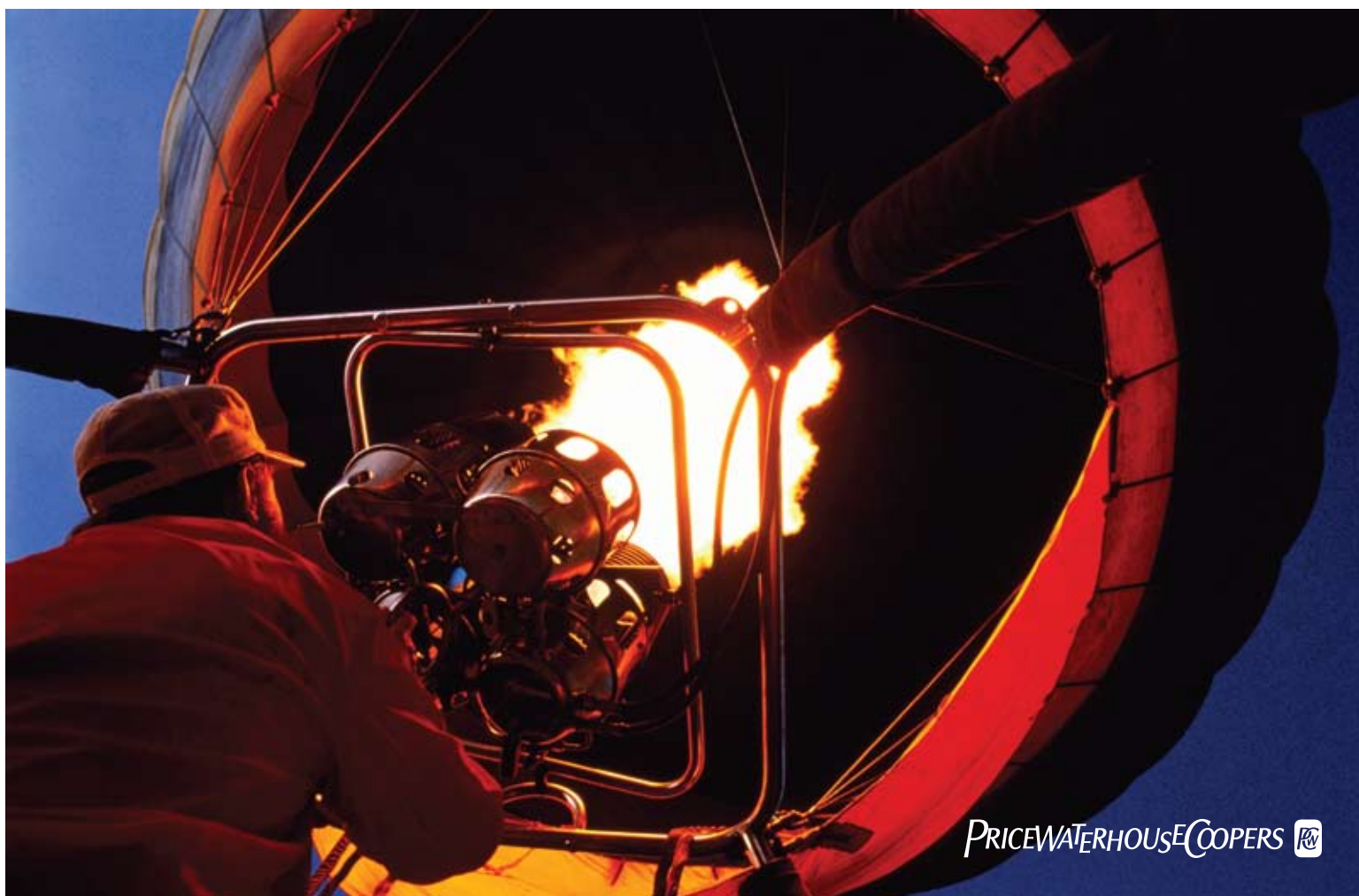


# Biotech

## Lifting Big Pharma's prospects with biologics

Findings from the MoneyTree™ Report

A quarterly survey produced by PricewaterhouseCoopers and the National Venture Capital Association based on data provided by Thomson Reuters





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The heart of the matter

# How Biotech is changing the pharmaceutical landscape.

Biotech companies face numerous challenges in 2009, led by dwindling cash reserves, a squeezed credit market and a poor IPO environment. However, recent events signal short- and long-term benefits for the biotech industry. A spate of megamergers of major pharmaceutical companies further underscores the growing need for pharmaceutical companies to diversify portfolios with targeted biologic drug products. Also, biotech will likely—in the long term—be buoyed by a strong push from the Obama administration to ramp up spending for basic biomedical research and development of personalized medicine.

As the so-called blockbuster drug “patent cliff” chips away at Big Pharma revenue, and in-house R&D continues with diminished returns on productivity, biotech firms will increasingly be positioned to fill product pipeline gaps by sourcing new innovations and drug prospects—especially with diagnostic and therapeutic biologics.

At the same time, venture capitalists are weathering the storm, plowing rounds of funding into their most prized biotech firms in the hope of an exit through an acquisition or, eventually, through an IPO. Biologics, in particular, continue to shine as the bright spots—particularly therapeutic and diagnostic monoclonal antibodies (mAbs) and immune response effectors (including vaccines and interferons)—with VC investment soaring by 45% and 90%, respectively, in 2008 over 2007, according to the MoneyTree™ Report, a quarterly study of venture capital investment activity in the United States, produced by PricewaterhouseCoopers and the National Venture Capital Association (NVCA) based on data provided by Thomson Reuters. Overall, VC investment in human biotech (excluding medical devices) fell by about 11% in 2008 against 2007, yet drew some major deals in the 50-million-dollars to 100-million-dollars range. The survey also found that funding of biotech seed and start-ups rose sharply in 2008, while later-stage funding, though dropping slightly, was still relatively robust, demonstrating that VCs are still investing in promising areas and holding firm—and expensive—positions in biotech companies with the brightest exit prospects.

Biotech companies (that survive cash shortages) with drug platforms that can potentially feed Big Pharma’s pipelines with biologics are in a propitious spot, with competition among cash-rich pharmaceutical companies to diversify likely driving further acquisitions of biotech companies in the half-billion- to billion-dollar range through 2009. Biotech companies struggling with solvency issues will become increasingly more open to being acquired, even at lower-than-expected valuations.

An in-depth discussion

**Biologics to drive drug  
innovation — despite  
difficult conditions.**

Dried-up credit, an anemic IPO market and a reluctant investor pool have taken their toll on the biotech industry. According to the Biotechnology Industry Organization (BIO), about 45% of all publicly listed biotech companies are operating with less than one year of cash remaining. Prospects for biotech IPOs will likely remain dim in 2009 on the heels of a very weak 2008, which produced just one IPO, raising \$5.8 million, according to BioWorld.<sup>1</sup> That compares to 41 IPOs raising \$1.9 billion in 2007 and 32 IPOs raising \$1.7 billion in 2006. With the IPO market effectively closed, cash-strapped biotech companies are looking to M&A exit possibilities such as partnerships, alliances or other business combinations.

It is the biologics sector which will likely drive such M&A activity. The global market for protein-based therapeutics (peptides, proteins, enzymes and antibodies), for example, is estimated to grow at 15% per year over the next decade, according to *Genetic Engineering & Biotechnology News*.<sup>2</sup> Among biologics, monoclonal antibodies have emerged as a particularly high-growth sector, with revenues estimated to grow at a CAGR of 16.9% from 2006 to 2012 compared with 0.8% from sales of small molecule drugs.<sup>3</sup> As a subsector monoclonal antibodies are already estimated to comprise about 25% of the broad biopharmaceutical market. In 2008, there were 20 New Molecular Entity (NME) FDA approvals and four new biologics, compared to 16 NMEs and two biologics in 2007.<sup>4</sup> “There is a healthy market in developing biologics meeting unmet needs, such as Alzheimer’s, but they will probably need data that demonstrates efficacy and safety with clinical endpoints, not simply surrogate endpoints. If they do that, they’ll get welcoming [FDA] approval,” said John E. Calfee, resident scholar, American Enterprise Institute for Public Policy Research. Additionally, generally-depressed valuations come at a time when pharmaceutical companies are filling their drug development pipeline in the face of fast-approaching “patent cliffs”.<sup>5</sup> However, biotech stocks jumped in late 2008 and early 2009, outperforming the S&P 500 and NASDAQ Composite for the first time in about five years, which may provide biotech companies with some leverage when negotiating valuations with acquirers.

## Biologics versus conventional drugs

Biologics	Conventional and NME drugs
Large molecules (>5000 molecular weight)	Small molecules (~500 molecular weight)
Biotechnologically produced or isolated from living sources	Chemically synthesized
Complex structure/mixtures (tertiary structure, glycosylated)	Simple well-defined structure
High target specificity	Less target specificity
Generally parenteral administration (e.g., intravenous)	Oral administration possible (pills)
Can be antigenic*	Generally not or unpredictably antigenic

\* Antigen is a substance that stimulates the production of an antibody.

1 Biotechnology Industry Statistics, Biotechnology Industry Organization, February 2009.

2 Hiller, Andrea, Fast growth foreseen for protein therapeutics, *Genetic Engineering & Biotechnology News*, January 1, 2009.

3 *Pharma 2020: The Vision*, PricewaterhouseCoopers, 2008.

4 Thriving in 2008: Approvals, deals and other silver linings, *BioWorld Financial Watch*, January 5, 2009.

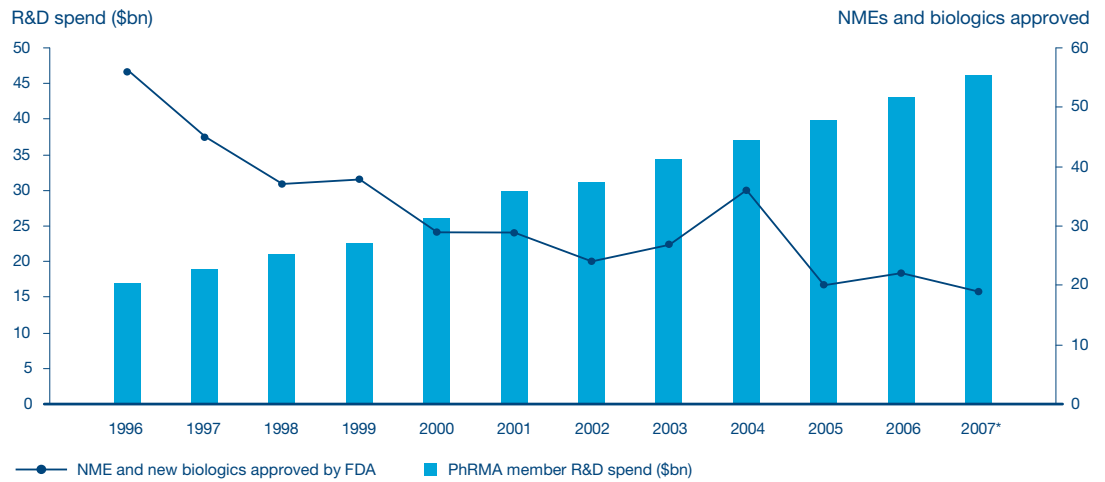
5 Aldridge, Susan, Ph.D., Affitech exploits antibody discovery platforms, *Genetic Engineering & Biotechnology News*, January 15, 2008.

## The “patent cliff” effect

The cash crunch and inhospitable IPO climate intersect as pharmaceutical companies strive to fill product pipelines and larger biotech companies look to expand market share in biologic drugs. As indicated in Figure 1, FDA approvals of NMEs

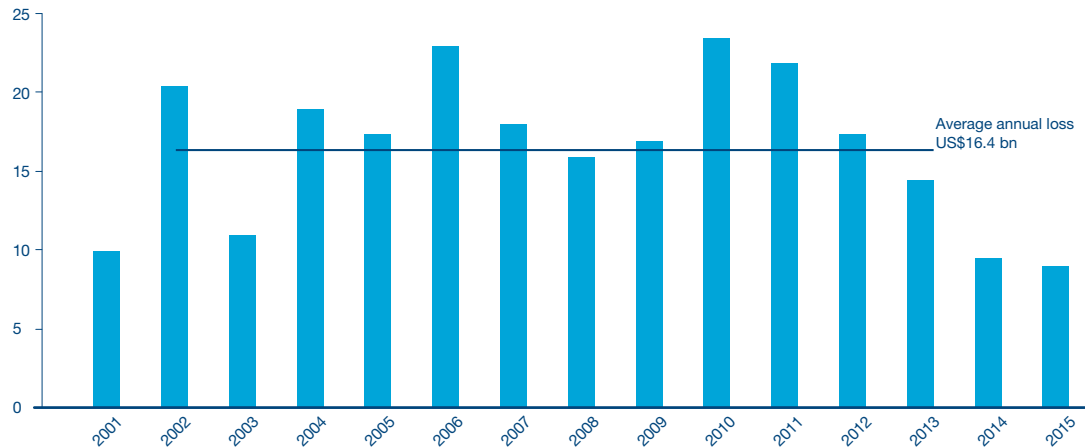
and biologics have fallen as pharma R&D spending has risen. Exacerbating matters are blockbuster drug patents facing expiration, leading to estimated losses averaging \$16.4 billion over the 2002 to 2013 period, as illustrated in Figure 2.

**Figure 1. Diminished R&D productivity\***



NME: New molecular entity. Excludes vaccines, antigens and combination therapies which do not include at least one new constituent.  
 \* PwC estimate

**Figure 2. Impending losses stack up due to “patent cliff”**



\$157 billion sales exposed to generic competition by 2011  
Source: IMS Health Midas

A broad appeal of biologics is not only their pipe-filling capability but also the potential difficulty for generic drug makers to replicate the original branded biologic, thus potentially extending the revenue stream, even after the biologic goes off patent. Manufacturing (or, rather, cell- or tissue-based growing) processes of the pioneer biologics drugs are, in general, far more difficult to duplicate by generic drug makers compared to chemically synthesized drugs. “I think the big attraction to mAbs (monoclonal antibody) is not only the amazing medical results but also how difficult it will be to enter the biosimilars market with mAbs,” said American Enterprise Institute for Public Policy Research resident scholar Calfee. “Once you have a mAb that really works, it is not the biosimilar market that will compete,

but other biologics companies that will find new antibodies. For example, Avastin has been on the market for 4 or 5 years, and already it is seeing competition. That’s the downside—you are inviting competition when you succeed,” Calfee added.

Additionally, diagnostic biologic products may increasingly drive partnerships and acquisitions as drug companies seek to develop biologic biomarkers for drugs either currently marketed or even in development, in a push toward so-called companion diagnostics. The FDA’s Office of Combination Products (OCP), established in 2002 to oversee diagnostic-drug combinations, received 333 applications for combination products in 2007, up from 236 in 2006.<sup>1, 2</sup>

<sup>1</sup> FY 2007 Performance Report to Congress from the Office of Combination Products, Food and Drug Administration, Department of Health and Human Services, 2007.

<sup>2</sup> FY 2006 Performance Report to Congress from the Office of Combination Products, Food and Drug Administration, Department of Health and Human Services, 2006.

## Biomarker + therapy: Biologic's lock and key

The convergence of pharmacogenomics (pairing drugs only with patients whose biology will respond to them) and therapeutics has in large part changed the landscape of biopharmaceuticals. A classic example is Herceptin, Genentech's monoclonal antibody which was FDA approved in 1998 to treat women with advanced, genetically tested HER2 positive breast cancers. GlaxoSmithKline's Tykerb is also used for HER2-positive patients.

Recently, people with a normal K-ras gene in tumors were found to respond to Erbitux/Vectibix. ImClone (Erbitux) and Amgen (Vectibix) used data from past studies to demonstrate that these drugs best benefited patients with a normal K-ras gene. About 40% of patients have mutant K-ras tumors. ImClone and Amgen are requesting the FDA's permission to notify physicians that patients with the mutant K-ras gene should not use these drugs. Genentech has stated that Avastin is effective in patients with both the mutant and normal K-ras gene.

**Figure 3. What are some marketed biologics?**

General category	MoneyTree™ subsector	Marketed examples	Components	Use
<b>Monoclonal antibodies</b>	Therapeutic monoclonal antibodies	<b>Humira™</b> (adalimumab)	rDNA antibody	Anti-TNF to treat rheumatoid arthritis
	Therapeutic monoclonal antibodies; DNA/RNA probes; medical diagnostic biotech	<b>Herceptin™</b> (trastuzumab)	rDNA humanized antibody	Breast Cancer. Example of Personalized Medicine used with HER2 genetic test.
<b>Vaccines</b>	Immune response effectors	<b>Prevenar™</b> (pneumococcal saccharide)	7 polysaccharide antigens conjugated to diphtheria protein	Vaccine against pneumococcus bacteria
	Immune response effectors	<b>FluMist™</b> (live influenzae virus vaccine)	Live influenza virus vaccine, intranasal	Immunity against influenzae
<b>Therapeutic proteins</b>				
Cytokines	Immune response effectors	<b>Avonex™</b> (Interferon B-1a)	Interferon-b rDNA glycoprotein	Multiple sclerosis
Enzymes	Other therapeutic proteins or therapeutic biotechnology products	<b>Activase™</b> (alteplase)	TPA (serine protease) rDNA glycoprotein	Acute myocardial infarction, acute ischemic stroke
Receptors	Other therapeutic proteins or therapeutic biotechnology products	<b>Enbrel™</b> (etanercept)	rDNA TNF-receptor/antibody fusion protein	Rheumatoid arthritis
Small proteins	Other therapeutic proteins or therapeutic biotechnology products	<b>Humalog™</b> (insulin lispro)	rDNA insulin small protein analogue	Type I diabetes
<b>Blood and blood products</b>	Other therapeutic proteins or therapeutic biotechnology products	<b>Advate™</b> (antihemophilic factor)	rDNA factor VIII	Hemophilia A
<b>Sugars, polysaccharides</b>	N/A	<b>Calciparine™</b> (heparin)	Heparin mucopolysaccharide obtained from mast cells, liver, lung, etc., of vertebrates	Prevent blood clotting in heart surgery or dialysis
<b>Nucleic acids</b>				
RNA	Therapeutic biotechnology products	<b>Macugen™</b> (pegaptanib)	RNA aptamer anti-VEGF inhibitor	Macular degeneration
DNA, RNA, RNAi	Therapeutic biotechnology products	Use in vivo or in vitro as gene therapy products	None marketed to date	None marketed to date
<b>Cells, Tissues</b>				
Cells (transplant)	N/A	Islet cells from donor pancreas	Human cells	Type I diabetes
Cells (gene-therapy)	Therapeutic biotechnology		None marketed to date	None marketed to date
Stem cells	Therapeutic biotechnology		None marketed to date	None marketed to date

rDNA = recombinant DNA technology  
 FDA has not yet approved any human gene therapy product for sale.  
 Source: PwC analysis (data collected as of December 2008)

## M&A in 2009: Biotech buying spree?

Big Pharma's buying spree has already begun in a flurry of recent megadeals, led by Pfizer's \$68-billion acquisition of Wyeth announced in January (expected to close in late 2009).<sup>1</sup> Pfizer noted that the acquisition was driven by its need to create "a broad, diversified portfolio." Wyeth holds a pipeline of vaccines, biologics and other products, as Pfizer faces losses of patent protections—most notably of Lipitor (comprising 25% of its revenue) in 2011.<sup>2</sup> Roche followed suit in March, upping its bid to \$46.8 billion to buy the remaining 44% of Genentech's shares it doesn't already own, and will wholly own the biotech pioneer's strong cancer drug portfolio and research pipeline. Merck's March announcement to acquire Schering-Plough for \$41.1 billion joined Big Pharma's chorus to diversify into high-growth biologics. Additionally, Schering-Plough had strengthened its foothold in biologics when it acquired Dutch biotech company Organon BioSciences in 2007. Other megamergers in 2008 included Eli Lilly and Co.'s purchase of ImClone Systems Inc., and Takeda Pharmaceuticals Ltd.'s purchase of Millennium Pharmaceuticals Inc.

Other high-profile mergers included Cephalon's February takeover bid for Australia's Arana Therapeutics for \$202 million, in a move to bolster its pipeline of biologics by acquiring Arana's inflammatory disease and oncology biologic compounds. In January, Cephalon and Ception Therapeutics, Inc. entered into an option agreement providing Cephalon with an option to purchase all outstanding capital stock of Ception. Ception is developing reslizumab, a humanized monoclonal antibody currently in clinical trials to treat pediatric eosinophilic esophagitis and eosinophilic asthma in adults. If reslizumab is ultimately approved—and the purchase option exercised—

Cephalon would have the opportunity to enter the biologics market.<sup>3</sup>

What effect will these megamergers have on merger and acquisition activity with small and medium-sized biotech companies? Likely, the best acquisition targets will have an attractive valuation, low risk and the right fit. "In the near term, big pharma will expect more and pay less," said Vijay Lathi, partner with New Leaf Partners. "With regards to biologics, I think the message is that their cost will need to be justified in terms of outcomes to get the type of reimbursement we've historically seen. In other words, reimbursement will come under pressure," Lathi added.

It is possible, however, that the combined entities of the megamergers will not be positioned to go on a buying spree of smaller biotech companies until their integrations wind down. "These mergers certainly require great attention within these companies," said Alan Eisenberg, Executive Vice President for Emerging Companies and Business Development at the Biotechnology Industry Organization (BIO). However, once preoccupation of rationalizing these merger companies is completed, there may be an uptick in acquisitions of biotech firms which add to acquirers' pipelines. And, naturally, other major pharmaceutical and biotech companies may well answer with their own moves into biologics-focused acquisitions. "The market seems to be presently oriented toward later-stage companies with positive cash flow or early-stage companies with platforms that have multiple applications," added Eisenberg. "However, it's not clear right now when we'll start to begin to see more M&A of smaller biotech companies." Eisenberg added.

<sup>1</sup> Pfizer to buy Wyeth for \$68 billion, cuts dividend, Reuters, January 26, 2009.

<sup>2</sup> Pfizer CEO: Wyeth takeover will be different, *Business Week*, January 26, 2009.

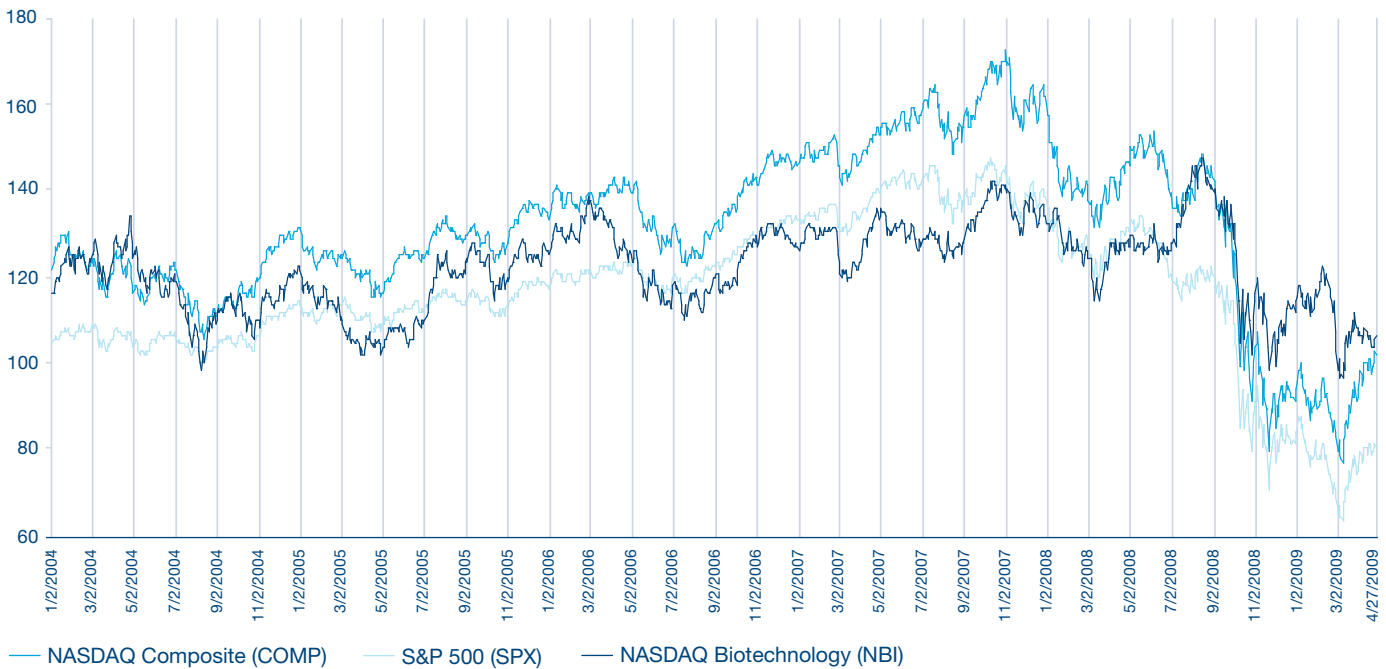
<sup>3</sup> Cephalon is offering to pay \$202 million for Arana Therapeutics, *Genetic Engineering & Biotechnology News*, February 27, 2009.

# Whither biotech valuations?

The NASDAQ Biotechnology Index fell roughly 60% in the March 2008-March 2009 period, helping to drive down valuations of private biotech companies. As valuations fall and companies continue to experience difficulty in securing credit, these conditions will likely result in an uptick in M&A activity across the bandwidth, resulting in biotech-biotech and pharma-biotech deals—especially for biotech companies whose valuations are attractive and carry limited relative risk. Despite the stock price slide of biotech companies, the NASDAQ

Biotechnology Index outperformed the S&P 500 in early 2009—for the first time since 2004 (see chart below). It outperformed the NASDAQ Composite index in October 2008, since underperforming since May 2003. Should this trend persist, it may result in actually lifting valuations of acquisition targets in private biotech companies. This rising trend could also very well have been a result of investors “building in” a consensus of market anticipation that the large pharmaceutical deals are a curtain-raiser to further acquisitions across the biotech sector.

Figure 4. Biotech stocks outperforms general markets in early 2009



## Continued partnering, alliance activity

Short of diving into acquisitions, pharmaceutical companies have waded into biologics through a spate of collaborative efforts to diversify in both product lines and geographic market penetration. Such alliances enable pharmaceutical companies to mitigate risks in the event that a promising innovation does not realize commercial viability. For example, GlaxoSmithKline entered into a \$1.4-billion pact with OncoMed Pharmaceuticals to license monoclonal antibody cancer therapies in late 2007.<sup>1</sup> Alnylam Pharmaceuticals forged a billion-dollar deal with Japan's Takeda Pharmaceuticals Co. Ltd. focusing on RNAi (RNA interference) therapies for cancer and metabolic disease.<sup>2</sup> Isis Pharmaceuticals Inc. and Genzyme Corp., too, partnered in a deal that could be worth \$2 billion (pending achieving certain research milestones) which includes licensing mipomersen, Isis' cholesterol drug targeting RNA that engineers the production of heart disease-causing proteins.<sup>3</sup> In 2008, MorphoSys and Galapagos forged an alliance aimed at developing therapeutic antibody products targeting bone and joint disease.<sup>4</sup> Novartis and Lonza established a partnership, in which Lonza would provide Novartis greater manufacturing capabilities of biologics drugs.<sup>5</sup>

The greater significance of this business combination activity is that pharmaceuticals are becoming more open to effectively buying R&D in the wake of years of declining productivity from in-house drug development. In essence, then, biotech start-ups are increasingly becoming important as incubators of new drug development not only for big pharmas but also large biopharmas. One safe route to benefit from start-ups has been through milestone-structured partnerships and alliances. But, given the recent wave of M&A activity—and the heightened competition that comes with it—acquirers may well be more inclined to forgo safer partnerships and move directly to acquisitions.

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1 GSK offers \$1.4 billion to license OncoMed therapies, *FierceBiotech*, December 10, 2007.

2 Alnylam inks major deal with Japan's Takeda, Reuters, May 27, 2008.

3 Jarvis, Lisa, Isis, Genzyme in heart drug deal, *Chemical & Engineering News*, January 14, 2008.

4 Morphosys and Galapagos to co-develop therapeutic antibodies in bone and joint disease, *Genetic Engineering & Biotechnology News*, November 26, 2008.

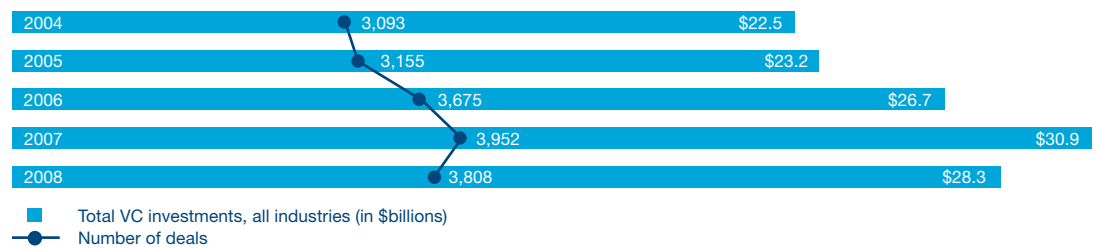
5 Novartis and Lonza partner in biologics development, *Pharmaceutical Business Review*, July 11, 2008.

# VC investment in human biotech still healthy despite economic turmoil

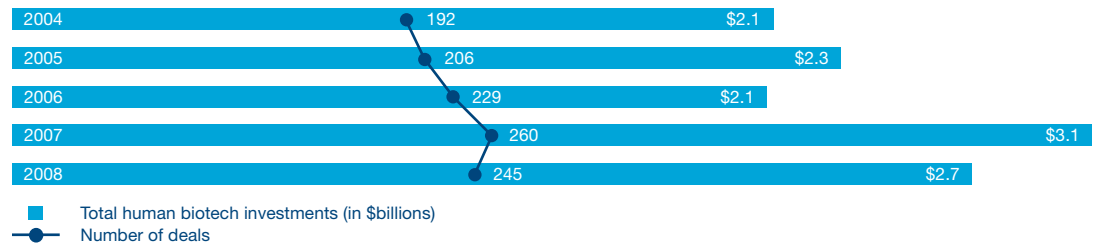
In the wake of deepening difficulties stemming from the lack of credit availability and overall recessionary pressures, VC investment in human biotech (excluding medical devices) companies fell by 11% to \$2.7 billion with 245 deals in 2008 compared to \$3.05 billion with 260 deals in 2007,

compared to the 8% decline in investment across all industry sectors, which fell for the first time since 2003, according to the MoneyTree™ Report. VC investment in the overall biotech sector, however, fell to a greater degree—or 14% to \$4.5 billion in 2008, from \$5.24 billion in 2007.

**Figure 5. Total VC investment—Overall investments**



**Figure 6. Total VC investment—Human biotech**



**Figure 7. Total VC investment—Overall biotech**



Source: PricewaterhouseCoopers/National Venture Capital Association MoneyTree™ Report (data: Thomson Reuters)

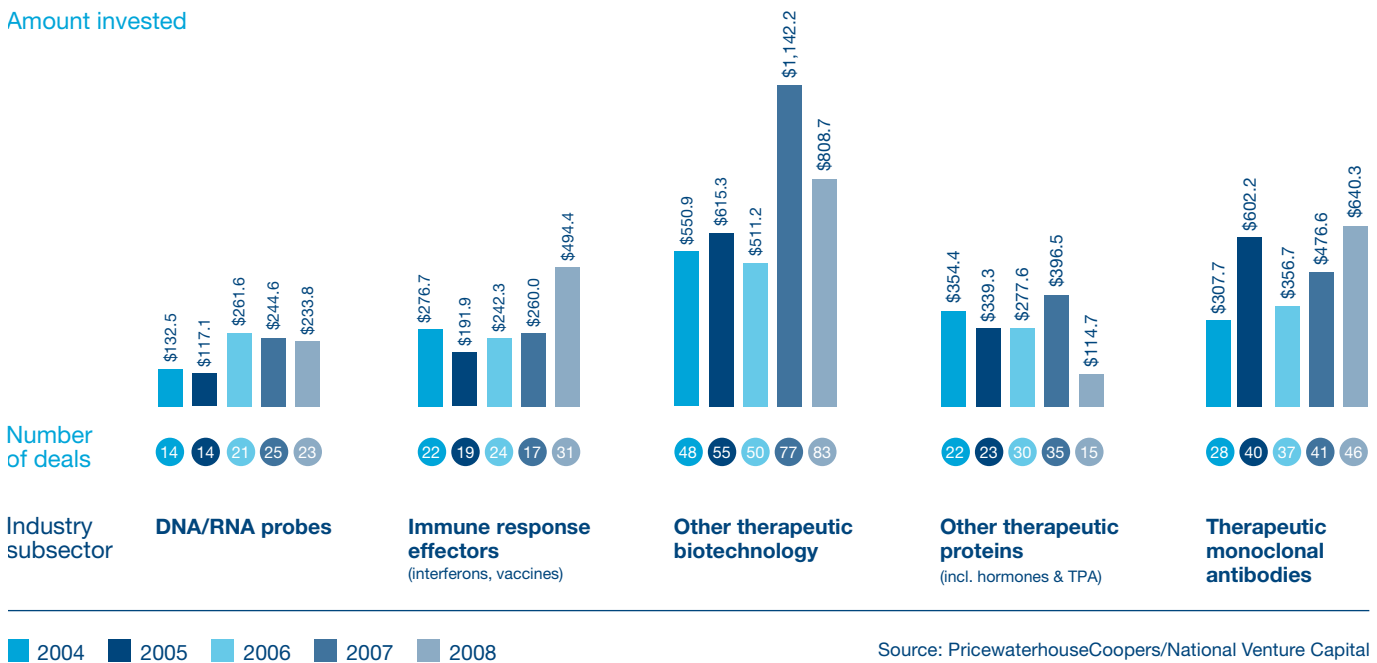
## Bright spot: Monoclonals, vaccines

Therapeutic and diagnostic biologics helped drive VC investment in the overall human biotech sector in 2008 and are the fastest-growing subsectors. The therapeutic monoclonal antibodies subsector drew increased investment in 2008 with \$640 million in 46 deals, up from \$477 million with 41 deals in 2007. Four of the top 10 human

biotech deals in 2008 were companies focusing on therapeutic monoclonal antibodies. Growing VC investment also occurred in the immune response effectors subsector (which includes vaccines and interferons), drawing \$494 million with 31 deals, up from \$260 million and 17 deals in 2007.

**Figure 8. Therapeutic mAb, immune response effectors—draw increased investments**  
(VC investment in human biotech, excluding medical devices)

Amount invested



Source: PricewaterhouseCoopers/National Venture Capital Association MoneyTree™ Report (data: Thomson Reuters)

## Funding strong in seed/start-up and early stages, falls in later stages

VC-backed human biotech companies drew increased investment at the start-up/seed (16.2%) and early stages (9.6%) of financing in 2008 compared to 2007. However, investment in the sector fell in both the expansion (17.1%) and later stages (21.1%) in 2008 compared to 2007. However, this trend may be challenged going forward. Given the heavier burden to

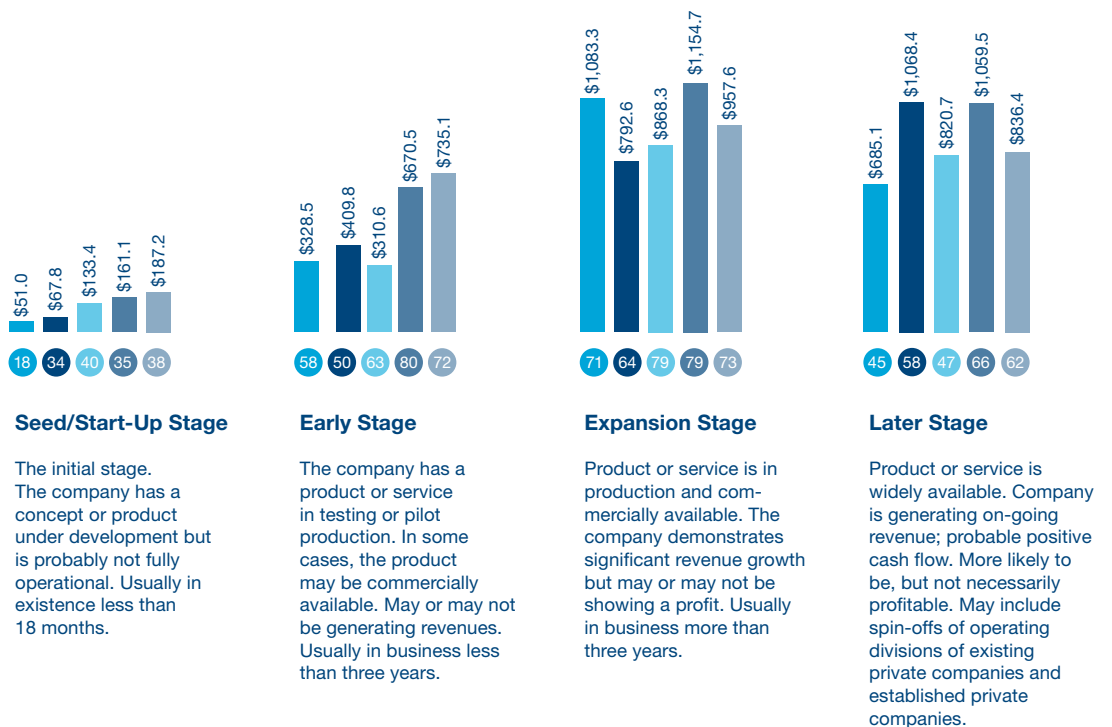
maintain capital-intensive later-stage funding in companies, VCs may well siphon off funding from smaller to bigger portfolio companies. "I think early-stage funding is going to be impacted, because VCs will need to concentrate short term on funding later-stage drugs and companies," said Ann Hanham, Ph.D., partner at Burrill & Co.

**Figure 9. Human biotech investments by stage of development**

Amount invested

Number of deals

MoneyTree stage



2004 2005 2006 2007 2008

Source: PricewaterhouseCoopers/National Venture Capital Association MoneyTree™ Report (data: Thomson Reuters)

## Strong companies draw strong investment, weathering storm

Though VC-backed investments fell overall, there were nevertheless some healthy doses of investment from VCs, suggesting that cash will continue flow to portfolio standouts. For example, Menlo Park, CA-based Pacific Biosciences of California, a DNA sequencing platform developer, received \$99.9 million. OncoMed, specializing in stem-cell cancer research, received two rounds totaling \$89.5 million. And Proteolix, Inc., which develops cancer and immune disease therapeutics, received \$79.0 million.

“Really good biotech companies will continue to get funded. If I get an exit in three-to-five years, I’m really happy, because my holding periods are usually five-to-ten years. I think some really strong companies in late 2009 will go public,” said Bryan Roberts, partner with Venrock. “It’s tough to look at these declining numbers of venture deals in a short-term time perspective, especially in biotech, which is not a price game—it’s a company selection game. If a drug works, it’s going to make money,” added Roberts.

**Figure 10. Full-year 2008 human biotech top deals**

Qtr	Company	City	State	Industry subsector	Stage of development	Investment sequence	Amount	Business description	Investors
3	Pacific Biosciences of California	Menlo Park	CA	DNA/RNA Probes	Expansion	4	\$99,999,600	Develops a DNA sequencing platform.	AllianceBernstein L.P., Alloy Ventures, Duff Ackerman Goodrich & Associates LLC, Intel Capital, Kleiner Perkins Caufield & Byers, Maverick Capital Ltd., Mohr Davidow Ventures, Morgan Stanley Private Equity
3	Proteolix, Inc.	South San Francisco	CA	Immune Response Effectors (interferons, vaccines)	Later Stage	5	\$79,000,100	Develops products that treat cancer and immune diseases.	Advanced Technology Ventures, Delphi Ventures, Latterell Venture Partners, Nomura Phase 4 Ventures, Ltd., US Venture Partners, Undisclosed Firm, Undisclosed Firm, Vertical Group, Westfield Capital Management
4	Biolex Therapeutics, Inc.	Pittsboro	NC	Therapeutic Monoclonal Antibodies	Later Stage	11	\$60,000,000	Develops therapeutic proteins based on the LEX System.	Clarus Ventures, Dow Chemical Company, Intersouth Partners, Investor Growth Capital, Inc., Johnson & Johnson Development Corporation, Mitsui & Co. Venture Partners (MCVP), OrbiMed Advisors LLC, Polaris Venture Partners, Quaker BioVentures, Inc., Undisclosed Firm
4	Bayhill Therapeutics, Inc.	Palo Alto	CA	Other Therapeutic Proteins (incl. hormones & TPA)	Later Stage	6	\$54,293,100	Develops DNA-based pharmaceutical therapeutics.	De Novo Ventures, Morgenthaler Ventures, US Venture Partners, Undisclosed Firm
3	ChemoCentryx, Inc.	Mountain View	CA	Immune Response Effectors (interferons, vaccines)	Later Stage	5	\$50,000,300	Develops oral drugs for autoimmune and inflammatory disorders and oncology.	Alta Partners, HBM BioVentures AG, Odlander, Fredrikson & Co. AB, OrbiMed Advisors LLC, Undisclosed Firm, Undisclosed Firm
3	Ironwood Pharmaceuticals, Inc.	Cambridge	MA	Other Therapeutic Biotechnology	Later Stage	9	\$50,000,000	Develops gastrointestinal and cardiovascular therapies.	Fidelity Biosciences, Morgan Stanley Private Equity, Polaris Venture Partners, Venrock Associates
4	OncoMed Pharmaceuticals, Inc.	Redwood City	CA	Therapeutic Monoclonal Antibodies	Expansion	8	\$46,331,100	Develops a series of therapies for solid tumors.	Adams Street Partners LLC, Bay Partners, De Novo Ventures, GSK Venture LLC, Latterell Venture Partners, Nomura International PLC, US Venture Partners, Vertical Group
3	OncoMed Pharmaceuticals, Inc.	Redwood City	CA	Therapeutic Monoclonal Antibodies	Expansion	7	\$43,125,000	Develops a series of therapies for solid tumors.	Bay Partners, De Novo Ventures, Morgenthaler Ventures, US Venture Partners, Undisclosed Venture Firm
3	Light Sciences Oncology, Inc.	Bellevue	WA	Other Therapeutic Biotechnology	Later Stage	5	\$41,000,100	Develops light infusion technology for the treatment of cancer.	Adams Street Partners LLC, Essex Woodlands Health Ventures, Novo A/S, Undisclosed Firm, Undisclosed Firm, Undisclosed Firm
4	Catalyst Biosciences, Inc.	South San Francisco	CA	Therapeutic Monoclonal Antibodies	Early Stage	6	\$40,400,000	Develops and engineers therapeutic protease products.	Burrill & Company, Essex Woodlands Health Ventures, HealthCare Ventures LLC, Johnson & Johnson Development Corporation, Morgenthaler Ventures, Novartis Venture Fund, Sofinnova Ventures

Source: PricewaterhouseCoopers/National Venture Capital Association MoneyTree™ Report, Data: Thomson Financial

# Watching Capitol Hill

The Obama administration has carried out a number of significant initiatives aimed at changing national healthcare policy, most of which will have short- and long-term effects on the biopharmaceutical industry. Under the February 2009 American Recovery and Reinvestment Act, \$19.2 billion was dedicated to healthcare IT, intended to realize the Administration's goal of building

a national, fully interoperable health IT records system within five years.

Such a system would vastly widen genomic informatics capability and build a foundation for potentially myriad fundamental changes steering US healthcare toward personalized medicine.

## Obama administration's healthcare initiatives' impact on biotech

Initiative	Provisions	Implications for biotech
American Recovery and Reinvestment Act, February 2009	\$19.2 billion dedicated to healthcare IT to build a national, interoperable health IT records system within five years	Potential to lower costs of clinical trials through more-efficient patient/participant recruitment as well as integrating pharmacogenomic data
American Recovery and Reinvestment Act, February 2009	\$10 billion in NIH biomedical funding	Potentially bolster the number of basic research discoveries that could be commercialized by biotech firms
Stem-cell research ban reversal, March 2009	Reverses restrictions on researching hundreds of embryonic stem-cell lines banned in 2001	Anticipated to open a new era of stem-cell-based therapy discoveries, and encourage public-private collaboration leading to commercialization

## Health IT and Biotech

Efficiencies gained through an interoperable electronic health records (EHR) infrastructure could potentially reduce the average costs of clinical trials, particularly Phase III, which cost between \$135 million and \$270 million.<sup>1</sup> The act also provides for \$1.1 billion for comparative effectiveness of treatments for diseases, which will likely benefit companies with drug products that already demonstrate efficacy based on a targeted, pharmacogenomic approach. The development of an EHR infrastructure will allow for collection and analysis of vast amounts of clinical data that would help enable these comparative effectiveness efforts.

EHRs could also have significant effects on biotech companies' capabilities to identify subpopulations with unmet therapeutic needs, and to carry out more-efficient and less-costly trials to test the safety and efficacy of new drugs. As more patient EHRs contain genotype information, biotech companies will more easily and more cost-effectively determine which therapies have outcomes on certain subpopulations, and making that data available to physicians (and patients) would likely lead to more-successful outcomes. "Defining the patient subpopulations for which products work presents a fundamental change in how

<sup>1</sup> Pharma 2020: The vision, PricewaterhouseCoopers, 2008.

both pharmaceutical and biotech firms will undertake [R&D] going forward,” said Gregory Downing, D.O., Ph.D., Director, Personalized Health Care Initiative, US Department of Health and Human Services. “Developing a drug that is known to be effective in a sub stratified population, and showing doctors how to use the drug on a specific subpopulation in a clinical setting—this is what will define successful biotech companies in the future,” Downing added. As EHRs become more robust, biotech companies will also be able to follow more closely the clinical outcomes of patients treated with their products and, therefore, acquire a more refined assessment of the safety of therapies, said Downing.

Additionally, these initiatives could be invaluable resources for biopharmaceutical research and development programs and may ultimately serve to make clinical trials more focused on the subpopulations that will most likely respond to a certain drug treatment. Small biotech companies had hoped the stimulus package would include provisions that would allow biotech companies a refundable tax credit against net operating losses. As the law currently stands, biotech companies may receive such credits only once they attain profits to apply the credit against. Legislation allowing cash-strapped and unprofitable biotech companies to effectively “cash in” on current losses is expected to be revisited later this year. The act does, however, provide a tax credit for developers of diagnostic tests that are aimed at improving the safety and efficacy of drugs.

## Bolstered NIH funding, stem-cell-ban lifting, could benefit biotech in long term

The act also provided \$10 billion in biomedical funding for the National Institutes of Health, with specific funding for cancer, Alzheimer’s and heart disease, among other conditions. This significant boost in NIH funding will revive flagging academic research budgets and will likely, over time, benefit biotech and pharmaceutical companies capable of taking discoveries from the lab to clinical trials. Furthermore, the administration’s fiscal 2010 budget calls for over \$6 billion for the NIH (on top of the Recovery Act’s \$10 billion), with a strategic emphasis on the development of cancer diagnostics, therapeutics and cures—part of the administration’s multiyear plan to double funding for cancer research. The budget also calls for efforts to make it easier for Americans to purchase drugs from other countries.

“The NIH money granted for basic biomedical research could have a beneficial, long-run effect on biotech firms, which will help bring promising discoveries from the lab to commercial viability,” said Alan Eisenberg, Executive Vice President for Emerging Companies and Business Development at BIO.

In March, President Obama reversed restrictions on embryonic stem-cell research, opening prospects for researchers to study hundreds of new embryonic stem-cell lines previously banned in 2001. It will likely also attract new investment in cell-based therapies—not only among academic institutions, but also private biotech companies. In early 2009, Geron Corp., a Menlo, CA-based biotech company, received FDA approval for the first embryonic-cell clinical trial in the US, to test against spinal cord injuries.

## The long-reaching effects of electronic health records

Biomedical innovations triggered by the Human Genome Project, begun in 1990, will likely realize transformational improvements in quality and efficacy of patient care when paired with parallel advances in health information technology. The stimulus package calls for the Centers for Medicare & Medicaid Services to incentivize physicians to convert to EHRs. This scheme, over time, will bolster public-private collaboration to continue to determine effective evidence-based innovations—specifically, diagnostic tests and, ultimately, prescribing the therapeutics

that will lead to the best outcome, based on patients' genomic makeup. These EHRs could potentially become an invaluable resource to support the development of new diagnostics and therapies, as well as streamlining—and lower the costs of—clinical trials. The data collected from patients' EHRs will, in effect, create a bioinformatics infrastructure that could spur further advances in research across academic and government research labs, as well as private and publicly listed biotech and pharmaceutical companies.

## Biologics 2.0: The unknown future of generic biologics

The US Congressional Budget Office has estimated that generic biologics could potentially cut American drug costs by \$25 billion over the next decade, or about 0.5% of spending on prescription drugs.<sup>1</sup> The Obama administration's healthcare initiatives clearly support increased use of generic drugs. As these policies have been promoted and legislated there has been a concomitant surge of business combination activity targeting developers and manufacturers of generic versions of both small- and large-molecule drugs. For example, Israel's Teva Pharmaceutical Industries Ltd., the world's biggest generic drug maker, signed a joint venture with Swiss chemicals company Lonza AG in a deal aimed at becoming a global supplier of generic biologics.<sup>2</sup>

Setting market and data exclusivity for biologics will have enormous implications for developers of biologics—and for

those companies positioning to enter the biosimilars market (also known as generic biologics or follow-on biologics, FOB). The FOB market is estimated to reach \$15 billion by 2013 (based on 10 branded biologics going off patent).

A number of bills have been introduced to Congress, setting anywhere from 5 to 12 years of data and market exclusivity for biologics. Apart from marking the number of years of patent protection, a major feature of such legislation will be to what extent FOB developers will be subject to the same safety and efficacy requirements, manufacturing standards and clinical trials as was the pioneer drug maker. Also, in reference to his proposed fiscal year 2010 budget, President Obama said that "the administration will accelerate access to make affordable generic biologic drugs available through the establishment of a workable regulatory,

<sup>1</sup> News Analysis: Biotech and generic industries lock horns over biosimilars, *Genetic Engineering & Biotechnology News*, March 4, 2009.

<sup>2</sup> Teva, Lonza, team up in biosimilars market, *Jerusalem Post*, January 21, 2009.

scientific and legal pathway for generic versions of biologic drugs.”<sup>3</sup> This pathway, Obama added, would support “new efforts... to establish a new regulatory pathway to approve generic biologics.”

“Down the road, the data and market exclusivity will have a big impact. But right now, nobody really knows how hard it will be to break patents....The intellectual property for biologics is so radically different than that of small-molecule drugs, and we really don’t know how hard or soft those patents will be,” said John E. Calfee, resident scholar, American Enterprise Institute for Public Policy Research.

The US has lagged well behind the rest of the world in generic biologics. According to the Generic Pharmaceuticals Association, some 42 companies globally are currently developing generic biologics, which are sold in Asia and Europe. FOB marketing in Europe requires the European Union’s Committee for Medicinal Products for Human Use (CHMP) as well as European Commission approval (examples include: Novartis’ epoetin zeta; Hospira’s epoetin zeta; and Dr. Reddy’s Laboratory, which manufactures two generic biologics in India which are versions of Roche’s Rituxan and Amgen’s Neupogen).

It’s still unclear how FOBs will play out in the US, given possibly steeper barriers to entry when compared to that of synthesized, small molecules. “The FDA will be very slow to approve biosimilars, doctors will be slow to persuade patients to use them and payers will be slow to make a wholesale shift to them. For payers to really get behind biosimilars, they will probably have to come to market at a discount of at least 30% of the branded biologic price, and I think hitting that discount will be challenging....The intellectual property issues are fuzzy, because it is unclear how easily or difficult their patents

will be defended. I’d be surprised if there is much activity in mAb biosimilars in the next 5 to 10 years,” said John E. Calfee, resident scholar, American Enterprise Institute for Public Policy Research, and co-author (with Claude Barfield) of *Biotechnology and the Patent System: Balancing Innovation and Property Rights*. “On the clinical trials requirements, it will probably be done on a sliding scale, based on the EU approach, which demands larger clinical trials for drugs that hold greater potential for having safety issues emerge. This would especially be the case with monoclonal antibodies. But there will be a lag, compared to small molecules, in the time between when the exclusivity period ends and the biosimilar hits the market—it could be months or a year, as opposed to almost immediately for small molecule drugs,” added Calfee.

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<sup>3</sup> “Obama healthcare budget includes FDA reform,” Megan Fox, Reuters, February 26, 2009.

What this means for your business

**Biologics likely to expand  
role in fueling Big Pharma's  
drug development.**

As biologic products continue to contribute larger shares of growth to pharmaceutical companies, targeted biologics products could potentially become “mini-blockbusters” in the billion-dollar range. These will likely be sourced by biotech companies—through either a partnership or an acquisition—in a marked departure from the multiple-billion-dollar blockbuster drug development model which appears increasingly unsustainable.

Biotech companies with biologic products—particularly those ready to enter Phase II clinical trials—will be well positioned to be acquired by large pharmaceutical companies intent on diversifying their portfolios, and to stem revenue shortfalls tied to patent expirations of blockbuster drugs.

Biotech companies with drug platforms in the high-growth sectors of biologics—such as vaccines and monoclonal antibodies and other therapeutic proteins targeting as-yet unmet therapeutics areas—will continue to be attractive acquisition targets.

Cash-strapped biotech companies with promising platforms will need to rethink their exit strategies amidst the current poor IPO market and squeeze on credit and venture funding, and become more open to forging partnerships or being acquired.

In the long term, biotech companies which are positioned to leverage the potentially rich and vast patient and outcome information collected through interoperable electronic health records systems will benefit in several ways: identifying areas of unmet needs to drive diagnostic and therapeutic innovations; and streamlining the complex and capital-intensive clinical trials process. Additionally, interoperable EHRs will likely better enable biotech companies to pair diagnostic and therapeutic products for the same disease as part of their drug development strategy and central to investors, Big Pharma, private and public payers, and other healthcare stakeholders.

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