firms have formed that invest only in greentech. In addition, the biggest investors are making renewable energy investments, if not forming clean energy funds of their own.

Vinod Khosla, founder of Santa Clara, Calif.-based Sun Microsystems Inc., founded Menlo Park, Calif.-based Khosla Ventures in 2004. At the beginning of 2007, the company's portfolio included cellulosic ethanol companies like Mascoma Corp., Coskata Inc., KiOR Inc. and Verenium Corp.; corn ethanol companies like AltraBiofuels Inc. and Cilion Inc.; and synthetic biology firms Gevo Inc., Amyris Biotechnologies Inc., Codon Devices Inc. and Draths Corp.

In April 2005, Bill Gates jumped into the biofuels business with a big commitment when Cascade Investment LLC, his venture fund, invested $84 million in Pacific Ethanol Inc.

Virgin Group, best known for airlines, phones and records, established the Virgin Green Fund to invest in companies working in renewable energy and resource efficiency. Its portfolio includes Gevo Inc., which is developing butanol, isobutanol and other advanced biofuels.

The Virgin Fuels investments include Cilion Inc., Ethanol Grain Processors LLC and Indiana Bio-Energy LLC.

Goldman Sachs & Co. became the first major Wall Street firm to make a commitment to cellulose ethanol in 2006, according to Iogen Corp. The New York-based firm invested C$30 million in Iogen's cellulose ethanol technology.

In May 2008, Kleiner Perkins Caufield & Byers (KPCB) announced the launch of the $500 million Green Growth Fund. The same day, the Menlo Park, Calif.-based venture capital firm announced the formation of the $700 million KPCB XIII, a fund that will invest in greentech, life sciences and information technology. KPCB got into greentech in 2002, when it formed the KPCB Greentech Innovation Network (GIN). Its goal is to form partnerships and build a map for the evaluation of technologies required for innovation in greentech.

The Future of Biofuels Investments

Despite the drop in investment funds, the biofuels industry is literally chugging away. According to the Renewable Fuels Association's *Ethanol Industry Outlook 2008*, bioethanol production increased 32 percent from 2006 to 2007 (4.9 billion gallons to 6.5 billion gallons). In addition, the number of U.S. biorefineries increased from 110 in 2006 to 139 in 2007. There were 34 biofuels deals in 2007, as compared to 22 the previous year, reports PWC and the NVCA. According to *Clean Energy Trends 2008*, it is estimated that more than 45 billion gallons of biofuels will be produced in 2017.

In looking to the future, it's best to go to the decision makers. That's just what the NVCA did in its

2008 Predictions Survey. Of the 170 VCs who responded to the survey, 80 percent said they believed the cleantech sector will continue to grow.

According to *Clean Energy Trends 2008*, the global biofuels market is set to grow from $25.4 billion in 2007 to $81.1 billion in 2017.

And while investment in biofuels were reported to be down last year, one thing is certain: The renewable energy field is here to stay. According to PWC's 11th Annual Global CEO Survey, 64 percent of CEOs are "concerned about rising energy costs" and 39 percent are "concerned about increased carbon emission regulations."

BioWorld predicts that VC investment in biofuels in the future will be concentrated on next-generation biofuels companies — companies developing biofuels from algae or through synthetic biology applications, as well as the more traditional cellulosic ethanol.

"There are perhaps a few venture capitalists who are investing in projects that would be looking at corn ethanol or things of this sort, but it's so patently obvious in retrospect that those are just broken and bankrupt ideas in many cases, in terms of long-term viability," said Jurvetson. "I think it's pretty well understood that those are not the way you want to go when there are much more reasonable feedstocks to look at, everything from waste to CO2 itself."

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chapter 3:

Perspectives: Insights on the Top Issues

Abigail Ruling Shows Feds More Concerned with Procedure than Progress

At what point does the biotech industry have an obligation to stand up and say that dying patients matter more than blindly following the rules?

By Greg Freeman
BioWorld Contributing Writer

If the biotech industry had any doubt that the federal government is more concerned with following a complex array of rules and procedures than with actually advancing medical improvements — and really, did anyone in the industry think otherwise? — the recent ruling by the D.C. Court of Appeals proves that dying patients are only a minor concern when there is still a government form to be filled out.

The D.C. Court of Appeals recently reversed an earlier decision by its own three-judge panel and ruled 8-2 against allowing dying patients to take potentially life-saving drugs that have not yet been approved by the FDA. The case had been filed in 2003 by the Abigail Alliance for Better Access to Developmental Drugs, along with the Washington Legal Foundation. The Abigail Alliance is named for Abigail Burroughs, a 21-year-old college student who died of cancer in 2001 after being denied access to Erbitux, the then investigational drug from ImClone Systems Inc. that early trials indicated might have helped her.

Over the past five years, the alliance has pushed for access to 12 drugs that had cleared at least Phase I testing. Some had completed Phase II or Phase III testing and were considered extremely promising. All of them have been subsequently approved by the FDA, and patients benefit from them every day. The patients who died before the FDA approval also could have benefited, if only the government had allowed tightly controlled access before full approval.

Gleevec is perhaps the best example of how bureaucracy trumps compassion. After Phase I testing in 1998, the medical community considered the drug to be safe and effective, so the alliance requested access for patients with chronic myelogenous leukemia in June 2001. The FDA said no, and by the time the Novartis AG drug was fully approved in 2002, about 3,600 patients had been denied access. Many of them died while waiting for their last best hope to get the government stamp of approval. The Abigail Alliance estimates that 1 million people may have died prematurely in recent years because the government denied them access to cancer drugs. The list of denied drugs is long: Eloxatin (Sanofi-Aventis), Erbitux, Revlimid (Celgene Corp.), Nexavar (Onyx Pharmaceuticals Inc., Bayer Pharmaceuticals Corp.), and on and on.

It's easy for professionals working every day in the biotech industry to get swept up in the "normalcy" of a system that is fundamentally wrong when applied to some desperate individuals. The biotech manufacturers are not at fault here, or at least they didn't come up with the system that gets in the way of people getting the help they need. Manufacturers and researchers are only playing by the very strict and complex rules imposed upon them by the FDA. When that bureaucracy is imposed on you and your work, you have no choice but to play along if you want to eventually have your drugs approved. The system becomes the norm, the way things are done.

But at what point does the industry have an obligation to stand up and say that dying patients matter more than blindly following the rules? Perhaps that time has come, now that the D.C. Court of Appeals ruling indicates there is little hope the

feds are going to alter their bureaucratic requirements on their own. The industry clearly has not done enough to advocate for its true end users, sick and dying Americans.

Caution vs. Paralysis

To be sure, the biotech industry has its own interests to protect here. No one wants to be the one who is a voice so counter to the norm that future relationships with the FDA are jeopardized, and handing out unapproved drugs with little control would be reckless — both for the safety of patients and for the financial security of the company. Fear of lawsuits and the possibility that a poor outcome could jeopardize the future of a drug that otherwise might have received FDA approval are valid concerns. With millions and years invested, manufacturers and researchers are entirely justified in being cautious.

But there is a difference between caution and paralysis. The feds can't find the distinction, but private enterprise should be able to exert more common sense and find the point at which patients with no other hope for recovery can be granted access to drugs that have shown promise in early trials.

Industry leaders should stand side-by-side with the Abigail Alliance and others advocating for a more compassionate, reasonable system that doesn't leave dying patients waiting for bureaucrats to satisfy themselves that all formalities have been met before releasing a medication that everyone knows is safe and effective. After all, we're talking about life-saving drugs here, not a new cure for baldness. If the potential benefit is negligible, then it can make sense to follow all possible protocols to make sure there is no harm. When the patient is already dying, how can that insistence on perfection be seen as anything but callous and cruel?

Biotech leaders should make sure they're standing on the humanitarian side of this life and death issue. No matter how much it can feel otherwise when dealing with the bureaucracy day in and day out, these business leaders should not forget that they're supposed to be serving sick Americans, not the FDA.

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This Century's First Civil Rights Bill: The Privatization of Personalized Medicine

The Genetic Information Nondiscrimination Act is a good start to giving Americans access to the maximum benefits that personalized medicine has to offer today.

By Ilene Schneider
BioWorld Contributing Writer

Thanks to a new law, no American will have to fear the insurance and employment consequences of undergoing genetic tests. Specifically, no one will have to choose between obtaining health information and being employed or insured.

After 13 years of debate, the Genetic Information Nondiscrimination Act (GINA) finally became a federal law in May 2008. The law defines "genetic information" as an individual's own genetic tests, the genetic tests of family members, and the manifestation of a disease or disorder in family members.

GINA makes it illegal for health insurers to deny coverage or charge a higher rate or premium to an otherwise healthy individual found to have a potential genetic condition or genetic predisposition toward a disease or disorder. GINA also makes it illegal for employers to use an employee's genetic information when making hiring, firing, placement or promotion decisions. Employers who violate the new law could be fined as much as $300,000 per incident. The group health insurance provisions will take effect in May 2009, and provisions that involve employment will take effect in November 2009.

GINA: Opposition and Accolades

Some GINA opponents said that the legislation was "a solution in search of a problem," because there is little evidence of actual employment discrimination on the basis of genetic information. In addition, they added that there have been few, if any, actions brought against employers in the 34 states that currently have laws banning genetic discrimination in the workplace. Critics argued that the law would expose employers to "frivolous" civil rights lawsuits regarding disputes over medical coverage and believe that GINA's confidentiality rules place too many recordkeeping requirements on employers. The U.S. Chamber of Commerce opposed the final version of the bill, claiming that the fines were too high and that limitations on collection of medical information on patients would hinder some medical practices.

Still, GINA appears to provide a winning combination of protecting the rights of employees and consumers while fostering good science and medicine. It promotes advances in biotechnology and health care, while providing a safe avenue for people to play a role in the clinical trials that enable the discovery and cure of genetic diseases. By so doing, it can ultimately save lives and even dollars.

GINA is the first major new civil rights bill of the new century, Sen. Edward Kennedy (D-Mass.), a cosponsor of GINA in the Senate, said in a press release. While some related federal and state laws existed before GINA, the new law will strengthen those safeguards by limiting insurers' ability to use genetic information to raise rates for an entire group, by extending protections to individual health insurance plans, and by establishing a nationwide level of protection.

"This bill unlocks the great promise of the Human Genome Project by alleviating the most common fear about genetic testing," Rep. Judy Biggert (R-Ill.), who cosponsored GINA in the House with its leading proponent, Rep. Louise Slaughter (D-N.Y.), said in a press release. "It will accelerate

research . . . and allow Americans to finally realize the benefits and health care savings offered by gene-based medicine."

Genetic Testing and the Promise of Personalized Medicine

When the first attempt at federal legislation to prevent the misuse of genetic information was introduced in 1995, only about 300 genetic tests were available. Most were for rare diseases and were usually performed in research settings. With the mapping of the human genome and the rapid discovery of genetic variants that contribute to risk of common diseases such as breast cancer, colon cancer, diabetes, heart disease and depression, the number of people who might benefit from learning what risks lurk in their genes is growing exponentially.

Today, genetic testing exists for more than 1,200 conditions. Some tests can be performed in the clinic, and individuals soon can take advantage of the promise of personalized medicine, knowing that they will not have to worry about discrimination if genetic markers — the indicators of risk for genetic disease — are found. Genetic tests can help diagnose genetic conditions and guide treatment decisions, help predict the risk of future disease, enable reproductive decision-making, and facilitate medication selection or dosing.

Benefits and Elimination of the 'Fear Factor'

Those who choose not to be tested will lose the opportunity to seek monitoring and preventive care to avoid conditions for which they are at heightened risk. On the other hand, an increase in genetic testing makes it more likely that researchers will come up with early, lifesaving therapies for a wide range of diseases with hereditary links. Genetic testing will help doctors catch problems early, perhaps leading to preventive treatment and lower lifetime costs. There also could be cost savings for health insurers (who must pay more to treat conditions that are not prevented or caught early) and employers (who bear the economic costs if employees require more sick days and medical leave).

By eliminating the "fear factor," GINA should benefit genetic research as well as individuals. Now that the bill has been signed into law, patients will be more likely to participate in research studies that involve the collection of genetic information. Scientists can assure clinical trial participants that neither their participation in a research study nor their genetic information legally can be used against them by their employers or health insurers. As scientists make advances in genetic research and technology, clinicians will be able to begin customizing treatments according to an individual's genetic profile. All of the above will have positive effects on the fields of biotechnology, clinical research and health care delivery.

A Good Start in a Long List of Legislation

What lies ahead for GINA, to make sure it properly serves Americans? According to the article "Keeping Pace with the Times — The Genetic Information Nondiscrimination Act of 2008" in the *New England Journal of Medicine*, federal agencies must write the implementing regulations that will provide the detailed guidance for health insurers and employers about how to comply with the new law. Health care professionals and patients need to understand the new protections, and clinical researchers, research administrators, institutional review boards and research participants must understand the new law and its implications. Genetic tests must be safe, reliable and marketed in a clear and truthful manner. Finally, we need to analyze the other areas of society that potentially involve genetic information, including life , disability and long-term care insurance.

Clearly, GINA is a good start for Americans to gain access to the maximum benefits that personalized medicine has to offer today, so long as the proper regulations and safeguards can be provided. As new opportunities in science present themselves, new legislation may be needed to take the potential of biotechnology a quantum leap further. Next time, let's hope Congress can do it in less than 13 years.

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Pharma: Seven Steps To 2020

The choices for pharma companies are two: Change now and control your destiny, or pursue business as usual and allow your fate to be controlled by others. Executives and board members at pharmaceutical companies need to ask themselves: Which path will we take?

By Simon Friend
BioWorld Contributing Writer

The global pharmaceutical industry is facing an unprecedented opportunity. Over the next decade, the market for pharmaceutical products will nearly double in size, reaching $1.3 trillion by 2020 to meet the medical needs of the aging global population and a surge in demand from emerging countries. Yet some pharma companies will never capture a share of this enormous market because they continue to bank the future of their business on a model that will no longer exist.

Anticipating and adapting to the changing dynamics in health care is the great challenge for the pharmaceutical industry. It is becoming abundantly clear that maintaining the current course is no longer an option. Pharmaceutical companies are fast approaching a fork in the road, and they must choose a path: Will they focus on innovation and offer value in the form of more targeted drugs, with proven outcomes and a suite of value-added services around them? Or will they go after the commoditized mass market, driving revenue with volume?

Along the way, there will be winners and there will be losers. The winners will be those who have the courage to pick the right path and begin making changes in their business models now.

Here are seven major steps that PricewaterhouseCoopers LLP believes that pharma companies can take in the years leading up to 2020.

Look Beyond the Blockbuster Model

The sales model of placing big bets on a handful of heavily marketed breakthrough products has become far less effective, due to rising product development costs, more demanding regulatory reviews and growing dependence on massive sales forces.

Technology changes and consumer demands for more specialized medicines will force pharma companies to reduce their reliance on mass market blockbuster drugs by developing products in new therapeutic areas and creating more personalized solutions. They also must look to smaller, smarter and less-costly sales teams that do not simply sell pills, but also generate revenue by selling related, added-value services.

Increase R&D Productivity

Scientific breakthroughs in pharmaceuticals are harder to come by, with much of the low-hanging fruit having been picked. The regulatory approval process also has become more demanding. Consequently, the cost of research and development continues to soar.

Pharma leaders must rethink how the industry approaches R&D. Research must be guided by medical requirements rather than sales potential: Instead of copycat medicines, pharma companies need to address unmet clinical needs.

Pharmaceutical companies also need to expand their pool of basic research sources beyond academic centers and niche biotech companies. In particular, they can draw upon the emerging talent in Asia, either by establishing a much stronger footprint in Asia or forging close links with leading centers of scientific excellence in the area.

Finally, researchers frequently narrow their focus early in a product's life, which often leads them on

the wrong track. They need to focus more on the big picture, understanding a disease's pathophysiology, before making decisions about a full program of experimentation.

Focus on Prevention, Not Just Treatment

Pharma companies historically have focused on the development of treatments for disease, but it is far less expensive to prevent illness than to cure it. As consumer-directed health care and cost control grow in importance, pharma companies should increase their focus on the prevention of disease through expanded vaccination and medicines with preventive properties. Companies may be forced by payers, patients and other key stakeholders to actively pursue this strategy as societal changes influence the world of health care.

Since failure to take prescribed products as directed is a leading cause of illness, pharma companies need to expand their work in patient compliance by developing personalized monitoring technologies and techniques to ensure that patients take their medicine as directed, improving both results and safety while creating a market with the potential for $30 billion in additional annual sales.

Make the Regulatory Process More Flexible

The current all-or-nothing regulatory process means that most new projects are an enormous gamble for pharma companies: They may spend hundreds of millions of dollars developing products that are never approved for sale. Instead, the industry needs to work with regulators to advance a more progressive system of in-life testing and "live licenses," using greater collaboration and data-sharing between pharma companies and regulators. These licenses will allow a drug's approved uses and distribution to expand over time, based on its performance in extended trials.

Moreover, as international markets become more important, the industry needs to encourage U.S. regulators to work more closely with their peers in establishing a truly global regulatory process that can reduce redundant processes, move products to market faster and reduce compliance costs.

Personalize the Distribution Chain

Increasingly sophisticated direct-to-consumer distribution channels are emerging. The development of new technologies enables automated dispensing of medicines direct to consumers. More primary-care medication prescriptions will be fulfilled automatically, with doctors writing prescriptions, checking insurance criteria and sending the prescription to online pharmacies. Using web-based biometric devices, pharmacies will be able to check patient identity and ship the medication to their homes overnight.

With increased direct-to-consumer distribution, the use of wholesalers likely will decrease. Pharma companies will be able to distribute products without middlemen, creating closer relationships, enabling the sale of additional services and a source of competitive differentiation. This possibility opens new opportunities for wholesalers around data management and prescription compliance services.

Go Global

The worldwide pharmaceutical market will more than double by 2020, but much of the growth will come from outside North America and Europe. The so-called "E7" emerging economies — Brazil, China, India, Indonesia, Mexico, Russia and Turkey — could generate up to a fifth of global pharmaceutical sales by 2020, up by 60 percent from 2004. As these countries become more prosperous, their people will adopt Western health profiles, eating richer foods, working sedentary jobs, and driving instead of walking or bicycling.

Pharma companies need to enter these markets aggressively, but they need to do so intelligently. Not only do they need to establish culturally sensitive local sales and distribution infrastructures, but

they also need to tailor therapies to respond to variations in the nature and incidence of disease that can be caused by differences in ethnic origin, diet and environmental factors.

Choose a Path

The enormous costs of producing and distributing innovative medicines mean that the pharma industry increasingly will split into one of two models. Some companies will become niche players, developing fewer, more targeted new drugs; others will go the generic route, focusing on volume, with sales of mass-produced drugs generating revenue.

Companies can succeed either way, but will have to choose which model they will pursue, forming strategic partnerships with other pharma companies, biotech firms or other industry players to fill in gaps. Those that choose to participate with the other health care players will stand an increased chance of success, as the demand-driven model of societal needs and expectations begins to take a grip on the future health care agenda.

* * *

If pharmaceutical companies undertake these steps, they will be better positioned to manage the seismic shifts that not only pharma but all of the health industries will undergo by 2020. The changes will enable them to benefit from the opportunities that will emerge from globalization, new technologies and new business models.

Although these changes need to be implemented over a period of years, companies must start now. Changes in the traditional ways of making and selling medicines could upend the entire industry, resulting in impacts very different from the mergers and acquisitions that occurred a few years ago. Rather than taking the customary approach of fully integrating an acquisition, a buyer could break it up, retaining some assets and selling the rest. For example, private equity firms, which have reshaped other industries, are gaining the buying power to enter the pharma sector.

The choices for pharma companies are two: Change now and control your destiny, or pursue business as usual and allow your fate to be controlled by others. Executives and board members at pharmaceutical companies need to ask themselves: Which path will we take?

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Immigration, Education and Respect for Science: Where Is the Biotechnology Community?

When our industry, which has brought untold benefits to humanity, is attacked as corrupt and greedy, or even as a conspiracy to poison people in poor countries, too many people believe it.

By Charles Hsu
BioWorld Contributing Writer

Most of us in the business world are used to keeping our heads down where politics are concerned. Our lobbies carefully sprinkle their enticements around in a relatively bipartisan way. We only make noise about matters we perceive as being of immediate consequence to us. In the case of the biotechnology community, the topics that make the cut are limited to arcane matters such as Small Business Administration funding thresholds, capital gains tax treatment and stock option expensing. How many people outside our industry even know such issues exist? Not many, and we seem to like it that way.

Meanwhile, there are bigger social and political debates that also affect us profoundly, though we seem content to pretend otherwise. However, if we go on pretending, we will do the next generation of biotech entrepreneurs two major disservices: We will bequeath them the consequences of our inaction on the big topics, and we will hobble their ability to win on even the narrow, more technical debates. Now, one might ask: Why are these two problems linked?

Looking Like a 'Special Interest' in the Worst Sense

One obvious reason is that when we ignore the big themes that most people care about, we don't build any broad political capital. When we show up later, demanding special treatment on some obscure matter of accounting or securities law, we look like a "special interest" in the worst sense of the word. Contrary to the routine assumption that taking on bigger issues is risking our political standing, it may be that NOT taking on those issues relegates us to nuisance status. We then end up letting the wrong people define the terms of debate, on matters both large and small. So let's be honest: It isn't working for us. Look at what has happened with stock option expensing (a failure for which we share culpability with the National Venture Capital Association and the IT community). By denying there was a problem to be solved, we ended up with the worst of several possible "solutions."

Assuming that most of us are motivated at least in part by self-interest, the heart of the problem is that we define self-interest too narrowly. Unfortunately, the public notices. So when our industry, which has brought untold benefits to humanity, is attacked as corrupt and greedy, or even as a conspiracy to poison people in poor countries, too many people believe it. Sending a talking head to debunk *The Constant Gardener* on CNN is too little, too late. We will only forestall such blatantly dishonest attacks by showing people that we actually care about issues beyond this quarter's bottom line. And, in the long run, caring is good for our business.

The question is whether we have the courage and foresight to stand up and insist on an honest debate about some of the larger forces threatening the future of our enterprise. We all know what some of these forces are: America's retreat from science, our growing xenophobia and the gutting of our educational system. Too daunting? Well, when have the big issues been easy?

Education and Immigration

To start with the hardest one: What can be done to reverse Americans' abandonment of science?

American kids are opting out of science at every stage in school, and the percentage of American college students choosing science majors has declined monotonically for the past 30 years. The most immediate concern is that recruiting for our companies has become daunting. There are not enough homegrown talents to populate the companies we start. Perhaps more important, in the long run, support for our enterprise is jeopardized as fewer and fewer voters are scientifically literate.

The recruiting problem brings us right up against the second threat: the backlash against immigrants. We survive, and thrive, on the influx of foreign students and graduates eager to apply themselves. With more than half of California's graduate-degreed biotechnology employees being non-U.S.-born (other regions are approaching these numbers) and with the aforementioned shortage of homegrown talent, we are extremely vulnerable to even short declines in immigration, and we're blind if we don't realize it.

Policies (such as the H-1B visa) that favor people with special skills have barely made a dent in the problem. Whether the H-1B is even a constructive solution is not clear; it certainly ignores the reality that it is not just the skilled who are needed here. In the Bay Area, as in many other booming technology centers, unskilled immigrants play an essential role in keeping the local economy functional and affordable, allowing young scientists to work for modest wages in the hope of a future payoff. What is going to happen if a third of these people have to leave, even under the "touchback" policies currently being debated in Washington? As for the skilled, they are being scared off by the widespread global coverage of America's broad and bipartisan embrace of xenophobia. If you don't believe that, spend a week in China or India and ask the young scientists there how they feel today about coming to America.

The recent, panicked movement in Washington to resolve the immigration issue produced congressional bills that everyone admits were deeply flawed, but at least they were a start. Those bills have died an ugly death because the voices of hysteria drowned out the voices of reason. Throughout this process, our industry was invisible. We are letting the wrong people, both on the left and the right, set policy that is indisputably critical to our future. Shouldn't we as a community break our silence and take a stand in favor of enlightened immigration policy? We might make some enemies in doing so, but is that really too high a price to pay for doing the right thing, for ourselves and for our national competitiveness? Besides, who will hate us for it? The same people who already hate us for doing stem cell research? What's to lose? If we, with all our education and awareness, don't lead, who will?

Science Getting Less and Less Cool

Immigration is a tough equation to solve. Reversing a cultural trend like loss of interest in science is tougher. We don't want to emulate Singapore — where government policy forces people into fields deemed strategic; it is against our notion of free choice to do that. However, we are doing worse than nothing! Knowledge industries thrive on a foundation of intellectual inquiry and scientific rigor. How is that foundation being affected by the attempts of religious fundamentalists to undermine it, and by the open rejection of science by our president and many of the leading candidates to succeed him? How can we remain competitive with developing countries that are teaching real science in their schools? Why is our industry silent?

There have been calls by science educators, scientists and even some politicians, like Al Gore, for a PR program to convince young people that science is cool. Oh boy! We can only hope they are not serious. Does anyone really think our target audience is that easily manipulated? They can see for themselves the standing of scientists and technologists in society. That standing is low and eroding. Despite the huge fortunes made by some high-profile Silicon Valley entrepreneurs, science is getting less and less cool. Why not? Our leaders

have shown the most profound disrespect for science, and kids learn by example.

It would be nice to appear nonpartisan at all times, but unfortunately, on this issue, there is clearly one party which is complicit in the war on science education. For this writer — a registered member of that party — the alliance with religious conservatives for the sake of winning votes is a cynical and Faustian bargain. Isn't it time we challenge our leaders to stand up to the forces of ignorance? Do we need those votes so badly that we willingly trash American leadership in science and technology as part of the bargain?

Everyone in our industry owes his or her livelihood to the principles of open-minded inquiry that defined the Enlightenment. It seems unthinkable to stand cynically by and let those principles be dismissed as "just another belief system," and an "immoral" one at that. Yet, that is what we have done. Why, other than fear or greed, is there anyone in BIO or PhRMA who is not withholding his or her votes and money from politicians who reject the Enlightenment? Why have Sens. Sam Brownback (R-Kan.) and Jim Inhofe (R-Okla.) and former senator Rick Santorum, among others, received a penny of our money? They hate everything that makes our industry possible!

Unprecedented Hostility to Science

Unfortunately, our leaders' disrespect for science extends beyond the classroom. The administration's unprecedented hostility to science-based policy-making, from stem cells to the environment, is not only dangerous, it has been deeply demoralizing to the scientific community on whom we rely for direction on such matters. It further contributes to the disdain our young people have for careers in science and technology and has explicitly frightened off talented young scientists in other countries who might have come here to work. Even on an issue as obvious as stem cell research, which is OUR issue, we have been shamefully timid, leaving a vacuum that state initiatives like California's cannot properly fill. Surely we can do better — if not through BIO, then as individuals — through our campaign contributions and our voices.

Public Education — Not Someone Else's Problem

Finally, regarding the crisis in public education: Our leaders are guilty of under-funding, and in fact actively undermining, our public school system. This is a bipartisan failing at all levels from Capitol Hill to the small town. We are caught between the radical public school de-funding lobby on the right, and the teachers' unions on the left, who are manning the barricades to protect job security at the expense of quality. The National Venture Capital Association has, at long last, undertaken a project (MAGNET USA, Maximizing America's Growth for the Nation's Entrepreneurs and Technologists), which addresses, in part, this issue. Yet it is far too little, and too incremental. Meanwhile, our industry has punted.

Broad public education is essential to the ecosystem in which our industries thrive. Is there anyone who sincerely disputes that? Along with immigration, mass education was the fuel that gave this country uncontested scientific supremacy in the late 20th century. It is now the basis on which developing nations like India and China are rapidly overtaking us. If our schools remain unable to pick up the slack, we are going to see our preeminence in knowledge industries evaporate. It has already happened in areas such as computers and pharmaceutical chemistry. We should be demanding enormous increases in public education spending, in exchange for concessions from the teachers' unions on issues like tenure (make them earn it), credentialing (end their monopoly on the process) and merit pay (long overdue). This requires confronting the partisans on both sides of the so-called "debate."

We in the biotech industry tend to view education as someone else's problem. It should be obvious how self-destructive that is. Tax policies impact how much we keep of today's harvest, but if we

don't pay attention to planting for the next season, what will there be to harvest then? Our compatriots at IT companies like Hewlett-Packard recognize this and are making huge investments in public education and training in the information sciences. What does HP see that we don't?

Where the Danger Lies

These are all issues on which it behooves our community, individually and collectively, to take an active stance. In some cases, it would seem we must risk our political neutrality. Would that really be so unprecedented? Besides, we might actually gain standing with groups that have never paid us any attention before. Over the years, we have vigorously rebutted such critics and enemies as the animal-rights terrorists and the corporate conspiracy theorists, but let's face it, their impact is marginal at best. In other words, PETA may be a little nutty, but it also is irrelevant. We have to be honest about where the danger lies today.

We are not shy about taking on the political establishment over issues that look purely instrumental, such as tax and regulatory policy. Our mistake now would be to think that matters such as education, science-based policy and immigration are somehow less instrumental, and thus not worth the same investment of political capital. Mark these words: If our community defaults on those larger issues, then in the future we may not receive, and certainly won't deserve, any further consideration when it comes to taxes and regulation.

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Biotechnology in Africa: Why the Controversy?

What Africa needs most at this time of intense European-American debate on developments and use of GIOs is the creation of widespread public and policymaker awareness and education on all facets of biotechnology and biosafety.

By Elseborn Mwangi
BioWorld Contributing Writer

This is a time of intense discussions about Africa's agricultural and economic performance, and the potential impact of biotechnology on the economy and the welfare of the continent. The two issues dominating the debate are the persistent poor performance of agriculture with associated widespread poverty, and the ability of biotechnology to resolve Africa's food crisis (taking into account its potential and perceived effects on the continent's enormous biological diversity).

Socioeconomics Set the Scene

Thirty years ago, Africa's population was about 200 million. Today it is 520 million, and it is projected to increase to 1.3 billion in the next 25 years. The continent has the highest population growth rate in the world.

Subsequently, the situation may not necessarily be one of food scarcity but rather the scarcity of income or purchasing power. Millions of people in Africa live on less than US$1 per day.

Agriculture Is at the Heart of Challenges (and Solutions)

Most people in Africa earn their living by producing food. Employment and income earning opportunities are closely linked to productive agriculture.

Africa faces a number of agricultural challenges, such as a shortage of arable land, inadequate rainfall, soil fertility, pests and diseases. In addition, Africa lacks a technological base whereby new intensive production techniques can be developed. These are needed to augment yields and reduce losses while conserving the natural resources base.

Beginnings of Biotech in Africa

The debate on biotechnology in Africa must be considered within the context of the continent's need for more food and the survival of its people. Biotechnology-derived solutions for biotic and abiotic stresses, if built into genotypes of plants and animals, could reduce the need for, and the high cost of, agrochemicals and water. New solutions also could reduce the deleterious effects of diseases and weeds, thus promoting sustainable agriculture production in Africa. Several countries, especially South Africa, Kenya, Zimbabwe and Egypt, are putting in place structures and capacities for biotech R&D. Improvements in productivity are beginning to emerge from the applications of conventional and modern biotechnology.

For example, to address the problems of soil fertility and fertilizer application, a number of countries have started to use Rhizobium inoculant in the production of grain legumes. In several countries it is now commonplace to apply tissue culture to address farmers' availability constraints of adequate disease-free planting materials and rapid improvement in crop production.

In Kenya, for example, tissue culture technology has been initiated in different crops and has resulted in increased production of banana, pyrethrum, potato, cassava, sugar cane and flowers, most of which have become commercial enterprises. The demand for such materials is demonstrably high,

and the changes in the household income levels of growers are becoming increasingly noticeable.

The use of DNA-based molecular markets is now applied in various forms to construct linkage maps of different species. This helps locate particular genes of relevance to the rapid improvement of crop and livestock breeding. Mapped markets are useful in speeding up the selection of traits for use in conventional cross-breeding procedures. These techniques are applicable to many African crop improvement programs such as those seeking to enhance disease resistance.

Biotech's Challenges in Africa

Although there are many initiatives that create the structures and mechanisms necessary for the development of biotechnology in Africa, major differences exist between countries in relation to the level of application.

Countries face challenges in making decisions about what their level of involvement in biotech should be. These challenges include:

- the development of a knowledge base appropriate to decision-making in the use of biotechnological approaches;
- priority setting for biotechnology aimed at solving specific problems of national importance;
- the establishment of policy and regulatory structures for biosafety and intellectual property protection;
- capacity development for enhancement of the above issues; and
- establishment of cooperative mechanisms for biotech development, its transfer, and sustainable applications in Africa.

Why the Controversy?

There is overwhelming evidence that the needs and drive for biotechnology in Africa are quite different from those of industrial countries. Africa's agenda is based on the urgent need for technology to enhance food production and to alter the course of widespread poverty, hunger and starvation. Industrial countries, on the other hand, are driven by market and profit. These distinctions must be understood and appreciated at the national, regional and global levels.

The ongoing debate about biotech in Africa has created fear, mistrust and general confusion to the public. It also has failed to seek the views of African policymakers and stakeholders. The debate about biotechnology for Africa should not be whether or not the continent needs biotechnology, but how biotechnology can be promoted, supported and applied in safe and sustainable ways that contribute to improved agriculture and to the social and economic welfare of the people of Africa. The need for biotechnology in Africa is very clear, and should not be confused with the marketing/food surplus-driven forces of the industrial countries.

Collective Considerations for Biotech

Many countries in Africa face severe reductions in agricultural research funding. Because most biotech R&D is more expensive than conventional research, it should be focused on solving priority national or regional problems where it has a comparative advantage. This means that African countries must develop appropriate policies for biotechnology, and mount efforts to identify key national priorities for biotechnology, bearing in mind the needs of the resource-poor who depend on agriculture for their livelihood. This approach should take into account national development policies, private sector interests, market possibilities, technology diffusion mechanisms and linkages.

The question today should not be whether or not Africa requires biotechnology, but rather how countries in Africa can be assisted in harnessing and safely applying biotechnology to support development. Egypt, Kenya, South Africa, Zimbabwe, Botswana, Malawi, Mauritius, Cameroon and Zambia either have, or are in the process of adopting, explicit biosafety regulations

and guidelines, and some are involved in negotiations for an international biosafety protocol. Biosafety frameworks should be accommodative and promotional, rather than prohibitive, advocating the establishment of adequate and sound biosafety regulations, risk assessment and management regimes, and instruments for monitoring use compliance.

African countries face a compelling need to develop long-term policies on biotechnology that:

- promote national biotechnology needs assessment and targeted research;
- provide incentives for the creation and financing of local private biotechnology enterprises;
- promote local public R&D of foreign industry partnerships; and
- improve and enhance scientific capacities and technology risk management into existing environmental, health and agricultural regimes.

Biotechnology R&D in Africa is presently focused on improving agriculture, with only very few initiatives targeting the ecological impact of genetically improved organism (GIO) development. The greatest effort is still focused on tissue culture application. The private sector is dominant in biotechnology development in industrial counties, but in Africa more than 85 percent of biotechnology R&D in the region is in the public sector, with universities and agricultural research institutions taking on most of the responsibilities. Except for South Africa, local private sector engagement in biotechnology is limited.

What Africa needs most at this time of intense European-American debate on developments and use of GIOs is the creation of widespread public and policymaker awareness and education on all facets of biotechnology and biosafety. This will enable the countries to make judicious decisions on the path to biotechnology use.

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chapter 4:

From the Bench: Scientific Breakthroughs and Market Impact

New Mechanisms of Action Promising for Type II Diabetes

While the market opportunity is "huge" for firms developing drugs to treat Type II diabetes, the problems that have arisen with glitazones and Byetta have created a hypersensitive environment,

By Donna Young
BioWorld Today Washington Editor

One of the greatest strains on the nation's financial stability is the increasing cost of health care. And in recent years, the focus has centered on the burden of obesity-related diseases, such as Type II diabetes, which has been described by the Centers for Disease Control and Prevention as "a growing epidemic."

About 24 million people in the U.S. have diabetes and about 90 percent have Type II, according to the American Diabetes Association (ADA). Another 57 million Americans have prediabetes — a condition in which blood glucose levels are higher than normal but not yet high enough to be diagnosed as diabetes. Diabetes cost the nation $174 billion in 2007, according to ADA.

Even during election season, the U.S. presidential candidates talked about the financial burden to the nation caused by obesity-related diseases and the personal responsibility of Americans to decrease those costs, said analyst Jason Kolbert, of Susquehanna Financial Group LLLP.

The reality of that burden, he said, makes it even more evident that new therapeutics urgently are needed to treat Type II diabetes, a condition in which the body either does not produce enough insulin or the cells ignore the insulin.

The traditional idea of replacing insulin in the body, Kolbert said, "is now really a last resort to treating diabetes."

Newer therapies are looking at the disease from various aspects, from the malfunction of insulin cells in the pancreas and their inability to secrete insulin to the way the body uses insulin, he said.

A decade ago, the hope for treating Type II diabetes centered on thiazolidinediones, also called glitazones, which act through the activation of a nuclear hormone receptor known as peroxisome proliferator-activated receptors (PPAR) gamma.

But not long after the drugs were introduced onto the market, patients began reporting adverse reactions, specifically with Parke-Davis/Warner-Lambert's Rezulin (troglitazone), which was found to be highly toxic to the liver, Kolbert noted.

That drug was withdrawn from the market in March 2000.

The FDA in 2007 called for black-box warnings on the other approved glitazones — Actos (pioglitazone, Takeda Pharmaceutical Co. Ltd.) and Avandia (rosiglitazone, GlaxoSmithKline plc) — alerting that the drugs may cause or exacerbate heart failure. The labeling for Avandia was revised again later to warn about an increased risk of myocardial ischemia.

Now under scrutiny are the glucagon-like peptide-1 diabetes drugs, such as Amylin Pharmaceutical Inc.'s Byetta (exenatide). The FDA has received at least six reports of deaths from acute pancreatitis in patients taking Byetta.

While the market opportunity is "huge" for firms developing drugs to treat Type II diabetes, the problems that have arisen with glitazones and Byetta have created a hypersensitive environment, resulting in the clinical burden being set much higher for new therapies, Kolbert said.

Moving forward, he said, the drugs must have good safety track records and demonstrate that they create no additional problems when they are combined with other therapeutics, given that multiple agents are used to treat Type II diabetes. And with the costs to develop newer drugs expected to rise sharply due to the FDA now calling for larger clinical trials of longer duration, early stage firms will be more reliant on big pharma to get their products to market, Kolbert said.

Nonetheless, he added, there currently is a "scientific renaissance" taking place in diabetes treatment discovery, with many early stage companies now focused on the underlying nature of the disease as an inflammatory condition.

XOMA's IL-1 Beta Approach

One such firm, Berkeley, Calif.-based XOMA Ltd., has focused its efforts on the role that the interleukin-1 (IL-1) pathway plays in diabetes progression.

Much of the damage done in patients with Type II diabetes is done by the death of islet cells — the cells that make insulin in the pancreas — secondary to the elevation of blood glucose, explained Alan Solinger, XOMA's vice president of clinical immunology.

"Originally, it was thought this was all damage directly from the high glucose, but they found out recently that the high glucose levels present in diabetics actually increases the inflammatory signals within the islet cells, causes release of IL-1 beta, which then feeds back on the cells and slows down the metabolism, and ultimately leads to the death of the islet cells," he told *BioWorld Financial Watch*.

The current therapy dogma in diabetes is either to replace the insulin that is missing in diabetics or to make the tissues that need insulin more sensitive to the circulating levels, Solinger said. Even though patients might seem to be well controlled on current agents, ultimately, he said, "their pancreases will poop out, and the remaining islet cells that are still making insulin will still die off, and they are left with a dead pancreas that cannot make insulin anymore, and they have to go on shots of insulin like the Type I diabetics need."

XOMA's approach, Solinger said, is to target the pathology that is causing the damage and stop the cell death. The company's investigational drug, XOMA 052, is designed to block the activation of the IL-1 receptor, thereby preventing the cellular signaling events that produce inflammation, he explained. Blocking IL-1 beta also may minimize cardiovascular risks, Solinger added.

XOMA 052, which also has shown signs of cell regeneration activity, is in Phase I/II testing, Solinger said, describing the current status of the studies as the "multiple-dose and dose-finding parts of our trials."

The firm expects to have a dataset from the two trials ready by the end of the second quarter of 2009 and to have formal Phase II studies under way before the second half of next year.

Targeting the NF-kappa B Pathway

San Diego-based Hollis-Eden Pharmaceuticals Inc. came to Type II diabetes drug discovery from a different anti-inflammatory approach, said CEO Richard Hollis.

"We came at this fundamentally, chemically and biologically, and we believe that by following those processes we are going to be able to produce a better pharmaceutical to treat Type II diabetes, because it is all within the system's biology," he explained. "It's all within endocrinology chemical messaging with hormones that is regulating this biology that goes awry in Type II diabetes."

Hollis-Eden is developing small-molecule compounds that are natural metabolites or synthetic analogues of steroid hormones produced by the adrenal glands, specifically focusing on dehydroepiandrosterone.

The firm's investigational compound, Triolex (HE3286), is an insulin sensitizer that acts by mod-

ulating the nuclear factor kappa B pathway and other proinflammatory pathways, Hollis said.

"Triolex works by down-regulating those precise pathways that are causing insulin resistance," he explained. "If we can mitigate the inflammatory signals that disrupt insulin signaling, we can provide a clearer pathway for the insulin signaling to reach its receptor and to do its job, and that is to improve insulin sensitivity and control blood glucose levels to normal levels in the body."

Interim results of the firm's Phase I/IIa study showed that Triolex 5 mg and 10 mg in obese insulin-resistant patients, or prediabetics, significantly improved insulin sensitivity and lowered fasting-blood glucose and insulin levels compared with placebo, said Jaime Riveros-Flores, the company's vice president of endocrinology and metabolism.

Notably, he said, the data showed that insulin-resistant patients displayed a significantly exacerbated inflammatory response characterized by higher levels of the proinflammatory cytokines, such as monocyte chemoattractant protein-1, tumor necrosis factor-alpha, IL-6 and IL-1 beta produced in lipopolysaccharide-stimulated peripheral blood mononuclear cells from the patients.

The study data showed a positive trend toward lowering those inflammatory cytokines in patients who received Triolex, which in turn was accompanied by signs of glucose lowering, Riveros-Flores explained.

Hollis-Eden is enrolling patients with Type II diabetes in a Phase IIb study. The firm anticipates having interim data from the 90-patient study by the end of 2008 or early 2009.

Regulating Glucose via Glucokinase Activators

Boulder, Colo.-based Array BioPharma Inc.'s approach to Type II diabetes drug discovery targets glucokinase, the enzyme that senses glucose in the pancreatic beta cells, stimulating insulin release in a glucose-dependent manner. Glucokinase also regulates glucose uptake and glucose production in the liver, said Steven Boyd, Array's senior director of medicinal chemistry.

Looking for molecules that increase the activity of an enzyme, as opposed to inhibiting an enzyme, is an "unusual approach" to drug discovery, he declared.

"This is one of the few examples that you can point to that actually changes the activity of an enzyme," Boyd said about Array's glucokinase activator (GK), ARRY-403.

Preclinical results showed that ARRY-403 demonstrated potent, highly glucose-blood-level dependent control of both fasting and non-fasting glucose concentrations, he said. The firm plans to initiate a Phase Ib study of ARRY-403 in the first half of 2009, and Boyd said Array intends to partner with a larger firm for its Phase II program.

Array is developing the compound as a monotherapy and as a drug that can be used in combination with other treatments, said James Trevillyan, principal research investigator of translational biology.

"There's clearly an unmet need for additional mechanisms to help control glucose, and we think that GK activators will add to that armamentarium with current drugs to help diabetics meet that goal," he said.

While firms like OSI Pharmaceuticals Inc. and Roche AG have more advanced GK activators in development, that class of drugs still is in the early stages. "So it's still an open game," said analyst Howard Liang, of Leerink Swann LLC.

Activating PPAR-delta Proteins

While PPAR has gotten a bad rap recently, John Didsbury, president of Raleigh, N.C.-based DARA BioSciences Inc., said his firm is taking a new approach with its insulin sensitizer, DB959, which is designed to activate the PPAR-delta protein, an enzyme that instructs cells to burn off fat and generates high levels of muscle fibers needed for endurance. The compound also uses PPAR-gamma activity to help control high blood sugar, Didsbury added.

The firm believes that approach can be beneficial in treating cholesterol and lipoprotein abnormalities in diabetics, he explained.

DB959, which is expected to enter Phase I testing in early 2009, has demonstrated a significant reduction in weight gain of about 70 percent compared with Avandia, and preclinical testing showed synergistic effects on insulin sensitivity arising from both PPAR-delta and PPAR-gamma activity, Didsbury said.

Although firms like DARA, Array, XOMA and Hollis-Eden all still are in the very early stages of development, said Susquehanna's Kolbert, their products' new mechanisms of action hold great promise for patients with Type II diabetes in a growing market. "With the stakes so high, we are going to see a lot of continuing work in Type II diabetes," he said. "Obviously, the demand for therapies to treat this disease is only rising."

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Combination Drug Approach Aimed at Cancer's Network

Despite advancements in developing targeted cancer therapies, success to date has been modest at best. "It's difficult to go to ASCO and see people get excited about a 20 percent response [rate]," said Jason Kantor, an analyst at RBC Capital Markets.

By Jennifer Boggs
BioWorld Today Assistant Managing Editor

Over the last several years — really starting with the 1998 approval of Herceptin as the first successful targeted therapy to hit the market — cancer has become a more treatable disease. Even so, most of the achievements have come in the form of small disease progression-free increments and limited response rates.

There's been a "massive proliferation of targets," said Jason Kantor, an analyst at RBC Capital Markets, who led a discussion on cancer drug targets and approaches at the 2008 BIO Investor Forum in late October. "We're seeing an avalanche of data," he added, ticking off some of the latest drug types that have gained traction in the oncology space: heat-shock protein 90 (Hsp90) inhibitors, histone deacetylase (HDAC) inhibitors and proteosome inhibitors.

But, despite advancements in developing targeted therapies, success to date has been modest at best.

"It's difficult to go to ASCO and see people get excited about a 20 percent response [rate]," Kantor said, referring to the annual American Society of Clinical Oncology meeting. He asked panelists during a therapeutic session on oncology targets, "When are we going to see an 80 percent response rate?"

The answer to that might come with a better understanding of the disease — or rather, diseases, since different cancers are able to grow and mutate via different pathways.

"We should be looking at cancer at a molecular level,

as opposed to tissue area," said Daniel R. Passeri, president and CEO of Cambridge, Mass.-based Curis Inc. The goal is to "shut down the network."

He offered Tarceva (erlotinib) as an example of a drug that is successful by market standards, but, "from a clinical standpoint, has limited efficacy." Tarceva, from Genentech Inc. and OSI Pharmaceuticals Inc., works by targeting a well-established cancer pathway, the epidermal growth factor receptor (EGFR), and is approved in non-small-cell lung cancer (NSCLC) and pancreatic cancer.

But a number of cells "have adapted to bypass that (EGFR) pathway," Passeri said.

And, in that way, cancer is much like HIV in its ability to mutate and become resistant to treatment. In HIV, the first approved antiretroviral therapy, AZT, was efficacious at first, but AZT-resistance soon prompted drug developers and clinicians to seek combination, or cocktail, therapies.

Similarly, Novartis AG's Gleevec (imatinib) met with success when it gained approval as a targeted therapy for chronic myelogenous leukemia, but mutations in the Bcr-Abl protein in CML patients have led to problems of drug resistance. A combination approach might counteract that resistance, and several companies are working in that area, such as GPC Biotech AG, of Martinsried, Germany, which recently presented preclinical data showing that its multitargeted protein kinase inhibitor, RGB-286638, demonstrated strong activity in animal models of CML that are Gleevec-resistant. Phase I testing is anticipated to begin later this year.

"We're really at the beginning of understanding" the combination approach in treating cancer, Passeri said. "They key is to understand which patients are amenable" to certain disease pathway disruption, and, as with HIV treatment, combinations might have to be changed or adjusted "as molecular characteristics change."

Curis is working with partner South San Francisco-based Genentech Inc. on its own combination study. In May 2008, Genentech initiated a Phase II trial to test approved vascular endothelial growth factor (VEGF) inhibitor Avastin (bevacizumab) with GDC-0449, a small-molecule Hedgehog antagonist, in metastatic colorectal cancer. That trial is designed to randomize 150 patients to receive FOLFOX or FOLFIRI chemotherapy in combination with Avastin, plus either GDC-0449 or placebo, with progression-free survival as the primary endpoint.

The aim is to "look at network disruption," Passeri said. "Avastin hits one [target], Hedgehog hits another."

Pamela Munster, a clinician at the University of California in San Francisco, with experience running breast cancer trials, agreed that single-pathway inhibitors "are not going to work," and the aim in cancer drug development should focus on "getting rid of single-agent trials."

But, she added, that becomes a "major issue" when dealing with two or more development-stage drugs.

Attempting a clinical study involving more than one unapproved therapy carries a whole host of regulatory risks — if the combination fails, how will researchers know which therapy fell short, for example — not to mention possible legal entanglements in trials involving two companies' drugs. So ongoing combination studies are restricted to designs involving either two approved products or an approved product plus an unapproved drug.

Ongoing late-stage trials include a Phase III study testing of Avastin plus Torisel (temsirolimus), an mTOR inhibitor from Madison, N.J.-based Wyeth, compared to Avastin plus interferon-alpha in advanced renal-cell carcinoma patients. The primary endpoints include tumor measurements and survival, and the trial is expected to conclude in 2012.

Another Phase III trial is evaluating the effect of Avastin added to chemotherapy and Herceptin in

HER2-positive breast cancer patients. Disease-free survival is the primary endpoint, and data are expected in 2012.

Multiple Phase II studies are testing Avastin in combination with other targeted therapies. Those include: Avastin plus RAD001 (everolimus, Novartis), an mTOR inhibitor, in advanced low- or intermediate-grade neuroendocrine carcinoma; Avastin plus Erbitux (cetuximab, ImClone Systems Inc.) plus irinotecan in trials involving second-line colorectal cancer patients and recurrent or metastatic head and neck cancer patients; and Avastin plus Velcade (bortezomib, Takeda) in recurrent malignant glioma.

Herceptin is being tested in a Phase II trials in combination mTOR inhibitors Sirolimus (rapamune, Wyeth) and deforolimus (Ariad Pharmaceuticals Inc.) in breast cancer patients. A separate Phase II trial is examining Herceptin plus Tykerb (lapatinib), a kinase inhibitor from London-based GlaxoSmithKline plc. Whether any of those combinations will yield superior results compared to single agent treatment still remains to be seen.

There already have been a couple of disappointments with the combination targeted therapy approach. In March 2007, Thousand Oaks, Calif.-based Amgen Inc. reported results from a Phase IIIb trial that added its approved Vectibix (panitumumab), an anti-EGFR antibody, to Avastin plus chemotherapy, which showed a lower progression-free survival rate in colorectal cancer patients compared to those receiving only Avastin and chemotherapy.

Another disappointment, a pilot Phase II study of Avastin plus Erbitux, with or without gemcitabine, in pancreatic cancer was terminated due to a lack of efficacy in both study arms.

And last month, Genentech and Melville, N.Y.-based OSI reported that the combination of daily oral dosages of 150 mg of Tarceva added to Avastin infused at 15 kg/mg every three weeks failed to improve overall survival in NSCLC patients whose disease had progressed following platinum-based chemotherapy. That combination, however, did exceed the median survival of 6.7 months reported from an earlier Tarceva study.

Even though it missed the primary endpoint, data from that study will "give us a big clue," Thomas Lynch, chief of hematology and oncology and director of the Center of Thoracic Cancers at Massachusetts General Hospital, said during a separate panel on the lung cancer space.

That clue, it seems, is the importance of biomarkers and molecular profiling. For example, data emerging from this year's ASCO meeting indicated that colorectal cancer patients with a mutated KRAS gene were unlikely to benefit from treatment with ImClone's Erbitux. Therefore, testing for that biomarker would help predict which patients would respond best to Erbitux treatment.

Molecular profiling is key for reaching a better response rate, agreed Curis' Passeri.

"It's exciting that we're seeing biological responses" in clinical studies, he said. "Now we have to refine it."

Despite the setback with the Avastin/Tarceva combination trial in NSCLC patients, additional studies are ongoing to test the combination of those targeted therapies in mesothelioma, liver cancer, locally advanced rectal cancer and as first-line consolidation chemotherapy after carboplatin, paclitaxel and Avastin induction therapy in advanced ovarian, Fallopian tube and primary peritoneal cancer and papillary serous mullerian tumors. All those studies are in Phase II.

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Discovery of Toxic Element in AD Forces Paradigm Shift

"This work is important because it will advise how drug intervention is best directed," said Ciaran Regan, professor of neuropharmacology at the School of Biomolecular and Biomedical Science, University College Dublin. "If you can reduce or stop the production of amyloid-beta as opposed to reducing the amyloid plaque load, treatment might be more effective."

By Sharon Kingman
BioWorld International Correspondent

A new study suggested that drugs to treat Alzheimer's disease (AD) should target the proteins that comprise the plaques that form in the brain in that condition, rather than the plaques themselves.

Ciaran Regan, professor of neuropharmacology at the School of Biomolecular and Biomedical Science, University College Dublin, in Ireland, told *BioWorld International*: "The results of our work have caused a paradigm shift in how we think about the plaques present in Alzheimer's disease. It seems that it is not necessarily the plaques that are causing the damage, but rather the intermediates that are forming those plaques."

An account of the research appeared in the June 22, 2008, issue of *Nature Medicine*, in a paper titled: "Amyloid-beta protein dimers isolated directly from Alzheimer's brains impair synaptic plasticity and memory."

The first author is Ganesh Shankar of Brigham and Women's Hospital and Harvard Medical School in Boston.

In Alzheimer's disease, a protein found in the membranes of neurons called amyloid precursor protein (APP) is broken down, forming amyloid beta-peptide.

The latter molecules stick to each other, forming dimers, trimers and other oligomers. Ultimately, these oligomers form the large aggregates known as plaques.

The Irish-American team of researchers isolated amyloid-beta monomers, dimers and trimers from the brains of several subjects who had died with Alzheimer's disease.

Because they knew that the severity of the dementia in Alzheimer's disease correlated strongly with the abundance of amyloid-beta in the brains of sufferers, the researchers then set out to characterize the physiological effects of the material they had isolated.

They focused particularly on soluble oligomers that are the first to form once amyloid-beta monomers are made.

In a series of experiments, the researchers showed that long-term potentiation — a long-lasting increase in communication between neurons that results from stimulating neurons and what is thought to be a model of learning and memory — was inhibited.

They also found that the converse was true. Long-term depression — the process by which neuronal synapses become weaker, a model of forgetting — was enhanced with the soluble amyloid-beta.

The researchers also trained rats to avoid a chamber in their environment.

They then injected the soluble amyloid-beta oligomer into the animals' brains and tested their subsequent memory for avoiding the chamber.

Animals that were injected three hours after training — at about the time that, according to other research, the synapses become remodeled follow-

ing memory training — entered the chamber again significantly faster than those injected with a control substance. That result suggested that the treated animals had an impaired ability to retain the learned behavior.

Further experiments showed that the insoluble cores of plaques from Alzheimer's brains did not affect long-term potentiation, but that this process was impaired when the plaque cores were modified to produce soluble amyloid-beta dimers.

Writing in *Nature Medicine*, the authors concluded that "plaque cores are largely inactive, but sequester amyloid-beta dimers that are synaptotoxic.

"We conclude that soluble amyloid-beta oligomers extracted from Alzheimer's disease brains potently impair synapse structure and function and that dimers are the smallest synaptotoxic species," they added.

"This work is important because it will advise how drug intervention is best directed," Regan said. "For example, if you can reduce or stop the production of amyloid-beta as opposed to reducing the amyloid plaque load, treatment might be more effective."

Regan said scientists had understood that amyloid-beta fragments contribute to the plaques, but the direct and toxic role of the molecules had not been fully appreciated.

While research already has shown how amyloid-beta can influence the connections between nerve cells and synapses, future studies will attempt to demonstrate how this synaptotoxicity manifests itself in live animals.

"In addition, we want to know whether exposing nerve cells and their synapses to amyloid-beta during the learning process actually reduces the number of synapses that form with learning," Regan added.

"We also want to know when neurodegeneration occurs: Does this happen immediately, or is it more long term?

"Thirdly, we want to find out whether the amyloid-beta oligomers themselves influence the way in which amyloid precursor protein is processed in the brain," Regan noted.

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Antibiotics for Resistant Bugs Possible in Two Years' Time

Scientists at Prolysis in Oxford, UK, have shown that members of a new class of drugs are effective in a lethal infection model that uses *S. aureus*.

By Sharon Kingman
BioWorld International Correspondent

A completely new class of antibiotics that works against methicillin-resistant *Staphylococcus aureus* (MRSA) could enter clinical trials within the next couple of years. The new drugs work by inhibiting bacterial cell division.

While bacterial resistance to all antibiotics is inevitable, researchers predict that, because none of the antibiotics in current use attack the same target as this new class of drugs, there should be no pre-existing resistance to the new antibiotics.

Scientists at Prolysis Ltd. in Oxford, UK, have shown that members of the new class of drugs, one of which is called PC190723, are effective in a lethal infection model that uses *S. aureus*.

Steve Ruston, CEO of Prolysis, told *BioWorld International*, "PC190723 is an important landmark compound that already has many attributes that you would want to see in a human medicine. There are other attributes that we are planning to optimize in order to create a compound with a very good chance of going through the remaining preclinical development hurdles, and gaining regulatory approval to begin human clinical evaluation."

That process will, he predicted, take almost two years. Prolysis then plans to find a licensing partner to assist with larger clinical evaluations, product registration and launch of the new product. A report on PC190723 appears in the Sept. 19, 2008, issue of *Science*, in a paper titled "An Inhibitor of FtsZ with Potent and Selective Anti-Staphylococcal Activity."

Prolysis was founded with the aim of discovering new antibacterial drugs using the guidance and insights of the bacterial cell biologist, Jeff Errington. Errington, who is now the director of the Institute for Cell and Molecular Biosciences at the University of Newcastle, UK, predicted that it should be possible to identify and develop novel compounds that would inhibit bacterial cell division.

In bacteria, cell division involves a large number of conserved and essential proteins. Loss of any of these proteins causes bacteria to die. Importantly, the bacterial cell division process is different from that of mammalian cells, so any drug developed that targets bacterial cell division should not cause side effects in human or mammalian cells.

Bacterial cell division starts with the formation of a ring by a protein called FtsZ. The FtsZ ring recruits other key proteins to form a complex that organizes the synthesis of the new cell wall, by forming a septum between the two daughter cells. Once the septum is complete, the daughter cells can separate. PC190723 works by binding to and inhibiting FtsZ activity. FtsZ is related to the mammalian protein beta-tubulin, which is the target for anticancer drugs such as Taxol. Taxol binds to a site in beta-tubulin that is analogous to the PC190723 binding site in FtsZ.

Researchers from Prolysis, led by Lloyd Czaplewski, director of research, reported in *Science* that PC190723 had potent antibacterial activity against all strains and species of staphylococci that were tested. Those included an MRSA strain and a multi-drug resistant strain of *S. aureus* (MDRSA) that is resistant to many of the major classes of antibiotics. The researchers also tested the drug in an infection model of staphylococcal septicemia, with very good results. Ruston said,

"The pharmaceutical industry has brought through very few new classes of antibiotics over the past 20 or 30 years, and the fact that this is a novel class of drugs means that it should have clinical utility for an extended period of time before resistance develops."

In the same issue of *Science*, Tomoshige Hiratsuka, of the Toyama Prefectural University in Japan, and colleagues reported finding a group of previously unrecognized bacterial proteins that could provide targets for new antibiotics. The proteins belong to a new pathway for the biosynthesis of menaquinone, a molecule needed for bacterial anaerobic respiration. Hiratsuka et al. have called it the futalosine pathway.

Writing in the same issue of *Science*, David Payne of GlaxoSmithKline plc, of London, concluded, "The lack of this pathway in humans and its presence in bacteria such as *Chlamydia* . . . *Helicobacter pylori* . . . *Campylobacter jejuni* . . . and Spirochaetes . . . could make it an attractive antibacterial drug target for these specific pathogens."

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Enormous New Gene Holds Out Hope as Therapy for Eye Disease

In total, 1 in 3,000 people are affected by retinitis pigmentosa. In about half of the cases, the disease is inherited in an autosomal recessive fashion. Researchers have identified about 20 different genes that appear to play a role in between 1 percent and 5 percent of autosomal recessive cases of retinitis pigmentosa.

By Sharon Kingman
BioWorld International Correspondent

The discovery of a new gene that, when mutated, appears to be responsible for many cases of the human eye disease, autosomal recessive retinitis pigmentosa, eventually could lead to new gene therapies for this condition.

The gene, which the researchers have called EYS, is the largest gene yet identified that is specifically expressed only in the eye. The protein encoded by EYS probably has a role in maintaining the integrity of the photoreceptor cells of the retina.

Physiologists hope that EYS will allow them to gain a better understanding of the process of vision in humans, including how the photoreceptor cells of the retina work. Intriguingly, EYS is not present in the mouse retina, nor in the retinas of certain insects, such as bees.

Shomi Bhattacharya, professor of experimental ophthalmology at the Institute of Ophthalmology, University College London, told *BioWorld International*, "There is no way of curing this disease until we understand the genetic basis for it. Now that we know the gene, and once we have worked out the biochemical basis for the disease, then it should be possible to treat patients for such conditions in the future using gene therapy."

Bhattacharya, together with his collaborators led by Guillermo Antinolo of the Hospitales

Universitarios Virgen del Rocio in Seville, Spain, gave an account of their research in the Oct. 5, 2008, issue of *Nature Genetics*, in a paper titled "EYS, encoding an ortholog of *Drosophila* spacemaker, is mutated in autosomal recessive retinitis pigmentosa."

An earlier study by researchers at the Institute of Ophthalmology proved that gene therapy for retinal degeneration could work in principle, Bhattacharya said. In that study, published in the May 22, 2008, issue of the *New England Journal of Medicine*, four young adults with Leber's congenital amaurosis (LCA) were given a treatment to replace the retinal gene that they lacked. The therapy involved delivering the gene, using an adenoviral vector, to the retina. One of the three patients showed an improvement in visual function following the treatment.

In total, 1 in 3,000 people in the general population are affected by retinitis pigmentosa. In about half of the cases, the disease is inherited in an autosomal recessive fashion. Researchers have identified about 20 different genes that appear to play a role in between 1 percent and 5 percent of autosomal recessive cases of retinitis pigmentosa. EYS represents a breakthrough because it probably accounts for a higher percentage (about 10 percent) of cases of autosomal recessive retinitis pigmentosa.

The trawling by Bhattacharya and Antinolo for additional genes responsible for retinitis pigmentosa had begun with the mapping of the RP25 locus to chromosome 6 in Spanish families, by the Antinolo group. The linkage region was quite large and contained in excess of 110 genes as potential candidates for RP25. After eliminating 15 candidate genes whose functions already were known and systematically screening a further 45 genes, the research team were helped by a study that mapped the RP25 locus in five additional families, greatly narrowing the area of interest.

In parallel, Bhattacharya and his colleagues also screened the genomes of affected individuals for deletions, using the technique known as array comparative genomic hybridization. That strategy helped them to identify a 100-kilobase section of the genome that was deleted in all affected members of one of the original families studied.

That segment contained six of the predicted genes, so the team then began to screen those genes for mutations. That approach allowed them to focus on two of those predicted genes, which were also in the same location as the 100-kilobase deletion. Further investigation showed that the two genes were, in fact, part of a much larger gene consisting of 2 million base pairs of DNA, which now is called the EYS gene. EYS has 43 exons.

Using the polymerase chain reaction to amplify messenger RNA derived from EYS, the team was able to show that a gene transcript of the expected size could be obtained from the retina, but not from other tissues, as well as from a cell line of photoreceptor-like cells. Additional work showed that six separate mutations were present in five of the affected families studied. Four of those mutations involved deletions and two involved nonsense substitutions; however, all six resulted in the creation of premature stop codons.

Because it has been shown that mRNA containing premature stop codons undergoes immediate decay, the authors speculated that the disease mechanism in the affected families may be due to a complete absence of a functional EYS protein.

Tests on 200 control individuals showed that none had any of the mutations identified in patients with disease.

Initial examination of the protein encoded by the EYS gene suggested that it is a large protein of more than 3,000 amino acids, and that it includes at least 21 domains that resemble epidermal growth factors. Its highly unusual structure resembles that seen in the *Drosophila* spacemaker (spam) protein.

Drosophila spam protein is expressed in the eye

of many species of insects, including fruitflies (*Drosophila melanogaster*) and houseflies (*Musca domestica* Linnaeus), where the photoreceptor cells of each ommatidium of the compound eye are separate from each other. In this type of insect eye, each photoreceptor cell has a direct connection with the brain. In other species of insect, such as the mosquito (*Anopheles gambiae*) and the honey bee (*Apis mellifera*), spam is not expressed in the eye and the photoreceptor cells of each ommatidium have fused together to form a single communication channel with the brain.

Bhattacharya predicted that biologists will be very interested to explore the meaning of these differences, and how the EYS protein plays a role in modulating retinal architecture and in vision.

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chapter 5:

NewCo News: Companies to Watch

ACT's Business Model Aims for Steady Stream of Cancer Drugs

Big pharma is "spending more money than ever [on research and development], yet the number of new chemical entities continues to decline," said Advanced Cancer Therapeutics President and CEO Randall Riggs.

By Jennifer Boggs
BioWorld Today Assistant Managing Editor

Hoping to bridge the gap between the lab and big pharma's sparse pipelines, 2007 start-up Advanced Cancer Therapeutics is working to rapidly develop the most promising early stage cancer compounds emerging from work at the James Graham Brown Cancer Center at the University of Louisville in Louisville, Ky.

The firm, which was founded in January 2007 though it officially started operations in October 2008, is not the typical university spinout firm. Under its agreement with the University of Louisville, ACT has access to the 20-plus potential compounds in development in labs at the James Graham Brown center — as well as access to the roughly 50 scientists at the center — which spends about $20 million to $25 million each year on drug discovery and preclinical work.

In return, the university holds a 30 percent stake in ACT, which would allow it to share in any revenue generated from its research.

"It's a different model," said President and CEO Randall Riggs, adding that it took founders and local venture capitalists Dale J. Boden and Ty Wilburn "two years to negotiate this business structure with the university."

The strategy is simple enough. ACT is permitted first right to refusal on compounds emerging from the cancer center and will focus on taking the chosen compounds rapidly through preclinical testing and toxicology. If the data still look efficacious at that point, the company will advance the candidates into Phase I.

And at the end of Phase I, ACT likely will look at options for licensing or selling the compound to a large pharma firm that has the resources and expertise to take it deeper into clinical development and potential commercialization.

Big pharma is "spending more money than ever [on research and development], yet the number of new chemical entities continues to decline," Riggs told *BioWorld Today*. "So we have to start thinking outside the box."

At ACT, "we have a very nice engine" for discovery and development, he added, describing the relationship with the James Graham Brown center as a "quid pro quo effort."

"We bring in the compounds without having to pay for them," Riggs said. ACT then aims to facilitate the rapid advancement of the most promising candidates — weeding out the less effective ones before they can rack up too much in development costs — into the hands of a larger company for late-stage work.

In addition to the university's stake in future revenue, Riggs said the deal allows the university scientists to "do what they do best" by focusing on their research without becoming entangled in the process of trying to translate their discoveries into commercial operations.

It's a business model encouraged by Donald Miller, who was named director of the James Graham Brown Cancer Center in 1999, Riggs said.

Miller previously founded Aptamera Inc. in 2001, with a single product — aptamer drug AGRO100 for cancer. Louisville-based Aptamera had moved the drug into Phase I in pancreatic cancer when it was acquired in 2005 by Antisoma plc, of London, for $21.5 million.

With ACT, "we wanted to continue that success, except this time, we'd create a company with a portfolio of products, which diffuses the risk and creates more value," Riggs said.

So far, ACT has in-licensed two product candidates. One is a macrophage migration inhibitor factor small-molecule compound aimed at blocking angiogenesis in tumor cells, and the other is a small molecule designed to starve cancer cells by blocking their uptake of glucose. But whether those two become the first clinical compounds advanced to the clinic by ACT still remains anyone's guess.

"I always emphasize that we want to find the Achilles' heel [in each product] quickly, so we can move on and avoid spending lots of money on something that won't be effective," Riggs said. "So many products we pick might fall, but that's OK because we have other products to go to."

More than 20 compounds are in early development at the James Graham Brown center, most of them small molecules, and "we're watching closely," he added. "We're looking at compounds at the preclinical/animal testing phase to see whether they clearly illustrate in vivo activity."

To date, ACT has raised a little more than $2 million, and Riggs said the firm is "hoping for about $8 million more," with the aim of getting two investigational new drug applications filed before the beginning of 2010.

The company only has two employees, relying heavily on the scientists at the cancer center.

As part of ACT's arrangement with the university, it also has access to a group of six medicinal chemists, who are responsible for optimizing the selected molecules for further testing.

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Q Therapeutics Seeks to Repair Rather than Replace Neurons

The name Q-Cells refers to the cells' ability to follow endogenous cues. The cells are harvested from donor tissue; isolated, purified and frozen; and then injected into the brain or spinal cord near the point of injury. From there, the cells migrate to the lesion and start their repair work.

By Trista Morrison
BioWorld Today Staff Writer

Deborah Eppstein, president and CEO of Q Therapeutics Inc., acknowledges that developing stem cell therapies to replace damaged organs is a daunting task.

That's why her company uses glial progenitor cells to repair rather than replace neurons, an approach she anticipates may be applicable in treating a host of neurodegenerative diseases.

The company's Q-Cells are "technically not stem cells," Eppstein explained. They are lineage-restricted glial progenitor cells that differentiate into oligodendrocytes, which produce the myelin sheaths that insulate neurons, and astrocytes, which make growth factors and support the health of neurons.

The name Q-Cells refers to the cells' ability to follow endogenous cues. "We don't have to direct them," Eppstein said, adding that the cells are harvested from donor tissue; isolated, purified and frozen; and then injected into the brain or spinal cord near the point of injury. From there, the cells migrate to the lesion and start their repair work, which includes remyelination as well as supporting neuronal health.

The Q-Cells were identified by Q Therapeutics' co-founder Mahendra Rao through research conducted at the University of Utah and the National Institutes of Health, where he headed stem cell work for the National Institute of Aging. Rao started the company in 2004 with help from Dennis Farrar, a founder of Myriad Genetics Inc. and other biotechs.

Q Therapeutics raised about $5 million in a Series A financing in May 2004. Earlier this year, the Salt Lake City-based company got another $8 million in the first close of its Series B round. Its investors include vSpring Capital, Invitrogen Corp., Epic Ventures, Toucan Capital, University of Utah Research Foundation, Salt Lake Life Science Angels and Q management.

Eppstein said Q Therapeutics hopes to raise between $7 million and $12 million in the second tranche of its Series B round, set to close in the first quarter of 2009. That money will allow the company to get its first clinical data, which Eppstein noted will include both safety and initial efficacy findings.

Q Therapeutics plans to conduct a dose-ranging Phase I/IIa trial at Johns Hopkins University to evaluate a single dose of Q-Cells in patients with transverse myelitis, a severe form of multiple sclerosis in which patients are wheelchair-bound. Preclinical studies are under way, and data published in the June 2008 issue of *Cell Stem Cell* showed that Q-Cells remylinated neurons in mice and improved survival in what otherwise would be a lethal murine model.

No abnormal affects have been observed in preclinical studies to date. The company expects to file its investigational new drug application in 2009 and start the trial shortly after.

Eppstein said the company has talked with several pharmaceutical companies that are "very inter-

ested in working with us" if the Q-Cells can create myelin in humans the way they have in mice.

In addition to demyelinating diseases such as multiple sclerosis, Q-Cells may be applicable in cerebral palsy, spinal cord injuries, white matter stroke, amyotrophic lateral sclerosis (ALS), Parkinson's disease and Alzheimer's disease. The company has grants supporting early research in ALS and spinal cord injury, and Eppstein said the team plans to seek additional grants to complement its venture capital investment.

Q Therapeutics also has a collaboration with the Buck Institute for Age Research to study Q-Cells in Parkinson's disease.

Because many of its intended indications are orphan diseases, Eppstein said Q Therapeutics may be able to conduct truncated clinical programs consisting of Phase I/IIa and Phase IIb/III studies. She doesn't anticipate needing to enroll large numbers of patients but said the company has a Q-Cell source sufficient to address multibillion-dollar markets.

In the interim, Q Therapeutics is developing drug discovery research tools based on its cells. Eppstein projected the tools could be on the market and starting to generate revenue within a year.

Q Therapeutics has 10 full-time employees.

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Dicerna Offers New Generation of RNAi Therapy: DsiRNA

Dicerna plans on administrating the DsiRNA-nanoparticles combination intravenously. The longer duration of action allows DsiRNA to be administrated every few weeks, similar to the "dosing paradigm . . . currently used for monoclonal antibody therapy."

By Daria Theodora
BioWorld Today Staff Writer

The already-crowded RNA interference (RNAi) therapeutic playground is welcoming Cambridge, Mass.-based Dicerna Pharmaceuticals, which enters the space through "a second doorway."

This new kid on the block brings in a second generation of RNAi technology, which the company said is an improvement over the current method and at a more upstream level.

The so-called dicer substrate technology employed by Dicerna works through the same pathway with the current RNAi therapy method that employs synthetic 21-mer small interfering RNA (siRNA). The difference is that the dicer-substrate small siRNA (DsiRNA) "enters the pathway further upstream much like microRNA would," CEO and co-founder James Jenson explained.

DsiRNA bind to an enzyme called dicer, which dice the substrates into shorter fragments, before being incorporated into RISC (RNA-induced silencing complex), triggering the interference of gene translation. The current synthetic 21-mer siRNA pass the dicer enzyme and directly enter RISC.

Advantages of the longer 27-mer DsiRNA over

the conventional siRNA therapy, according to Jenson, include increased potency, longer duration of action and the ability to attach targeting moieties for specificity.

"One can attain . . . five- to tenfold greater potency [in knocking] down a specific target than a 21-mer targeting the same sequence," Jenson said, then quickly added that increased property is a tremendous advantage "in a field which delivery is still optimized."

Dicerna, founded in 2007, currently is pursuing three programs internally: solid tumors/oncology, although the specific target molecules are not yet public; diabetes, specifically gluconeogenesis; and hepatitis C virus. For those, Dicerna plans to partner with other companies that already have the FDA-approved delivery methods.

"We consider this to be the most efficient way to begin our drug development program: a well-validated target that is suitable for dicer substrate and combine them with nanoparticle technology that exists today," Jenson said.

Dicerna plans on administrating the DsiRNA-nanoparticles combination intravenously. The longer duration of action, which Jenson said is another advantage of DsiRNA and of a great interest to potential pharma partners, allows DsiRNA to be administrated every few weeks, similar to the "dosing paradigm . . . currently used for monoclonal antibody therapy."

There are several partnering discussions underway, he noted, and Dicerna is going to license existing technologies on a target-by-target basis.

Dicerna also is developing the second-generation approach for its products — targeted moieties, which Jenson said will be "very much a part of the future of RNAi therapeutics: more targeted . . . RNAi drugs, as opposed to the current approach involving nanoparticle encapsulation."

That can be achieved by utilizing the unique advantage of dicer-substrates: the ability to attach targeting moieties to target specific tissue or cells. "You can attach either a peptide or an aptamer or antibody fragment that will target a specific receptor on the cell surface," Jenson said, explaining that the attached moieties will be clipped by dicer inside the cell and be degraded naturally.

The process recently has been shown in a study by John Rossi, professor of molecular biology and dean of the graduate school of biological science in Beckman Research Institute of the City of Hope in Duarte, Calif., and also Dicerna scientific cofounder. It was published in the August 2008 issue of *Molecular Therapy*.

The study itself was an approach for human immunodeficiency virus-1 (HIV-1) therapy, which Jenson mentioned that Dicerna is not pursuing, but is opened to partnering.

The intellectual property for the DsiRNA, which was invented by Rossi and Mark Behlke, "covers a range of 25- to 35-nucleotide (nt) long" and according to Jenson, that, plus the fact that the dicer-substrates have enhanced biological properties, provides Dicerna with a strong IP position "that is separate from the Tuschl I intellectual property estate that covers the 21-mers."

Jenson noted that City of Hope also provided MDRNA Inc. (formerly Nastech), of Bothell, Wash., with the right to dicer-substrate technology, but no other companies have access to that IP now. Jenson added that DsiRNA IP will not interfere with Tuschl II as well. Alnylam Pharmaceuticals Inc., also of Cambridge, Mass., currently holds exclusive rights to the Tuschl II patent on a worldwide basis, and has a license to the Tuschl I IP. Both patents are keys to conventional siRNA methods.

Dicerna aims to have its first investigational new drug application (IND) package by the end of 2009 and to file in early 2010.

Roberto Guerciolini, Dicerna senior vice president of pharmaceutical development, was previously chief medical officer and senior vice president of development at Sirna Therapeutics Inc., now part

of Merck & Co. Inc., and was part of the team that developed the first IND for chemically modified siRNA then, Jenson said.

The company closed a Series A financing round July 15 for $21.4 million, and Jenson said he expected that would get Dicerna to the IND process.

The company plans to employ about 30 people in house, and currently is halfway there, and they will work out the in vivo biology. Integrated DNA Technology Inc., of Coralville, Iowa, is its "chemistry department," Jenson added. Behlke, who is also Dicerna's co-founder, is currently the vice president of molecular genetics and biophysics and chief scientific officer there. Jenson said IDT, a supplier of oligonucleotides, "will make for us anything that fits in our agreed-upon workplan."

Investors of Dicerna include Oxford Bioscience Partners' Doug Fambrough, previously the director of investors at Sirna; Skyline Ventures' Stephen Hoffman, previously involved with both Alnylam and Sirna; and new partner Abingworth.

"Alnylam is an Abingworth portfolio company," Jenson noted, "we have three investor groups who are very familiar with the RNAi space. . . . We think that's another validation of [dicer-substrate] technology . . . and the validation of the independence of IP doorway."

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Zafgen Shrinks Fat by Inhibiting Angiogenesis in Adipose Cells

An obesity drug that is both efficacious and well tolerated easily could become a blockbuster. The overall U.S. market for weight-loss remedies and diet products was more than $50 billion in 2006, but prescription pharmaceutical products account for less than 1 percent of the total market.

By Trista Morrison
BioWorld Today Staff Writer

Zafgen Inc. is developing small-molecule angiogenesis inhibitors that target adipose cells, essentially shrinking fat.

The concept certainly seems logical: Angiogenesis inhibitors like Avastin (bevacizumab, Genentech Inc.) have established that stopping blood vessel formation in cancer cells can shrink tumors, and the success of Lucentis (ranibizumab, Genentech Inc.) proves the same mechanism can stop excessive blood vessel growth in wet age-related macular degeneration.

Yet Zafgen CEO Thomas Hughes said the company is "not aware that anyone else" has thought of applying angiogenesis inhibition in obesity.

"It's very interesting; it's very unique; it's why I'm here," said Hughes, who made his public debut as head of the Cambridge, Mass.-based start-up this week. He previously served as vice president and global head of cardiovascular and metabolism disease at the Novartis Institutes for BioMedical Research Inc.

Credit for Zafgen's approach goes to co-founder Maria Rupnick, whose research at Boston Children's Hospital established that the ability of fatty tissue to expand depends on blood vessel formation. In 2002, she published a study in the *Proceedings of the National Academy of Sciences* demonstrating that treatment of obese mice with various angiogenesis inhibitors led to significant weight loss that restored the mice to near normal weights.

The antiangiogenesis treatments also resulted in decreased endothelial cell proliferation and increased apoptosis, as well as decreased appetite and increased metabolic rate.

Zafgen's orally available small molecules specifically inhibit angiogenesis in adipose cells, the blood vessels of which are "inherently different" from those found elsewhere in the body, Hughes said. While he declined to discuss specific targets, he said Zafgen's approach is "more of a process targeting" than tissue-targeting approach and seeks to manipulate the close relationship between adipocytes and the endothelial cells in capillaries.

Preclinical studies have yet to be published, but Hughes said the data indicated "absolutely profound" efficacy in several "gold-standard models" of obesity. And while he noted that it is "very early days" and that "real safety studies" haven't yet been done, that efficacy has occurred "in the absence of any tolerability issues."

An obesity drug that is both efficacious and well tolerated easily could become a blockbuster. According to a report from JPMorgan Securities Inc., the overall U.S. market for weight-loss remedies and diet products was more than $50 billion in 2006, but prescription pharmaceutical products account for less than 1 percent of the total market.

That's because available weight-loss drugs like F. Hoffmann-La Roche Ltd.'s Xenical (orlistat) and Abbott's Meridia (sibutramine HCl monohydrate capsules C-IV) deliver only modest efficacy and suffer from high discontinuation rates due to side effects.

Several new obesity drugs are in late-stage clinical trials, and most work on targets in the brain to regulate hunger and metabolism. For example, Arena Pharmaceuticals Inc.'s lorcaserin agonizes the 5-HT2c serotonin receptor, Orexigen Therapeutics Inc.'s Contrave combines anti-addiction and depression drugs, and Vivus Inc.'s Qnexa combines appetite and metabolism regulators with a drug that increases feelings of fullness.

Hughes said Zafgen's approach should be compatible with drugs seeking to regulate food intake or metabolism. The company expects to begin clinical trials next year, although details regarding the clinical pathway — which could involve monotherapy or combination therapy for obesity or for a subset of patients such as obese diabetics — have not been solidified.

Founded in 2005, Zafgen raised $2 million in a Series A round in 2006 and $20 million in a Series B round in October 2007. Investors include Atlas Venture, Third Rock Ventures and Great Point Ventures.

Hughes said the money should last about 18 months given the company's "capital efficient" model.

Potential partners already have "identified themselves as being interested" in Zafgen's technology, Hughes said, although it would be "premature" to discuss any partnering plans this early in the game. For now, Zafgen intends to focus on completing preclinical work and getting into the clinic, but Hughes said the company is "not naive — we don't think for a moment that we will carry this through to registration on our own."

published in *BioWorld Today*

chapter 6:

Partnering in Biotech and Pharma

The Impact of Big Pharma on the BioPartnering Industry

Not a week seems to go by that doesn't bear news of a big pharma company announcing plans to "become more biotech-like" in its operations or making moves to partner with biotechs or to otherwise exploit the benefits of biologics technology to revitalize its own vegetating pipelines.

By Michael Harris
BioWorld Executive Editor

Big pharma is not in as dire straits as everyone is proclaiming. Pharma's plight, specifically regarding the lack of impending internally produced drugs, is serious, but the companies have the money and infrastructure to survive. Those two dynamics are relevant, however, only because they can be used to grab the lifeline that the availability of biotech talent and innovation offer.

The State of Big Pharma, Today and Tomorrow

Relative to pharma, the current activity level in the biopartnering trend is a move that should've been made five to 10 years ago. If big pharma had invested in admittedly riskier biotech projects such as RNAi, cancer, anemia or literally anything genomics-related, many of the cutting-edge therapeutics involved in the current biopartnering deals could've been that much closer to, or in, the marketplace. Although it is a late move, it is still being done in time enough to qualify as a proactive move. Big pharma profits have slowed, but not even the totally unproductive weight at the bottom of the pharma sector has stopped the decades-long collective industry annual growth streak.

Big pharma sent out an SOS, and then summarily answered it to save its own soul through M&A with the biotechnology market. Biotech has always been there as a source of investment and partnering for pharma, but it was not until big pharma's back was against the wall that it was motivated to mingle on the level that we are now seeing.

If pharma's slew of patent expirations were earmarked for 2015 to 2020 or if its pipelines were stocked with imminently marketable candidates, I don't think the biopartnering trend would be any more dynamic than it was a decade ago. During that time, pharmaceutical companies either primarily chose only Phase III about-to-become therapeutics for partnering deals or they selectively acquired only companies that had such widely regarded late-stage favorites and/or already-marketed products.

I believe pharma's innovative era is arguably gone for good and that the creative epoch resides with biotechnology through the next century. Medicine, like disease, evolves, and thankfully, we have a therapeutics technology that has the product track record, as well as the potential, to parallel the escalating prevalence of disease and take up the mantle that pharma originated and shouldered almost exclusively for more than 100 years.

Biotech Leading Therapeutics into the 21st Century

I think even most pharmas would agree with me — perhaps not publicly — that biotechnology is poised to assume the leadership role in drug development for the 21st century. Actions, nevertheless, speak just as loud as words. Not a week seems to go by that doesn't bear news of a big pharma company announcing plans to "become more biotech-like" in its operations or making moves to partner with biotechs or to otherwise

exploit the benefits of biologics technology to revitalize its own vegetating pipelines.

For example, in July 2008, Eli Lilly and Co., Merck & Co. Inc. and Pfizer Inc. joined forces to create Boston-based Enlight Biosciences LLC. The company already is making headway in bridging the gap between innovation and industry that has been evidenced by the uptick in biotech acquisitions by pharmaceutical firms.

And when Roche announced its bid to acquire the remaining shares of Genentech Inc., Roche Chairman Franz Humer said in a conference call that his company will do "everything that's necessary" to maintain Genentech's entrepreneurial spirit and unique science-driven culture. This includes preserving the company as an independent unit within Roche and providing plenty of operational and creative freedom, according to *BioWorld Today*.

Without the R&D that has rendered biological therapeutics such as Avastin, Herceptin, Lantus, Truvada and many other first-of-a-kind (in concept and efficacy) drugs that address society's most debilitating and prevalent indications such as cancer, diabetes and HIV, we presume that relative fatality rates would be at least 25 percent higher than they are presently.

Prior to the commercialization of these drugs, comparative pharmaceutical treatment consisted of almost equally debilitating treatments such as chemotherapy, aggressive painful injection schedules and pain-management morphine-level applications.

I'm not predicting pharma will be going out of business, but it will transform into something else. At the very least, and most likely, it will use its resources to integrate the best of both industries and re-emerge as the new and improved "biopharmaceutical" market. A corrective period will thin out the number of companies, inasmuch as some of the smaller companies do not have the capital or the regarded candidates necessary to survive the inevitable market shake-out.

Biotech vs. Big Pharma: Not Coming out Swinging

The lack of contentiousness in what could have been a hostile environment distinguishes this relationship from similar ones in other industries. Even Biofuels vs. Big Oil has had some public clashes in the news and some personal wars-of-words at a few conferences. One would think these two drug development industries had merged a long time ago, as they have been observed co-existing at industry events, forging deals together for decades and even fighting it out in litigation with much less malice than Coke vs. Pepsi.

These two industries have always seemed to have essentially what the other needed in spades. What pharma has is tangible (money, resources) and what biotech has is academic (innovation). It's the confluence of a rich history and a bright future.

Would you rather be rich or smart? It doesn't matter right now in this trend, as both are giving the other what they each need, while doing no harm.

We'll see how they interact as they merge closer to being one industry (biopharma) that makes more of the same products (biotherapeutics), but I don't foresee either side jeopardizing what is proving to be the win-win factor for the ages.

A New Driver in Big Pharma and Biotech Partnering

The predominant new driving factor would be the imminent reality of gene therapy technologies and drugs on the market. The impact from that factor will likely turn the biopartnering trend into a permanent drug development market core dynamic, considering the large number of stalled clinical applications that could stand to be jumpstarted by the cellular manipulation capabilities that RNAi and other genomics-based technologies have shown in lab and, increasingly, in clinical programs.

Gene therapy cannot proceed without a prolific level of biopartnering business activity, as the technology is the exclusive derivative property of

biotech, but its advancement cannot be facilitated any better than by big pharma's corporeal forte of cash and clout assets, as well as its need. The two industries are perfectly suited to merge brainpower and pocket power to produce marketability.

The fact that most gene therapy candidates are in early-stage development assures a protracted run for the trend, easily as much as five more years of substantial biopartnering transactions, before the trend would peak with a sizeable number and a reliable flow of relative products available to consumers.

For more insight into biopartnering, check out one of BioWorld's latest market reports, The BioWorld BioPartnering Report 2009: Strategies and Paradigms of the Deal. *Visit www.bioworld.com for more information.*

published in *BioWorld Perspectives*

Partnering Execs Give Perspective on Current and Future Trends

"Everybody knows that there are a number of big pharmaceutical companies looking to partnering to bolster their portfolio and to counter lost sales through patent expiries. As a result it's become a much more competitive market," said Warwick Bedwell, Roche's vice president, global head of business development, pharma partnering.

By Amanda Lyle
BioWorld Perspectives Managing Editor

The end of 2008 brought job cuts, a financial crisis and much worry and speculation about the future. Biotech IPOs were almost nonexistent in 2008. Venture funding was down compared to the previous year. Cutting costs often resulted in cutting jobs. But one segment of biotech has continued to move forward, further securing its role as a necessary component of the industry. Partnerships still offer promise.

The total number of biotech deals fell slightly in 2006, then rose in 2007, according to BioWorld research. In 2008 there were fewer biotech-biotech M&As, but more pharma-biotech M&As, as compared to last year. Preclinical to Phase II deals are on the rise, and one of the fastest growing areas is biotech collaborations with universities and nonprofits.

BioWorld conducted numerous interviews with industry experts about partnering in the biotech industry as part of this year's research for the recently released *BioWorld BioPartnering Report 2009: Strategies and Paradigms of the Deal.* We asked big pharma companies what they look for in a licensing candidate, how to best present non-confidential data, what not to do when entering partnering discussions, and how to make the partnering process run more smoothly. Also included in the report is detailed contact information for licensing contacts at big pharma and big biotech companies. For more information about the report, visit www.bioworld.com.

Below are a few excerpts from the "Industry Interviews" chapter of the report. We asked the following experts for their perspectives on the current and future trends in the biopartnering industry:

• **Greg Wiederrecht** is the vice president and head of the External Scientific Affairs department of the Merck Research Laboratories division of Whitehouse Station, N.J.-based Merck & Co. Inc. The External Scientific Affairs department is responsible for the scientific assessment of all licensing and partnering opportunities for the company. Wiederrecht manages a group of 73 scientists and administrators, divided by various therapeutic and platform areas, who identify and assess opportunities outside of Merck's walls.

• **Warwick Bedwell** is the vice president, global head of business development, pharma partnering, for Basel, Switzerland-based Roche. Pharma partnering is the department responsible for identifying, accessing, evaluating and pursuing opportunities with external partners. Roche's business development group works closely with the licensing and alliance management groups to optimize deal negotiations, contracting and the creation of successful relationships with Roche's partners.

• **Bob Little** is the vice president and chief commercial officer at Halozyme Therapeutics Inc., of San Diego.

• **Safi Bahcall** is the president, CEO and cofounder of Lexington, Mass.-based Synta Pharmaceuticals Corp.

• **Todd Davis** and **Gregory Brown** are cofounders and managing directors of Cowen Healthcare Royalty Partners. Davis previously was a partner at Paul Capital Partners, where he focused on making royalty-related investments for the Paul Royalty Funds and was responsible for U.S. sourcing. Brown also previously was a partner at Paul Capital Partners, where he was responsible for global sourcing for the Paul Royalty Funds, as well as the execution and management of more than $235 million in royalty-related investments.

BioWorld: What trends in biotech/pharma partnering have you noticed over the past few years?

Greg Wiederrecht (Merck): Some of the trends are that now, more than ever, biotechs want to be sold, so there is an increasing number of outright acquisitions. It's also quite accurate to say that the deals are getting increasingly expensive, and that is simply because of supply and demand. The late-stage opportunities are well-picked over; there is no low-hanging fruit left.

Alliances are in many cases getting to be the only significantly expanding source of biotech funding. The public markets are not providing the needed capital, and the IPOs are way down. . . . And equity financing is not providing sufficient funding.

Another trend is that deal-making is going up and up. I don't see any end to that trend. None of the large pharmas can feed the beast, and by the beast I mean the pipeline, on their own.

Another trend is that there are more regional deals being done, and more deals done on biologicals. And by regional deals I mean, historically, most companies would take a worldwide license; if you licensed from biotech you'd want a worldwide license, or sometimes you might get a worldwide license ex-Asia, or a worldwide license ex-Japan, or a worldwide license ex-Europe. Especially in the Asia territories, there are lots of compounds that have been licensed out that are not accounted for in certain regions, so we're seeing increasing numbers of deals where the license is for China only or the license is for Eastern Europe only.

Merck prefers the rights not being split up. But for those compounds that historically have not been accounted for in all markets, the rest of the regions are becoming of increasing interest, particularly for those that are successful.

Warwick Bedwell (Roche): Everybody knows that there are a number of big pharmaceutical companies looking to partnering to bolster their portfolio and to counter lost sales through patent

expiries. As a result, it's become a much more competitive market. What we're seeing is that deals are being made for assets much earlier on than perhaps they were a few years ago. There are more deals completed for Phase I and Phase II assets and there are certainly fewer high quality Phase III opportunities available.

We're also seeing, in general, increases in up-front payments. Perhaps the up-front payments for a Phase III opportunity a few years ago are now being mirrored in the deals for a Phase I/Phase II. That's just a result of supply and demand and the number of compound opportunities that are out there.

What's also interesting is that due to the credit squeeze that's been occurring within capital markets, more biotech companies are turning to M&As rather than in-licensing, which was the case a few years ago. A number of companies now may start off with an in-licensing approach, but then as discussions continue, that turns to a discussion on an M&A.

Finally, we're seeing the emergence of new biotech markets. The biotech industry started earlier in the U.S. than in the EU and rest of the world. While there are still 20 to 30 percent more biotech companies in the U.S. than in the EU, the disparity in numbers and the stage of the companies is reaching more of an equilibrium. There is an emerging biotech industry in Canada, Australia, Korea, Israel and China among others — which will also be increasingly important sources for opportunities in the future.

Bob Little (Halozyme): The obvious one is that the amounts paid in license deals are getting much larger even for quite early-stage programs. We currently have a situation where many of the big company research pipelines are drying up and have been unproductive for some time. They are also being hit with generic competition as the patents for blockbusters expire. They are spending more money on infrastructure and processes and less on productive research, so they're reaching out to in-license earlier and earlier stage compounds. But there are only so many available late-stage programs and so the supply vs. demand conundrum is creating higher values for earlier stage products. Even preclinical terms now have become pretty significant. That's the one trend we've obviously seen in the past several years, and it's continuing to escalate.

A trend in the past year, especially with the depressed market cap of small to medium biotechs, is the straight acquisition of a company rather than entry into an expensive collaboration or license. You're also seeing more and more acquisitions that are being kept as stand-alones so that big pharma companies themselves are trying to emulate biotech by having their own stand-alone biotech companies within the larger company umbrella, therefore hopefully allowing them to maintain the benefits of a fast-moving biotech culture and attain greater research productivity. So far, however, the problem has been retention of key talent who would rather not work under the big company umbrella, but prefer to move to the next entrepreneurial opportunity. Those are a couple of the trends that I've seen that are the most obvious ones in the past couple of years.

Safi Bahcall (Synta):

- Improved experience on all sides, based on growing list of comparable deals, can speed up negotiation and deal process.
- Greater range of structures and scenarios being explored.
- Greater value of deals.

Gregory Brown (Cowen): We find there's a lot of activity in later-stage investing and many of those opportunities lie with companies that are acquiring products, acquiring divisions or divesting products. The trading of products back and forth is a market we've actually seen accelerate.

We see two main drivers for this increase. Biotechs have realized that it takes longer for

products to get approved, so they're seeking earlier commercialization opportunities. In some cases it could be a company that wants to develop some presence in the market so they need capital to finance a sales force channel. By establishing this channel, biotechs can form relationships with physicians who are going to prescribe their innovator product, but also potentially their later-stage products.

Many pharmaceutical companies will also divest their slower-growth products as they try to make room in their sales force channel for their innovator products. As a result, there's a very robust market of products that are marketed, may have plateaued or be tailing off in sales but that are still generating significant amounts of revenue.

BioWorld: In what ways do you think the partnering industry will change in the future?

Wiederrecht: With the low-hanging fruit gone, there will be increased early-stage partnering, which happens to be our sweet spot. We're seeing an increase in big pharma to big pharma partnering. We're seeing a big increase in competition from the big Japan companies. They're going to be more competitive. Companies like Takeda and Eisai and Daiichi Sankyo are going to be competitive with the traditional leading health care companies in going after deals.

Besides the Japanese companies competing with leading health care companies, the biotech companies are going to have competition from biotechs coming out of places like Korea and Japan and Australia and Singapore, so the American and European biotechs will have that competition. A lot of the fee-for-service-based deals will probably, because of the lower costs, be moving to the Asia-Pacific.

Bedwell: There are a lot of very good, earlier stage opportunities in development around the world. Good science is everywhere. At this particular point, there seems to be fewer quality Phase III opportunities available to partner, but that should change over time.

Little: We are seeing more and more big pharma companies creating their own biotech clusters, such as Pfizer and Novartis, for example.

From a biotech standpoint, the other profound change that you're going to start to see, and I think we already are seeing it, is the advent of biosimilars. As legislation changes in Europe and potentially could change here in the U.S., two trends are happening. One is, big pharma companies are saying they're interested in entering into the biosimilar field. In addition, you're also going to see heightened awareness of lifecycle management of major biologics compounds as patents start to expire to try to offset the impact of the market entry of biosimilars. This will create more and different partnering opportunities as both big pharma and established biosimilars players create pipelines of compounds. This is where, for example, Halozyme's recombinant hyaluronidase technology is really at the forefront of this trend in terms of providing differentiation from biosimilars for innovators.

Our technology, in general, allows biologics players to take enzymes such as our Enhanze Technology platform and create an interesting value proposition, such as the ability to go from I.V. to subcutaneous infusion with additional patent exclusivity that allows differentiation from the biosimilar that uses the original dosing format.

I think the other issue is that as you see companies adapting lifecycle management technologies, such as our Enhanze Technology platform, prior to patent expiration. It is a much lower risk and lower cost program than developing a whole new molecular entity. It is actually a very cost-efficient way for pharma companies to differentiate themselves from the biosimilars. Especially as the technology moves forward and as the legislation changes here in the U.S., most likely in the next few years, I think you'll see this become ever more important.

Todd Davis (Cowen): We have seen a tremendous increase in the number of later-stage product opportunities.This has been driven a lot by private

equity and venture capital firms who have poured a significant amount of capital into the sector over the past five to seven years — especially in the specialty pharmaceutical area.

This is a shift from the early 1990s when these types of companies were funded not necessarily by venture capital and private equity firms but by corporate spin-outs. Companies like Jones Pharmaceuticals were acquiring products at one to two times sales, and they were trading at five to six times sales. These returns coupled with the market's efficiency were big drivers for the increase in private capital funding over the past five to seven years. As a result, there are more companies and more later-stage products available today.

The complete interviews are available in the BioWorld BioPartnering Report 2009: Strategies and Paradigms of the Deal. *To learn more about the report, visit www.bioworld.com.*

published in *BioWorld Perspectives*

special bonus section

The Top 25 Biotech Drugs

The Billion-Plus Blockbusters: The Top 25 Biotech Drugs

Biotechnology drugs are a real market, generating billions of dollars and pushing the industry toward overall profitability. And that trend shows signs of longevity.

By Michael Harris, Amanda Lyle
& Kathleen Kite-Powell
BioWorld Today Staff Writers

By the end of this decade, the biotechnology market will have advanced to the $100 billion level. Its list of drugs has been the lure that continues to attract interest from an array of market-facilitating elements.

A Growing Industry

Biotherapeutics account for 7.5 percent of all drugs on the market, comprise approximately 10 percent of the total expenditure for marketed drugs, and their use is growing at more than 20 percent per year. Biotechnology drug candidates constitute 32 percent of all pipeline research programs.

In addition, biological drugs are administered in life-saving or end-stage applications 74 percent more than chemically derived pharmaceuticals.

Globally, the 25 top-selling biotechnology drugs accounted for $67.3 billion, or 81 percent, of total biotech drug revenue in 2007, leading a market that was valued at $83 billion; however, that top-heaviness in market revenue proportion does not necessarily indicate a lack of industry-wide innovation. It tends to signify the vital applications of biotech drugs in indications of unmet, or drastically underserved, patient needs.

The biotechnology drug development market emits signs of growth, as various indicators point upward. There were 17 biotechnology product approvals in 2008 through mid-April, compared to 9 in the first quarter of 2007. For the full year 2007, there were 21 biotech drug approvals, compared to 17 in 2006 and 19 the year before. (See page 72 for a chart of Biotech Drug Approvals, 1982 to 2007.)

Each of the seven biotech companies with $1 billion-plus in revenue in 2007 increased its total revenue from 2006 and experienced first quarter 2008 sales that have put the companies on track to surpass 2007 year-end totals.

A lot of the confidence the biotechnology market attracts from investors, whether traditional venture capitalists or unconventional pharma financiers, comes from its unique, effective and profitable drugs, led by the products in this Top 25 lineup.

Innovative concepts and perpetually potential breakthroughs without any tangible product can only go so far in attracting investment, recruiting talent, assuaging stockholders or making money. But biotechnology drugs are a real market, generating billions of dollars and pushing the industry toward overall profitability. And that trend shows signs of longevity.

Many biotechnology-derived drugs are often indicated to treat long-term diseases such as diabetes, cancer, chronic kidney failure and multiple sclerosis. The dosing schedule for biopharmaceutical drugs can last, at high expense, for years or often as long as patients' lifetimes. These drugs typically cost much more per patient than conventional pharmaceuticals and are increasingly attracting venture attention in stages as early as academic research.

The Top Biotech Drugs

Every year, BioWorld's *Top 25 Biotechnology*

Revenue of the Top 50 Biotech Drugs in 2007

	Drug name (maker)	Indication	Revenue for 2007
1	**Rituxan** (Genentech)	Non-Hodgkin's lymphoma, rheumatoid arthritis	$5,467M
2	**Enbrel** (Amgen)	Rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, plaque psoriasis	$5,275M
3	**Herceptin** (Genentech)	Breast cancer	$4,809M
4	**Avastin** (Genentech)	Colorectal cancer, non-small-cell lung cancer	$4,070M
5	**Aranesp** (Amgen)	Anemia	$3,614M
6	**Remicade** (J&J)	Crohn's disease, ankylosing spondylitis, arthritis, ulcerative colitis, rheumatoid arthritis, plaque psoriasis	$3,327M
7	**Lantus** (Sanofi-Aventis)	Types I and II diabetes	$3,160M
8	**Humira** (Abbott)	Rheumatoid arthritis, psoriatic arthritis	$3,064M
9	**Gleevec** (Novartis)	Chronic myelogenous leukemia, gastro-intestinal stromal tumors	$3,050M
10	**Neulasta** (Amgen)	Infection associated with chemotherapy-induced neutropenia	$3,000M
11	**Taxotere** (Sanofi-Aventis)	Breast cancer, non-small-cell lung cancer, prostate cancer, gastric cancer, squamous cell carcinoma of the head and neck	$2,941M
12	**Procrit/Eprex** (Ortho Biotech)	Anemia	$2,885M
13	**Epogen** (Amgen)	Anemia	$2,489M
14	**Prevnar** (Wyeth)	Prevention of diseases caused by *S. pneumoniae*	$2,439M
15	**Tamiflu** (Roche)	Influenza	$2,067M
16	**Rebif** (Merck Serono)	Multiple sclerosis	$1,912M
17	**Avonex** (Biogen Idec)	Multiple sclerosis	$1,870M
18	**Copaxone** (Teva)	Multiple sclerosis	$1,713M
19	**Pegasys** (Roche)	Hepatitis B and C	$1,623M
20	**Truvada** (Gilead Sciences)	HIV	$1,589M
21	**Betaseron** (Schering)	Multiple sclerosis	$1,586M
22	**Humalog** (Eli Lilly)	Diabetes	$1,475M
23	**Erbitux** (ImClone Systems)	Colorectal cancer, head and neck cancer	$1,430M
24	**Neupogen** (Amgen)	Chemotherapy-induced neutropenia	$1,277M
25	**Kogenate** (Bayer)	Hemophilia A	$1,262M

SOURCE: BioWorld research from company press releases and SEC filings.

Drugs Report profiles the leading drugs in the field, and provides insight into the markets for these $1 billion-plus blockbusters. (See the preceding page for a table of the Revenue of the Top 25 Biotech Drugs in 2007.)

The following are excerpts from the profiles of the top 10 biotech drugs for 2007. Revenue for each drug was obtained from company websites and SEC documents. In addition, revenue figures are for worldwide sales, sometimes a result of figures from two companies that market a product.

1. Rituxan

Rituxan is a biotechnology therapeutics heavyweight that is excelling in fighting to extend its relevance, as it encounters R&D obstacles in secondary indication trials and looming biosimilars competition in the near future.

The CD20 antigen that the drug targets is present in more than 90 percent of NHLs. Like Remicade, Rituxan is a chimeric monoclonal antibody, meaning that it uses both human and mouse components. It sells for about $18,000 per year wholesale, per patient.

2. Enbrel

Immunex Corp. developed Enbrel and marketed it into a $750 million product before the company was acquired by Amgen Inc. for $10.3 billion in July 2002. At the time, Amgen estimated Enbrel's sales to reach $3 billion in 2005. It surpassed that mark by far in 2007. Amgen, which markets the product in the U.S. and Canada, reported $3.23 billion in sales, and Wyeth reported Enbrel sales of $2.045 billion outside of the U.S. and Canada.

Enbrel has been a billion-dollar product since 2002 and has increased its revenue by more than 250 percent since. It is currently marketed by both Amgen and Wyeth. Immunex, now a subsidiary of Amgen, manufactures the drug.

3. Herceptin

During their lifetime, about 8 percent to 9 percent of women will develop breast cancer. The disease usually is considered more aggressive when tumors produce excess amounts of a protein called human epidermal growth factor receptor-2 (HER2). About 25 percent of breast cancer patients have high amounts of HER2 on the surface of tumor cells, as found by testing of breast tissue biopsies. If a woman has a HER2-positive tumor, she has a higher chance of recurrence and therefore, a decreased chance of survival.

If a patient's tumor is found to be HER2 positive, she is a candidate for Herceptin therapy. Even though the drug is only useful to a subgroup of patients, Herceptin proves that pharmacogenomics drugs (genetically personalized drugs with a limited patient pool) can bring in as much revenue as drugs made to treat all persons having a more common disease.

4. Avastin

Avastin is the first anti-angiogenesis drug approved for the treatment of cancer. The drug inhibits new blood vessel formation and growth from pre-existing vessels, angiogenic growth that is known to increase the supply of nutrients and oxygen to growing solid tumors. Therefore, inhibition of angiogenesis helps slow or stop tumor growth.

Avastin is a therapeutic agent in the form of a monoclonal antibody that acts by binding to VEGF, blocking activity of this vascular endothelial growth factor, thereby blocking angiogenesis and denying nutrients to cancer cells and severely impeding tumor growth. Avastin fills a niche in the treatment of advanced cancers that gives the drug not only great therapeutic value to patients and their families, but financial worth to the company that produces it.

5. Aranesp

Amgen Inc.'s erythropoiesis-stimulating agent (ESA) Aranesp is the result of what could have been a huge loss in the anemia market. Amgen's epoetin alpha is licensed to Ortho Biotech

Products LP, except for one indication in the U.S. Outside of the U.S., Ortho Biotech markets it as Eprex for all approved indications; inside the U.S., the drug is marketed as Procrit for indications other than kidney dialysis. Amgen's Epogen, the only indication the company retained rights to in the country, is indicated in the U.S. for the treatment of anemia in patients with ESRD. Its blockbuster Aranesp is a longer-lasting formulation of EPO.

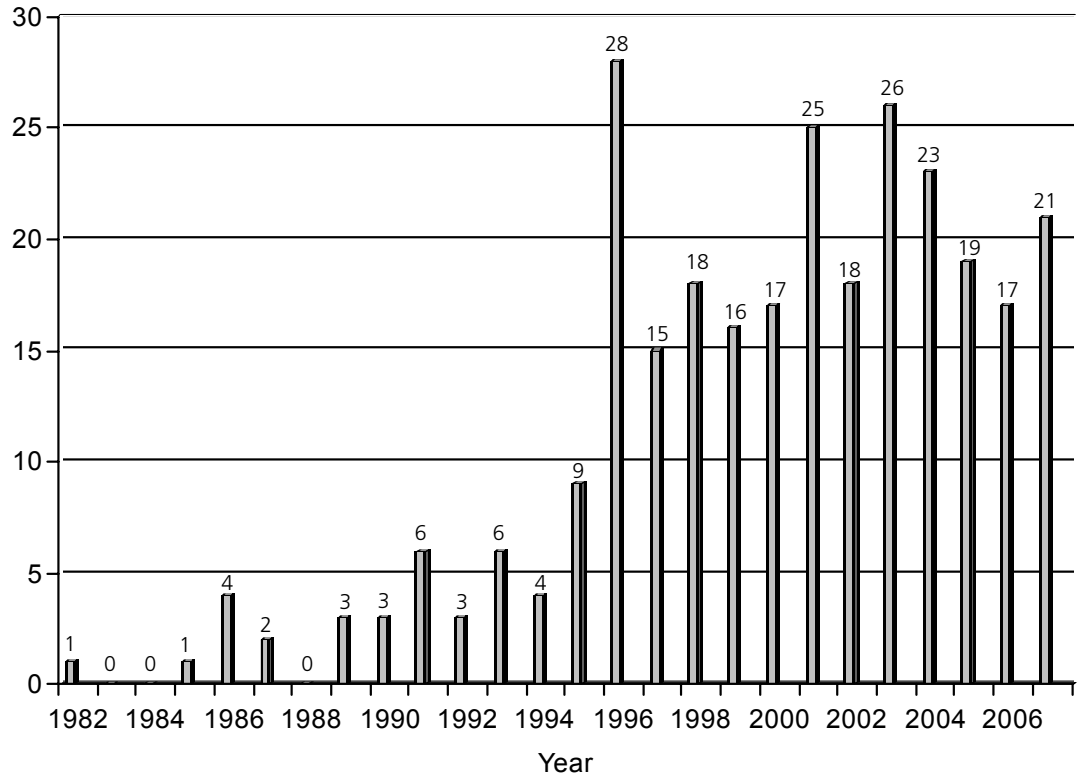
As a recombinant erythropoietic protein, the drug is similar to epoetin alpha, except that it contains two additional sialic acid-containing carbohydrate chains, which result in increased activity, making darbepoetin alpha a longer-acting form of EPO, or second-generation Epogen.

6. Remicade

Remicade is a TNF inhibitor that treats a variety of immune-mediated inflammatory diseases (IMIDs) that constitute a more than $5 billion market. TNF inhibitors such as Remicade and its biggest competing drug, Enbrel, owe a lot of their value to the broad applications associated with their use: Enbrel is approved in rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis (AS) and psoriasis, while Remicade can claim all of those, as well as Crohn's disease, its initial commercial indication, and ulcerative colitis.

Remicade was developed by Centocor Inc., a Johnson & Johnson company. As a chimeric monoclonal antibody, Remicade uses both mouse

Biotech Drug Approvals, 1982 to 2007



Source: BioWorld Snapshots: Biotechnology Products On The Market Since 1982.
Note: The above chart refers only to the first approval of a biotech drug. Approvals for additional indications are omitted, but would increase the total number of approvals by 106 if included.

and human components. It was discovered in the Department of Microbiology at the New York University School of Medicine.

7. Lantus

Lantus, for the third consecutive year, produces the most revenue of all the drugs that address the globally expansive and expanding market that treats diabetes. Lantus has increased its 2007 revenue by 30 percent, tallying $3.16 billion, compared to $2.17 billion in 2006.

Lantus, an insulin application therapeutic, was the first drug that offered patients a reliable and effective alternative to the high-maintenance and intrusive insulin pump. Lantus' precise dosing delivery dispenses reliable therapy and stable in vivo insulin levels and activity on a daily schedule for the majority of its patients.

8. Humira

Humira's revenue has been increasing rapidly over the years, more than doubling in sales from 2005 to 2007. In 2006, Humira's first full year on the market in its secondary indication of psoriatic arthritis, its revenue increased enough to go over the $2 billion mark, up from its $1.4 billion total in 2005. The year 2007 brought it over the $3 billion mark. Abbott's 2007 10-K estimates worldwide Humira sales to be $4 billion in 2008.

Cambridge, UK-based biotechnology company Cambridge Antibody Technology Group plc (CAT) developed the technology for Humira and initiated the research program. In 1995, it signed an agreement with Knoll Aktiengesellschaft, which was acquired by Abbott in March 2001.

9. Gleevec

In Europe and Australia, imatinib mesylate is marketed as Glivec. In the U.S., the drug is Gleevec. Gleevec was first identified as a potential agent for the treatment of chronic myelogenous leukemia (CML) in the late 1990s. Dr. Brian J. Druker with the Oregon Health and Science University worked with Novartis to develop it.

A drug that functions by directly turning off the signal of a protein associated with cancer, Gleevec is a 2-phenylaminopyrimidine derivative that specifically inhibits a number of tyrosine kinase enzymes. In the case of CML and GISTs, Gleevec blocks abnormal tyrosine kinase enzymes that are characteristic of those cancers.

10. Neulasta

Neulasta is used to decrease the prevalence of infection brought about by neutropenia in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia. More specifically, Neulasta is a man-made form of the natural granulocyte colony-stimulating factor (G-CSF) that promotes an increase in neutrophils, a white blood cell (WBC) type essential for the body's resistance to infection.

Neulasta is made using the bacteria *Escherichia coli* to manufacture the drug, after which it is collected and purified. The molecule is chemically conjugated with monomethoxypolyethylene glycol (PEG) to extend the drug's half-life. The mechanism of action of the drug involves binding to cell surface receptors of neutrophil precursors to change cell behavior through signaling, ultimately inducing more infection-fighting neutrophils to be produced. Neulasta's efficacy is tracked by noting improvement in patients' WBC counts.

This special bonus section was compiled from BioWorld's recently released Top 25 Biotechnology Drugs Report 2008. *For more information or to order a copy of the report, please visit www.bioworld.com.*

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