Burrill & Company’s 27th Annual Report on the Life Sciences Industry

Biotech 2013 • Life Sciences
Healthcare and Biogreentech
Innovation from Discovery to Delivery

Capturing Value

Burrill & Company’s annual report is an invaluable, one-stop resource for making sense of today’s changing life sciences landscape. Today’s companies need to think differently about how they create and capture value. Preparing you for this ever-changing world, Biotech 2013 • Life Sciences: Capturing Value

- Provides analysis of the life sciences industry with data, graphs, and industry highlights including new product approvals, advances in technology, and details of financing and M&A transactions.
- Examines how pharmaceutical companies are responding to increasing demands from payers to demonstrate the value of new products and cut the time and cost of R&D.
- Tracks the convergence of wireless, mobile, and Internet technologies transforming the economics and delivery of healthcare worldwide.
- Looks at what countries around the globe are doing to establish life sciences industries and the opportunity companies have to access capital in markets where their work may have greater value.
- Explains the challenges biofuels developers face in expanding production to commercial scale.
- Analyzes the global interplay between business, policy, regulation, and reimbursement.

Comprehensive, unparalleled coverage of key trends makes Capturing Value a critical resource for life sciences professionals.

G. Steven Burrill has been involved in the growth and prosperity of the biotechnology industry for more than 45 years. An early pioneer, Mr. Burrill is one of the original architects of the industry and one of its most avid and sustained developers. He is currently chairman of Alivecor, and serves on the boards of directors of Catalyst Biosciences, Depomed, Newbridge Pharmaceuticals, Novadaq Technologies, Tangacept, and XDx. Previously he served as chairman of the boards of Bioimagene, Abunda Nutrition and Pharmasset. He has received the Richard Bolte, Sr. Award for supporting industries from the Chemical Heritage Foundation, a lifetime achievement award from Scrip Intelligence’s, the BayBio Pantheon DINA lifetime achievement award for his biotech leadership worldwide, and the Alan Cranston living legend award for advancing biomedical research globally. In 2002, he was recognized as a biotech investment visionary by Scientific American magazine.
Biotech 2013 - Life Sciences
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Innovation from Discovery to Delivery
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Acknowledgements

Biotech 2013-Life Sciences: Capturing Value, our 27th annual report on the life sciences industry, is the result of an intense, collaborative effort. Daniel S. Levine led the charge on this year’s edition, along with writing, editing, and research from Marie Daghlian, Michael Fitzhugh, Vinay Singh, and Sheryl P. Denker. Carol Collier designed this year’s book and had assistance with graphics and layout from Deven Cao.

Many of Burrill & Company’s team lent their expertise and assistance to this year’s book. This includes Sergey Axenovich, Ann Hanham, Dirk Lammerts, Irena Melnikova, Konstantin Skyrabin, Sarah Thompson, Greg Young, Derek Wong, and Roger Wyse.

In addition, we appreciate the generosity of our many friends in the industry, who shared their thoughts and insights with us during the creation of this book. In particular, we would like to acknowledge Jim Lane, editor of Biofuels Digest; and Greg Scott, president and founder of ChinaBio.
BIOTECH 2013 – LIFE SCIENCES: CAPTURING VALUE

Burrill & Company’s 27th Annual Report on the Life Sciences Industry

Though economies around the world are improving from the global recession, the recovery remains fragile and austerity continues to be the watchword of the day. As healthcare costs continue to rise worldwide, systems are shifting to value-based models of care as a way to rein in costs.

In this emerging environment, drug and device makers will need to be able not only to prove the safety and efficacy of their products, but the value as well. In addition, countries around the world are mandating the use of generic drugs and imposing price controls, or even in extreme cases, turning to compulsory licensing.

As companies work to reinvent the process of research and development to address flagging productivity, they now face the prospect of a narrowing opportunity to recover costs and profit from their work. This is causing them to rethink their business models and reconceive their businesses in the most fundamental ways.

It is easy to be distracted by the pressures on companies today and to forget how exciting a time this is for our industry. As we mark the 60th year of the publication of James Watson and Francis Crick’s landmark work on the structure of DNA, we are on the cusp of whole genome sequencing becoming a standard part of clinical practice. New targeted therapies are delivering on an era of precision medicine. And, the convergence of information technology with healthcare is leading to new tools that will not only create great savings by changing the way healthcare is accessed and delivered, but also empower people to take control over their own health and wellness.

The growing middle class around the world and the rise of emerging economies are creating new demand for not just healthcare, but food, fuel, and manufactured goods. We are faced with great challenges, but it is our industry that is forging answers.

No longer will companies be able to innovate and assume the value of their work will be apparent. Instead, they will need to be prepared to prove the value of their products in a world where value is transient, value is payer dependent, value is geographically different, and value is undefined. And, as pressures on pricing intensify, they will need to be creative in forging new strategies to capture value.

G. Steven Burrill
CEO, Burrill & Company
April 2013
Introduction:

Two Strands
In 1953, James Watson and Francis Crick made their groundbreaking discovery about the structure of DNA. Sixty years later, no one could have envisioned how that fundamental discovery would help give rise to the biotechnology industry, or how far reaching the use of biotechnology would extend. Indeed, today biotechnology is not only transforming the way we diagnose and treat disease, but how we produce goods, feed our planet, and fuel the world.

Chapter 1: Value

Seeking Value
Today’s pressure on pharmaceutical companies reflects greater pressures throughout the entire healthcare ecosystem as payers, patients, and providers wrestle with escalating costs and drive healthcare systems around the world away from being cost-based to becoming value-based. For pharmaceutical companies, this means not only a greater emphasis on creating value, but seeking new ways to capture value as well, particularly at a time when drugs will need to demonstrate they provide benefits commensurate with their costs and governments and payers squeeze down prices. The challenge for drugmakers, broadly speaking, is to find new ways to both create value and capture value.

Chapter 2: Personalized Medicine

A Quest for Precision
As payers increasingly demand proof of value of new therapies and regulators seek greater certainty about the safety and efficacy of drugs, drug developers are focusing more on targeted therapies as a better route to clinical, regulatory, and economic success. They are also finding that the blockbuster era is not dead, only that the era of the one-size-fits-all blockbuster is coming to an end. Beyond precision medicine, targeted therapeutics, and treatments tailored to individual patients, the greater promise of personalized medicine lies in radically transforming medicine. Through improved diagnostics, new understanding of the human genome, and an array of new monitoring devices in the emerging world of digital health, healthcare is on the cusp of realizing the deeper vision of precision healthcare—defined by its focus on personal, predictive, and preventive care.

Chapter 3: Digital Health

Tying It All Together
Inexpensive, ubiquitous computing is revolutionizing the delivery of healthcare. Opportunities for health interventions and advice once tied to limited moments and places are becoming ever more closely woven into everyday life as smart sensors, algorithms, and persistent connectivity enable new approaches to wellness. Data once locked in disconnected silos is now being pieced together to paint richer pictures of the dynamic forces shaping our understanding of complex human behaviors and biology. Realizing the advantages made possible in this new world of digital health will be difficult at times, but the potential payoffs are too great to ignore.

Chapter 4: Healthcare

Demanding Value
At the heart of the Affordable Care Act is an ambitious and seemingly contradictory goal of expanding and improving care while cutting costs. The challenge is not unique to the United States. Healthcare systems around the world are struggling with the need to provide more for less and experimenting with ways to accomplish that, including value-based approaches that tie payments to outcomes, focusing on preventive care, and requiring proof that new products provide economic as well as health benefits. The hope is that by increasing efficiency, aligning incentives, and cutting waste, healthcare systems will be able to reverse long-term trends of rising costs, and if not cut spending, at least bring growth in spending under control to manageable levels.

Chapter 5: Regulation and Policy

Keeping Pace
In a world of growing scientific complexity, regulators and policymakers are adapting. They are revising laws, reviewing programs, and raising expectations. Key legislation impacting industry was renewed in 2012, reshaping and reaffirming the ties between the structure of medical device companies, and the FDA. The mounting cost of innovative therapies and tightening national budgets has continued to shape policy decisions the world over. In this time of government budgets are under pressure while industry faces new fees and taxes. Meanwhile, comparative effectiveness research and value assessments are becoming more common and forcing industry to work in new ways with regulators and payers.
Chapter 6: Global Markets
The Geography of Value
As the world moves toward becoming an interconnected, borderless marketplace, opportunities are growing for companies to leverage specific geographical markets, national economic growth incentives, diverse local customs, and regulatory regimes as a means to successfully achieve their goals. Governments around the world see the importance of investing in the life sciences to build innovation-based economies that can provide high quality jobs and transform their societies for the better, especially amid the austere economic times and global problems facing the world today. The challenge for innovative companies is to understand and be able to take advantage of opportunities when and where they arise. Those that succeed are poised to reap huge rewards for their efforts, both in monetary terms and in terms of improved human health and welfare.

Chapter 7: Biogreentech
The Value of Sustainability
Innovative companies are using the tools of biotechnology and engineering to improve crop productivity and develop low-carbon, renewable, bio-based fuels, chemicals, and products as alternatives to those made with fossil fuels. In 2012 they made headway toward creating a viable biorenewables industry in a challenging economic climate, and demonstrating their technologies at scale. While their success is not yet assured, the drivers of the industry are there with energy and food prices only going up, land becoming scarcer, and demand on natural resources intensifying. In a finite world, biotechnologies that can move us to a low-carbon future will eventually gain value, and deliver it to the benefit of mankind.

Chapter 8: M&A and Partnering
Restraint and Constraint
With capital markets still difficult for emerging growth biopharmaceutical companies, Big Pharma showed self-restraint in 2012. In fact, 2012 was notable for the small number of multi-billion dollar deals. Life sciences M&A transactions totaled $109.4 billion globally, a 31 percent drop compared to 2011. On the partnering front, leading pharmaceuticals sought to strengthen their pipelines and sought access to new markets through creative dealmaking that often required their partners to shoulder substantial risks. That will continue in 2013. But as Big Pharma absorbs past acquisitions, it might be ready to dive back into the M&A pool and make a big splash in the near term. Many of these companies are sitting on large stores of cash and it is likely that there will be a pickup in acquisitions in 2013.

Chapter 9: Finance
Changing Perspectives on Value
One of the biggest challenges for life sciences companies is access to capital. Approaches to address unmet medical needs remain complex and expensive to develop, and there is no single path to financing a company today. The traditional path from venture financing to IPO that characterized the biotechnology industry in the early days served it well, but is no longer a reliable model for most companies. Instead, companies need to consider new and creative approaches to funding. Non-dilutive sources of capital are available to those that think globally about funding opportunities and seek out a range of new funding sources that play an increasingly important role, particularly for early-stage companies. These sources include not only government grants, but also non-profit patient advocacy, disease-focused, and philanthropic groups. Public and private capital is still available to fuel growth, just more expensive and challenging to obtain.

Endword:
Value is What You Get
For much of the history of the biotechnology industry, the practical question faced by therapeutics companies throughout the discovery and development process was, “Will we be able to get this approved?” That has changed. Though companies are no less concerned about their experimental products proving safe and efficacious, the overriding question for executives and investors evaluating a potential product’s worth has become, “Can I get paid for this?”

About Burrill & Company
A look inside Burrill & Company and its venture capital/private equity, merchant banking/investment banking, and media operations.
INTRODUCTION:

Two Strands

Sixty years since Watson and Crick—quite an industry we’ve built!

In 1953, James Watson and Francis Crick made their groundbreaking discovery about the structure of DNA. Sixty years later, it’s hard to believe that anyone could have envisioned how that fundamental discovery would help give rise to the biotechnology industry, or how far reaching the use of biotechnology would extend. Indeed, today biotechnology is not only transforming the way we diagnose and treat disease, but how we produce goods, feed our planet, and fuel the world.

The work, considered by many to be among the most important in biology, helped set the stage for the biotech century. The discovery of the double helix structure of DNA holds lessons for our industry today and some reminders for entrepreneurs, researchers, investors, and executives as they seek to advance science, build companies, and address a list of intractable global problems.

In many ways, two strands seems an appropriate metaphor. Crick was sophisticated and brilliant, Watson was direct and inspirational. Like two complimentary personalities, the biotech industry has been driven by dualities of innovation and capital, imagination and rigor, science and entrepreneurship.

As with DNA itself, there is a tendency to embrace the elegance of simplicity, even though things are often more complex than they first appear. Watson and Crick are credited with the discovery of the structure of DNA, but their work depended on the work of others that came before them, as well as collaborators.

In 1943, Oswald Avery found that when DNA was transferred from a dead strain of pneumococcus to a live strain, the donor’s hereditary characteristics came along. This brought the breakthrough understanding that DNA, not protein, carries hereditary information, guiding future discoveries. In 1949 technological developments in paper chromatography and the photoelectric ultraviolet spectrophotometer allowed Erwin Chargaff to determine that in DNA, the amounts of adenine and thymine, as well as those of cytosine and guanine, were the same, and that the composition of DNA varies from one species to another, evidence of molecular diversity.

By the early 1950s, scientists understood that genes, consisting of DNA, contained the information of heredity and that they were passed from generation to generation with fidelity. It was the X-ray diffraction experiments of Rosalind Franklin and Maurice Wilkins, together with the modeling experiments of Watson and Crick, that solidified the physical structure and gave value to the scientific information. Franklin’s famous X-ray diffraction image, known as photograph 51, revealed the helical repeat structure of the DNA molecule. Watson and Crick proposed a double helix with base-pairing, and the “copying mechanism for the genetic material” was established.

In many ways, technological advances fueled the race to define the structure of DNA in the same way that technological advances fueled the race to decipher the genome. And with the mapping of the human genome has come a move toward more personalized therapies, predictive diagnostics, and clinical applications of whole genome sequencing.

Since the discovery by Watson and Crick, layers of complexity have been added as scientists learned it is not just what is contained in DNA structure that shapes human development and underlies wellness and disease, but how DNA is influenced by diet, the environment, and an evolving list of “omes,” such as the proteome, the epigenome, the metabolome, the microbiome, and others. In 2012, scientists shattered cozy notions that a gene consists of a tidy package of expressed and non-expressed DNA. On the basis of next-generation sequencing and interpretation of non-coding regions, the ENCODE Consortium proposed to redefine the gene.

As appreciation has grown for the complexity of the world of genomics, so too has the appreciation for what it takes to carry a research discovery from the lab to a product on the market that benefits patients. As with Watson and Crick, the groundbreaking work they did was the result of collaboration. It was not just collaboration between the two, but with others as well.

Collaboration today has become essential to driving advances in the industry. In the early days of biotech, collaboration was a practical way to access capital needed to advance new therapies to market, but today, collaboration has become essential as a way to address the high cost and length of time it takes to bring new innovative therapies and other products to market. In fact, industry is now entering into unprecedented collaboration with competitors, academics, payers, and regulators to ensure innovation is sustainable.

The work of Watson and Crick was essential to the enormous value that was created in the wake of their historic discovery. Appreciating DNA structure facilitated Paul Berg, Stanley Cohen, and Herbert Boyer’s successful gene splicing work, Frederick Sanger’s method for sequencing DNA, Kerry Mullis’ development of PCR, and, of course, the Human Genome Project itself. All of this has fueled creation of the multi-billion global biotechnology industry, but increasingly the challenges for companies in the evolving environment are how to bring products to patients and how to profit from their hard work.

Two strands: value creation and value capture.
<table>
<thead>
<tr>
<th>Year</th>
<th>Event</th>
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</thead>
<tbody>
<tr>
<td>1953</td>
<td>Rosalind Franklin and Maurice Wilkins complete X-ray crystallography images and analysis indicating the helical structure of DNA. Double helix model developed and completed by James Watson and Francis Crick.</td>
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<tr>
<td>1958</td>
<td>Severo Ochoa and Arthur Kornberg receive Nobel Prize for work on mechanisms of ribonucleic acid and deoxyribonucleic acid synthesis.</td>
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<tr>
<td>1968</td>
<td>Robert W. Holley, H. Gobind Khorana, and Marshall W. Nirenberg receive Nobel Prize for work on translating the genetic code and connecting it to protein synthesis.</td>
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<tr>
<td>1971</td>
<td>Paul Berg’s landmark experiment creating the first recombinant DNA molecule.</td>
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<tr>
<td>1973</td>
<td>Stanley Cohen and Herb Boyer develop recombinant DNA technology. They demonstrate that DNA molecules may be cloned in foreign cells.</td>
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<tr>
<td>1975</td>
<td>Sanger dideoxy chain-termination method of DNA sequencing developed.</td>
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<td>1976</td>
<td>Genentech founded by Boyer and Robert Swanson.</td>
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<tr>
<td>1977</td>
<td>Maxam and Gilbert chemical modification and base cleavage method of DNA sequencing developed. Bachetti and Graham DNA transfer method developed. Boyer at UCSF and Keisch Ikuura at City of Hope Medical Center express mammalian somatostatin protein in bacteria.</td>
</tr>
<tr>
<td>1978</td>
<td>Expression of recombinant human insulin. Eli Lilly and Company sign joint-venture agreement with Genentech to develop the production process for Humulin.</td>
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<td>1980</td>
<td>U.S. Supreme Court rules in Diamond v. Chakrabarty that genetically modified organisms are patentable.</td>
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<td>1982</td>
<td>Approved by the FDA, Humulin is the first biotechnology product to appear on the market. Commercial release of first protein synthesizer machine by ABI.</td>
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<td>1983</td>
<td>Kary Mullis conceives of Polymerase Chain Reaction and develops it in collaboration with Cetus Corporation colleagues Henry Erlich and David Gelfand.</td>
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<td>1985</td>
<td>Monsanto begins work on GM plants.</td>
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<td>1986</td>
<td>Cetus files first patent application.</td>
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<tr>
<td>1989</td>
<td>Science Magazine declares Taq polymerase “molecule of the year.” Hoffmann-La Roche and Cetus begin joint development of diagnostic applications for PCR.</td>
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<td>1991</td>
<td>Hoffmann-La Roche acquires worldwide rights and patents to PCR. RMD founded exclusively to develop diagnostic and other tests utilizing PCR technology.</td>
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<td>1993</td>
<td>Microarrays for gene expression and sequence analysis.</td>
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<td>1995</td>
<td>High-throughput dye-based DNA sequencing.</td>
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<tr>
<td>1998</td>
<td>RNAi screening to specify gene function. Mass spectrometric genotyping of single-letter changes in the DNA, known as single-nucleotide polymorphisms, or SNPs.</td>
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<tr>
<td>1999</td>
<td>U.S. blood centers implement nucleic acid technology testing for HCV and HIV under an Investigational New Drug application. Massively parallel high-speed DNA sequencing developed by Jonathan Rothberg.</td>
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<tr>
<td>2000</td>
<td>COST OF HUMAN GENOME PROJECT $3 BILLION</td>
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<td>2001</td>
<td>First draft of human genome sequence.</td>
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<tr>
<td>2004</td>
<td>Roche’s AmpliChip CYP450 test available for use in Europe and cleared by the FDA. The product is the first microarray-based test, and first pharmacogenomic test, to receive clearance for diagnostic use in the U.S.</td>
</tr>
<tr>
<td>2005</td>
<td>Next generation sequencing: four-color DNA massively parallel sequencing by synthesis; sequencing by supported oligonucleotide ligation and detection, known as SOLiD, based on repeated rounds of ligation and cleavage of oligonucleotide probes. International HapMap Project publishes SNP database of common variation in the human genome.</td>
</tr>
<tr>
<td>2008</td>
<td>COST PER GENOME $15 M</td>
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<tr>
<td>2009</td>
<td>Patent for Ion Torrent sequencing, an advance that transfers chemical information to digital information.</td>
</tr>
<tr>
<td>2010</td>
<td>COST PER GENOME $40,000</td>
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<tr>
<td>2011</td>
<td>COST PER GENOME $10,000</td>
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<tr>
<td>2012</td>
<td>COST PER GENOME $5,000</td>
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<tr>
<td>2013</td>
<td>COST PER GENOME $1,000</td>
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Value

Today’s pressure on pharmaceutical companies reflects greater pressures throughout the entire healthcare ecosystem as payers, patients, and providers wrestle with escalating costs and drive healthcare systems around the world away from being cost-based to becoming value-based. For pharmaceutical companies, this means not only a greater emphasis on creating value, but seeking new ways to capture value as well, particularly at a time when drugs will need to demonstrate they provide benefits commensurate with their costs and governments and payers squeeze down prices. The challenge for drugmakers, broadly speaking, is to find new ways to both create value and capture value.
CHAPTER 1:

Seeking Value

Drugmakers are responding to a new world in which safety and efficacy alone are no longer the measures of a drug’s approval and acceptance.

On August 3, 2012, the U.S. Food and Drug Administration approved Zaltrap, a new therapeutic to treat colorectal cancer. Colorectal cancer continues to take a deadly toll globally; it is responsible for more than half a million deaths each year and is the fourth leading cause of death in the United States.

Zaltrap, developed by Regeneron Pharmaceuticals and Sanofi, inhibits angiogenesis, the process of blood vessel formation needed to fuel tumor growth, essentially choking off the blood supply to the tumors. The FDA approved Zaltrap for use in combination with FOLFIRI chemotherapy, a combination of folic acid, fluorouracil and irinotecan, for patients whose cancer has spread to other parts of the body and whose tumors are resistant to or progressing after oxaliplatin-containing chemotherapy. Zaltrap was hailed by the drugmakers as a novel agent that “provides a new option to address the unmet medical need” by the drugmakers.

But the clinical trial results suggest the benefits are limited. Patients who received Zaltrap in combination with FOLFIRI chemotherapy lived an average of 13.5 months compared to an average of 12 months for those receiving FOLFIRI and a placebo. Reduction in the size of the tumor occurred in 20 percent of patients receiving the Zaltrap plus FOLFIRI combination compared to 11 percent for those receiving FOLFIRI and a placebo. Progression-free survival for patients—the time that the patient lived without the cancer progressing—averaged 6.9 months in the group that received Zaltrap and FOLFIRI. That compared to an average of 4.7 months for the group that got FOLFIRI and a placebo. In addition, because of safety concerns, the agency approved Zaltrap with a boxed warning, the strongest warning the FDA requires, to alert doctors and patients that the drug can sometimes cause fatal bleeding, as well as the development of holes in the gastrointestinal tract. It can also make it more difficult for wounds to heal. That’s in addition to the most common side effects that include decreased white blood cell count, diarrhea, mouth ulcers, fatigue, high blood pressure, increased protein in the urine, weight loss, decreased appetite, abdominal pain, and headache.

In the safety and efficacy nexus with the FDA, Zaltrap passed muster, but for others concerned about questions of value, Zaltrap reflected what’s wrong in healthcare today.

Critics of Zaltrap say the drug provides the same survival benefit as Genentech’s Avastin when either drug is added to standard chemotherapy. Like Zaltrap, Avastin is also used to inhibit angiogenesis in patients with colorectal cancer, but Zaltrap does so at more than twice the price. It’s an expensive drug. At launch, Sanofi priced Zaltrap at an average of more than $11,000 a month for treatment compared to about $5,000 a month for Avastin. Concerned about the question of Zaltrap’s value, Memorial Sloan-Kettering Cancer Center decided not to give the drug to its patients. In an October 2012 op-ed in The New York Times, three physicians at Sloan-Kettering (two of whom have served as paid consultants to Genentech) say the decision should have been a “no-brainer.” The exclusion of Zaltrap from Sloan-Kettering’s formulary, though, didn’t come easy, according to the doctors. That’s because, they say, the culture of medicine equates “new” with “better.” “Our refusal to adopt this remarkably expensive therapy,” they wrote, “risks being labeled ‘rationing,’ not rational.”

In fact, they note that major clinical practice guidelines, such as those from the National Comprehensive Cancer Network, agree that Zaltrap is not any better than Avastin for these patients. They noted that a product that offers no benefit over a competitor’s but sells at twice the price would never make it to market in most industries. But the FDA’s responsibility is to review drugs for safety and efficacy, not value. “Ignoring the cost of care, though, is no longer tenable,” wrote the three physicians, Peter Bach, Leonard Saltz, and Robert Witty. “Soaring spending has presented the medical community with a new obligation.”

A product that offers no benefit over a competitor’s but sells at twice the price would never make it to market in most industries. But the FDA’s responsibility is to review drugs for safety and efficacy, not value.

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Source: Office of Health Economics

**Figure 1.1**

2012 TIMELINE

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<tr>
<th>Date</th>
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<tr>
<td>January 7</td>
<td>Bristol-Myers Squibb agrees to pay $2.5 billion to acquire Inhibrix and gain access to its experimental compound for the treatment of hepatitis C, INX-189.</td>
</tr>
<tr>
<td>January 10</td>
<td>Life Technologies says its new gene sequencing device will be able to sequence a genome in a day for $1,000.</td>
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<tr>
<td>January 19</td>
<td>IPO: Renewable Energy Group, $72 M</td>
</tr>
<tr>
<td>January 20</td>
<td>M&amp;A: Amgen acquires German biotechnology company, Micromet, for $116 M</td>
</tr>
<tr>
<td>January 25</td>
<td>Roche announces its intention to buy genome sequencing company, Illumina, for $5.7 billion.</td>
</tr>
<tr>
<td>January 26</td>
<td>IPO: Kaldeco, cystic fibrosis.</td>
</tr>
<tr>
<td>January 27</td>
<td>New drug approval: Erivedge (Erivedge) Indication: basal cell carcinoma</td>
</tr>
<tr>
<td>January 31</td>
<td>New drug approval: Kaldeco (Kaldeco) Indication: cystic fibrosis.</td>
</tr>
<tr>
<td>January 31</td>
<td>IPO: Verastem, $55 M</td>
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A product that offers no benefit over a competitor’s but sells at twice the price would never make it to market in most industries. But the FDA’s responsibility is to review drugs for safety and efficacy, not value.
When choosing treatments for a patient, we have to consider the financial strains they may cause alongside the benefits they might deliver.”

The authors argued that more and more, it is patients that are bearing the high cost of these new drugs and often with great financial consequences. They reported that in 2006, a quarter of cancer patients said they exhausted their savings to pay for treatment. A 2011 study noted that 2 percent of cancer patients wound up in bankruptcy due to their illness.

In a letter to the editor, Sandra Swain, president of the American Society of Clinical Oncology wrote in response to The New York Times report that Sloan-Kettering’s decision to exclude Zaltrap from its formulary “reflects a much-needed willingness to address the elephant in the room: unsustainable costs in cancer care.” “As doctors, we have a responsibility to provide high-quality, high-value care according to the best available evidence,” she wrote. “This means ensuring that every test, treatment, and procedure offers patients meaningful benefits and avoiding those that do not.”

Sanofi responded to the controversy swiftly by taking steps to cut the price of its drug in half, according to a report in The Cancer Letter. In a statement Sanofi provided The Cancer Letter, the company said it believes Zaltrap is “priced competitively as used in real-world situations.” “However, we recognize that there was some market resistance to the perceived relative price of Zaltrap in the U.S.—especially in light of low awareness of Zaltrap in the U.S. market,” Sanofi said. “As such, we are taking immediate actions across the U.S. oncology community to reduce the net cost of Zaltrap.” The Cancer Letter notes that Sanofi did not specify the extent of the cuts, but reported that “knowledgeable sources” said the company is cutting the price of the drug in half.

Lee Newcomer, senior vice president of oncology at United Healthcare told The New York Times he could not recall a drug company making such a significant cut to the price of a cancer drug. “It was the first time physicians have stood up and said, ‘Enough is enough’,” he said. “And I think that was a watershed moment.”

Drugmakers feel the heat

Drugmakers have faced a difficult period during the last several years as a number of trends have converged. The cost of drug development has soared, regulators have raised barriers for approval, governments have increased pricing pressures on drugs, and competition from generic drugs has grown fierce and has rapidly eroded multi-billion dollar franchises of the industry’s biggest revenue producers. The sharp increase in the cost of drug development has failed to produce a concomitant rise in the output of new drugs and biologics [See Figure 1.1].

It was the first time physicians have stood up and said, “Enough is enough. I think that was a watershed moment.”

Lee Newcomer,
Senior vice president of oncology at United Healthcare

Continued on page 13
President’s Plan Seeks to Double Drug Approvals

A call to unleash “extraordinary innovation and investment”

Advisors to President Barack Obama issued a report in September 2012 calling for doubling the output of innovative new medicines for patients with important unmet medical needs. The group also recommended actions to improve drug efficacy and safety through collaboration between industry, academia, and government.

The President’s Council of Advisors on Science and Technology estimated that its ambitious goal would be achievable within 10 to 15 years. To get there, it said, America will need to unleash “extraordinary innovation and investment in the service of public health.”

The advisory group is comprised of the nation’s leading scientists and engineers, appointed by the President to augment the science and technology advice available to him from inside the White House and from cabinet departments and other federal agencies.

“The pace of new therapeutic development has not kept up with the explosion in scientific knowledge,” said PCAST co-chairs John Holdren and Eric Lander in a letter accompanying the report. “The number of novel drugs has remained constant for several decades, even as R&D budgets have substantially increased.”

The U.S. Food and Drug Administration approved 30 new molecular entities and biologics during 2011 and 39 in 2012. To double just 2011’s performance, drugmakers would need to secure 60 approvals during 2011 and 39 in 2012. To double just 2011’s performance, drugmakers would need to secure 60 approvals.

The group also recommended actions to improve drug efficacy and safety through collaboration between industry, academia, and government.

Based on that feedback, the group made eight recommendations. It suggests improving drug discovery and development efforts by supporting federal initiatives such as National Center for Advancing Translational Sciences at NIH, and catalyzing the creation of broad-based partnerships to accelerate therapeutics discovery, development, and evaluation.

To improve drug evaluation, the group said the FDA needs to pursue accelerated approvals more frequently paired with post-approval studies to evaluate drugs addressing unmet needs; it suggests the agency create a new pathway for approving drugs shown to be safe and effective for a specific subgroup of patients; and recommends the FDA to explore approaches for adaptive approvals, a framework for iteratively expanding the market for a drug as new evidence about its risks and benefits becomes available.

Post-marketing surveillance of new drugs should also be supported by a congressionally authorized line item appropriation of $40 million per year to expand the FDA’s Sentinel Initiative, the group said. That initiative is creating a national electronic system to help the agency track the safety of drugs, biologics, and medical devices once they reach the market. In addition, PCAST calls for the reform of FDA management practices and the creation of a study to determine whether current economic incentives are aligned to promote innovation.

To implement its ideas, PCAST recommends creating a public-private “Partnership to Accelerate Therapeutics” within a year that includes representatives from industry, academia, ethicists, physician societies, pharmacists, patient-focused research foundations, advocacy groups, healthcare providers, insurers, and the federal government. By late 2015, PCAST calls for the reform of FDA management practices and the creation of a study to determine whether current economic incentives are aligned to promote innovation.

To implement its ideas, PCAST recommends creating a public-private “Partnership to Accelerate Therapeutics” within a year that includes representatives from industry, academia, ethicists, physician societies, pharmacists, patient-focused research foundations, advocacy groups, healthcare providers, insurers, and the federal government. By late 2015, PCAST calls for the reform of FDA management practices and the creation of a study to determine whether current economic incentives are aligned to promote innovation.

Finally, by late 2017, the group estimates the FDA should have cleared its backlog of guidances—possibly by farming out their creation to the experts assembled in the partnership—and put in place a fully-funded safety monitoring system, such as Sentinel.

The authors of the PCAST report acknowledge the limitations of their influence, recognizing that “reimbursement policy will have an increasing impact on innovation in drug development,” but they say that the federal government should exercise leadership to ensure the United States has “a strong ecosystem for drug discovery and development.”
due to falling success rates for drugs in clinical development as drug makers sought to tackle more intractable diseases, such as Alzheimer’s and cancer. The study found that success rates fell to one in 10 in the 2000s compared to one in five during the 1980s. The increasing complexity of the science underlying drug development and rising regulatory barriers has slowed the process of bringing drugs through research and development to approval. In the 2000s, that time grew to 13.5 years from just six years in the 1970s. The report notes that the cost of capital has risen as well. In order to provide adequate returns to investors to attract the capital necessary to fund the risky process of drug development, drugmakers in the 2000s needed to provide an 11 percent return, up from 8 percent in the 1970s.

Other estimates produced in 2012 suggest the price tag could be significantly higher than $1.5 billion. Bernard Munos of the InnoThink Center for Research in Biomedical Innovation puts the number at around $4 billion when the cost of failure rates are included in the calculation.

In February 2012, Munos walked Forbes’ Matthew Herper through the various drug companies’ R&D spending and approval numbers. Herper and his colleague Scott DeCarlo then went back through 15 years of annual reports and, after adjusting R&D spending for inflation, came up with some astounding figures. At the low end, Amgen spent $3.7 billion for each drug it brought to market while AstraZeneca spent a staggering $12 billion (See Figure 1.4). “The high cost of developing drugs shouldn’t be a badge of honor for drug firms; there’s no reason it has to be this expensive. And using the cost of research to justify the prices of prescription drugs was always a dumb move on the pharmaceutical industry’s part,” wrote Herper. “Just because something is expensive doesn’t make it good.”

**Perceived improvements questioned**

There is a general perception that Big Pharma is moving past the difficulties it has faced in recent years as it has cut staff, narrowed focus, and bolstered flagging pipelines. Proponents of such a view point to a string of new drug approvals and late-stage drugs that represent innovative products and big market opportunities. But a September 2012 study from BernsteinResearch’s Tim Anderson raises concerns that the data isn’t yet there to support such optimism (See Figure 1.5). He notes that data from KMR Group, which come directly from pharmaceutical companies, paints a “mixed picture” and that it shows “several potentially disturbing R&D trends.”

Anderson found that drugmakers’ pipeline success rates across every phase of development have been slowly worsening or, at best, staying flat. He found late-stage pipeline success rates slipped to just 65 percent during the years 2007 to 2011, as compared to the 70 percent rate registered between 2003 and 2007. Meanwhile, mid-stage and early-stage assets experienced even deeper declines against a backdrop of slowly lengthening product development periods (See Figure 1.6). Instead of finding new signs of R&D productivity, Anderson has found that the number of preclinical drugs needed to yield a single approved product has been increasing steadily, hitting a point during the period 2007 to 2011 in which 30 preclinical products were needed just to secure one approval, as compared to just 12 preclinical products required during 2003 to 2007.

Despite the gloomy picture, Anderson points out that there are reasons why perceived

**Value**

Estimates of the cost of drug development vary widely. Most recently, in a December 2012 study from an independent U.K. research organization, the Office of Health Economics, the mean cost was put at $1.5 billion.
improvements may not yet be reflected in the KMR data. They include the fact that KMR uses multi-year grouping of data that may mask more recent improvements. He also notes that the mega-mergers between Pfizer and Wyeth, Merck and Schering-Plough, and Roche and Genentech could also skew the data because of disruptions to their pipelines. There has also been an industry-wide move to fail early and weed out weak early-stage candidates, as well as a shift away from me-too drugs that may impact the productivity picture in ways not captured by the data. Anderson said in the absence of more granular data, it’s difficult to know whether the industry has reversed the trend of recent years. “It will probably take another year or two to more clearly say whether pharmaceutical industry R&D trends are improving,” he writes. “If this is not happening, then drug companies will continue to limp along, desperately seeking alternate solutions to try and deliver on their growth objectives.”

The quest for value

Today’s pressure on pharmaceutical companies reflects greater pressures throughout the entire healthcare ecosystem as payers, patients, and providers wrestle with escalating costs and push healthcare systems around the world away from being cost-based and towards value-based models. For pharmaceutical companies, this means not only a greater emphasis on creating value, but also on seeking new ways to provide benefits commensurate with their costs and governments and payers squeeze down prices. The challenge for drugmakers, broadly speaking, is both to find new ways to create value and capture value. Creating value and capturing value are two separate things. In simple terms, creating value is providing more for less. A generic drug that delivers the same therapeutic benefit as a branded equivalent for a fraction of its cost creates the added value represented by the difference in the price between the two drugs.

Capturing value, though, has to do with creating profits. The two can go hand-in-hand, but can also work against each other as demand for greater value by customers can force prices down. Drug companies can find opportunities for capturing value by creating new value. For instance, a time-release version of an existing drug that can improve compliance and reduce side effects creates value, but could also command a higher price than an older version of the same drug, providing an opportunity for greater value capture by the drugmaker.

Looking beyond their own walls

In an effort to address the industry’s poor R&D productivity, there has been a move in recent years to improve the return on investment by partnering with academic institutions, forging new ties with competitors and governments to address common challenges and share the cost of pre-competitive research, and finding ways to improve R&D productivity. The industry has with great speed moved to downsize its internal research efforts and increasingly invested in external sources of innovation. The result has been a large number of initiatives with uncertain results. It is in the midst of a grand experiment to reinvent itself and it will likely be years before it will be able to determine whether the new roads on which it is travelling provide faster, less expensive, and more successful paths to market.

One area that has come under scrutiny is clinical trials. As much as $5 billion in clinical trials costs could be saved by eliminating unnecessary procedures, according to researchers at the Center for the Study of Drug Development at Tufts University School of Medicine. They found that clinical trial data is being double counted in 25 percent of the procedures administered to patients may be unnecessary because they are not directly tied to the endpoints of clinical trials. The study, presented at the Drug Information Association’s annual meeting at the end of June 2012, found these unnecessary procedures add between $3 billion to $5 billion annually in overall clinical trial costs.

At a time of growing pressure to rein in drugs development cost, the study suggests that procedures identified as non-core to the protocol may represent opportunities for drug developers to significantly reduce clinical trial costs and improve productivity without sacrificing safety. “This study is groundbreaking in that it links, for the first time, clinical trial economics to protocol complexity,” said Ken Getz, senior research fellow and research assistant professor at the Center for the Study of Drug Development, who served as principle investigator. “The results have

### 2012 TIMELINE

**April 27**
New drug approval: Stendra
Indication: erectile dysfunction

**May 1**
New drug approval: Eleyso
Indication: Gaucher disease

**June 8**
New drug approval: Perjeta
Indication: breast cancer

**June 11**
AstraZeneca pays $3.4 billion to share in BMS/Amylin diabetes franchise.

**June 24**
Mohamed Morsi is declared the winner of Egypt’s first freely held presidential election becoming its fifth president and the first head of state outside the military.

**June 27**
AstraZeneca’s Belviq is the first prescription weight-loss drug approved by the FDA in more than a decade.

**June 28**
The U.S. Supreme Court upholds Obama’s individual health-care mandate as a tax.

**July 9**
President Obama signs into law the reauthorization of PDUFA V and MDUFA III.

**July 17**
New drug approval: Qsymia
Indication: obesity

**July 29**
Amylin agrees to be acquired by Bristol-Myers Squibb for $7 B

**July 15**
Human Genome Sciences agrees to be acquired by GavisSmithKline for $3 B

**July 18**
Durata Therapeutics

**IPO**
June 26
Tesaro
$81 M

**IPO**
July 18
Durata
$67.5 M

**Figure 1.5  LONGER DEVELOPMENT TIME**

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<td>2006</td>
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Drug cycle times increase 1998 to 2011

Number of years

Source: KMR, Bernstein Research Analysis

**Figure 1.5:** Longer Development Time

Drug cycle times increase 1998 to 2011.
Drugmakers, Academia Create iPS Stem Cell Bank

Biorepository will accelerate and enhance drug development.

Roche and Oxford University are leading an effort that brings together ten pharmaceutical companies and 23 academic institutions to launch Stem-banc, which will focus on generating 1,500 induced pluripotent stem cell lines for use in drug development. Coordinated by Roche and managed by Oxford University, Stem-banc aims to use iPS cells to develop human disease models for testing potential drugs in development.

“The aim of Stem-banc is to generate and characterize 1,500 high-quality human induced pluripotent stem cell lines derived from 500 patients that can be used by researchers to study a range of diseases, including diabetes and dementia,” said Martin Graf, coordinator of the project at Roche. “The cell lines will help implement patient models that will facilitate the drug development process thanks to the possibility of reproducing the disease mechanism in vitro.”

Induced pluripotent stem cells are derived from ordinary adult cells reprogrammed into stem cells that can then be used to generate any kind of cell. The groundbreaking work in this field earned a Nobel Prize in Physiology or Medicine in 2012 for John Gurdon of Cambridge University, who developed the first technique to reprogram cells.

IPS cells can be differentiated into a variety of cell types that can be used for a broad range of in vitro tests in research and early-stage drug development. Because the IPS cell lines are derived directly from real patients, they include the genes that may be implicated in diseases of interest. The cell lines in Stem-banc will be generated from samples obtained from screened and defined groups of patients, thus providing a solid patient database with accurate and detailed data on the diseases to enable better insight into the disease mechanisms.

Roche scientists had already been working with partners at Harvard University, Massachusetts General Hospital, and Boston Children’s Hospital to create more than 100 human induced pluripotent stem cell lines that can be used to model cardiovascular and neurological diseases. But because it takes up to six months to convert an adult’s skin cells into IPS cells, more collaborators were needed to collect all 1,500 samples. Drugmakers involved in the collaborative effort include Roche, Pfizer, Sanofi, Abbott Laboratories, Boehringer Ingelheim, Eli Lilly, Johnson & Johnson, Merck, Novo Nordisk, and On人间.

The partnership plans to spend $75.5 million (€55.6 million) to create the IPS cell bank. The European Union’s Innovative Medicines Initiative is contributing $35.3 million (€26 million), the European pharmaceutical trade group, European Federation of Pharmaceutical Industries and Associations is contributing $28.3 million (€21 million), and the rest is coming from the companies and academic institutions.

The Stem-banc project will focus on peripheral nervous system disorders, especially pain, dementia, neurodysfunctional diseases such as migraine, autism, schizophrenia, and bipolar disorder; and diabetes. The project will also investigate the use of human IPS cells for identifying drug targets and biomarkers, screening potential drug treatments, and toxicology testing.

Stem-banc is just one of seven projects announced by the Innovative Medicines Initiative that aim to tackle some of the biggest challenges in drug development. The Innovative Medicines Initiative is the world’s largest public-private partnership in health, a coordinated program of the European Union and the EFPIA, each of which has contributed $1.3 billion (€1 billion) to support collaborative research projects. Other recently announced projects include data integration and management, “green” drug development, and drug delivery and behavior in the body.

Formed alliances to tackle common problems. Though not new, the focus on pre-competitive alliances or so-called “co-opetition” accelerated in 2012 as drugmakers sought to band together to more cost-effectively address areas of common concern. One of the most dramatic examples of this is TransCelerate BioPharma, a joint effort of ten global biopharmaceutical companies announced in September 2012. They formed the pre-competitive collaboration to identify and solve common drug development problems, an eye-opening for participating companies and will no doubt serve as a jumping-off point for pharmaceutical and biotechnology companies to examine ways to reduce the number of non-core procedures to improve clinical trial efficiency and substantially reduce study budgets.”

The study was conducted over an eight month period and is based on data from 15 international sponsor companies of all sizes. Using software from Medidata, the researchers collected and analyzed more than 115 clinical trial protocols and categorized more than 22,000 medical procedures. About 25 percent of all clinical trial procedures were found not to be directly tied to the trial end-points as agreed upon prior to the study by the FDA for demonstrating the safety and efficacy of the drug or therapy in question. These procedures represented about 20 percent of the clinical trial’s budget or an estimated $1 million per clinical study.

“By distinguishing between core and non-core procedures early on in the trial process, this research underscores the critical roles study design and protocol development play in overall clinical trial costs,” said Marla Curran, director of clinical statistics at GlaxoSmithKline. “Even with this study’s conservative estimate of the procedures organizations could potentially eliminate, it’s clear that the industry can take a closer look at trial design to improve efficiencies while still meeting regulatory requirements.”

We’re all in this together.

To improve R&D productivity, pharmaceutical companies have turned to each other and
ment challenges, improve clinical studies, and accelerate the pace at which medicines make it to market. “We aim to reduce bottlenecks in R&D and increase efficiency,” said Garry Neil, interim CEO of the new Philadelphia-based venture, TransCelerate BioPharma. “We have an obligation to stakeholders to find ... new and transformative ways of doing things. We are really working collectively in a way we haven’t done before.”

TransCelerate’s initial members include Abbott, AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Eli Lilly, GlaxoSmithKline, Johnson & Johnson, Pfizer, Genentech, and Sanofi. Other companies have been welcomed to join. The group was formed in August 2012 and announced at a meeting of R&D heads at BioPharm America, a conference held in Boston. Each of the ten founding companies will combine financial and other resources, including personnel, and work together to share meaningful information and expertise to advance the collaboration. But the companies have not announced how much money or how many employees they’ll dedicate to the venture. “There is widespread alignment among the heads of R&D at major pharmaceutical companies that there is a critical need to substantially increase the number of innovative new medicines, while eliminating inefficiencies that drive up R&D costs,” said Neil, who is also a managing director and partner at Apple Tree Partners, a New York City-based venture capital firm.

TransCelerate will initially focus on improving drugmakers’ approach to clinical studies by funding projects to streamline and standardize their execution. As shared solutions in clinical research and other areas are developed, the group will then involve industry alliances.

Janet Woodcock, director of the FDA’s Center for Drug Evaluation and Research, applauded the group’s effort to address “a series of long-standing challenges in new drug development.” She said TransCelerate “has the promise to lead to new paradigms and cost savings in drug development, all of which would strengthen the industry and its ability to develop innovative and much-needed therapies for patients.”

Shared concerns

The pharmaceutical industry is not alone in its concerns about the difficulty it has had taking discoveries and turning them into products that benefit the health and well-being of patients. Academia too has been putting a greater emphasis on translational research, in part in response to concerns about the lack of specific drugs to point to as proof of return on the National Institutes of Health’s massive investment in biomedical research, and in part because of the reality that, in the current environment, NIH budgets will continue to be under pressure and the ability for researchers to secure grants in a highly competitive environment means a greater failure rate for grant proposals. Academic institutions are being pushed toward closer working relationships with industry by a need to access new sources of funding, as well as by a recognition that in order for the work of academic researchers to benefit people, it needs to reach the marketplace.

While the robust pace of academic-industry alliances continued in 2012, several unique initiatives provided new models intended to address the dearth of funding for translational research to carry discoveries from the lab to proof-of-concept. “The valley of death,” the term used to describe the wasteland where discoveries too early in the development process to attract industry or venture funding but too advanced to attract government backing, is well known to physicianscientists. Though a variety of initiatives in recent years has tried to address the gap in funding translational research, the difficulties in commercializing discoveries is often made worse due to the lack of understanding of the development process. A unique national effort by Cleveland’s University Hospital is hoping to provide both guidance and funding to address the problem. Backed with $250 million in philanthropic, university, and venture funding, the Case Western Reserve Medical School affiliated hospital system is taking an innovative, two-pronged approach to seeing inventions from the lab make it to the marketplace. The effort marries a non-profit, grant making entity named University Hospitals Harrington Discovery Institute and a for-profit accelerator that will select promising projects and carry them to proof-of-concept where they can then be licensed or spun-out to form new companies. University Hospital said by aligning the non-profit and for-profit entities, it will, for the first time at an academic medical center, provide a comprehensive model to advance discoveries into development and create novel drugs and therapies for patient care. The Harrington Project is named for the Harrington Family, owners of Edgepark Medical Supplies. The family donated $50 million to fund the project. The program will not be limited to people affiliated with University Hospital, but will reach out to physician-scientists nationwide.

“One of the challenges that we have today is that many biomedical discoveries end up staying on the shelf; they never get commercialized.”

Achilles Demetriou
Chief Operating Officer, University Hospital, Cleveland

2012 TIMELINE

August 3: New drug approval: Zaltrap
Indication: colorectal cancer

August 6: Research halted on keenly watched experimental Alzheimer’s drug bapineuzumab, under development by Pfizer and Johnson & Johnson.

August 6: Curiocity: NASA’s advanced Mars rover, lands safely on Mars.

August 23: Bristol-Myers Squibb halted development of its hepatitis C drug after nine patients were hospitalized and one died during a clinical trial. BMS had paid $2.5 billion to acquire Inhibitex and gain access to the asset.

August 24: A senior U.S. appeals court rules NIH is legally allowed to fund human embryonic stem cells.

August 27: Mitt Romney and Paul Ryan are nominated for President and Vice President at the 2012 Republican National Convention.

August 28: Alnylam inks $29 million dollar deal with Monsanto to develop biotech solutions for the agriculture industry.

August 29: Eli Lilly halts its late-stage clinical trial of its drug mGlu2/3 for treatment of schizophrenia, over efficacy worries.

August 29: New drug approval: Neutroval
Indication: chemotherapy-induced neutropenia

August 29: Eli Lilly halts its late-stage clinical trial of its drug Neurontin for treatment of migraines.

August 30: New drug approval: Linzess
Indication: Irritable bowel syndrome

August 31: New drug approval: Xtandi
Indication: prostate cancer

September 5: ENCODE project finds that 80 percent of DNA once thought of as “junk” actually plays a critical role in gene regulation.

September 10: Genentech loses more than half its market value and hits an all-time low when it halts a mid-stage breast cancer trial after interim data on its experimental drug finds it is no better than current treatments.

“One of the challenges that we have today is that many biomedical discoveries end up staying on the shelf; they never get commercialized.”

Achilles Demetriou
Chief Operating Officer, University Hospital, Cleveland

“...”
Putting Academic Research to the Test

Reproducibility Initiative hopes to validate findings to avoid doomed drug development efforts

A crisis in academic research is brewing as some estimates suggest the majority of research from academic labs can’t be reproduced. That has serious consequences for biopharmaceutical companies that spend significant time and money pursuing promising new drug targets suggested by academic studies only to find they can’t validate them.

The scientific services marketplace Science Exchange, along with the open access journal PLOS, and the open data repository Figshare in August 2012 launched the Reproducibility Initiative in the hopes of addressing the problem.

It’s no small matter, according to Elizabeth Iorns, CEO of Science Exchange. She said studies have found that up to 70 percent of academic research results could not be reproduced. Major drug companies have invested millions of dollars in pursuing promising new targets for drugs only to find they can’t show the targets are worth hitting.

Fueling the problem are several factors. They include what Iorns said is a bias to publish positive results, pressures on academic journals to publish high-profile and novel research, and an unknown level of academic fraud.

The Reproducibility Initiative provides both a mechanism for scientists to independently replicate their findings and a reward for doing so. Scientists who apply to have their studies replicated are matched with experimental service providers based on the expertise required. The initiative leverages Science Exchange’s network of more than 1,000 expert providers at core facilities and contract research organizations. She said the cost will not exceed 20 percent of the original study.

Iorns is working to raise funding for reproducibility studies, but initially, researchers will need to provide funding to validate their work. Asked if academic researchers will have an incentive to submit work, let alone fund studies that may debunk their own findings, she said she believes so.

So far, scientists have been reluctant to embrace the concept. Among their concerns are the cost of validation at a time when funds are tight, questions about who will validate the validations, the inherent complexity of experimental methods, and concerns over cell lines and animal models that have taken years to develop.

Scientists will receive the results of their validation studies and have the opportunity to publish them in the journal PLOS One. They can also upload their primary data to the open-access repository Figshare.

But a bigger incentive, she said, may be that investors, drug developers, foundations, and other potential sources of funding will place a greater value on research that has been independently validated.

“It’s important to realize the impact of the research depends on whether it’s actually true,” said Iorns.

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2012 TIMELINE

September 4: New drug approval: Bosulif; Indication: leukemia

September 11: The E.U. agrees to change its drug-oversight rules with the aim of speeding safety assessment.

September 12: New drug approval: Aubagio; Indication: multiple sclerosis

September 12: New drug approval: Choline C 11; Indication: prostate cancer screening

September 17: The world’s largest genome sequencing center, BGI, announces it will acquire Illumina Complete Genomics for $117.6 M.

September 18: Vivus beats obesity drug rival, Arena, to the U.S. market for $117.6 M.

September 19: Life Technologies begins shipping its new-generation DNA sequencing, the Ion Proton.

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“Reproducibility Initiative,” a program that helps verify academic research findings, has validated results for $100 million in academic studies.

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Business Wire
Wisdom of Crowds Tapped to Fix Drug Development

Transparency Life Sciences cuts clinical trial costs with digital technology

Tomasz Sablinski has what he calls his “rule of eighties,” which says 80 percent of clinical trials are trials that nobody wants, cost 80 percent too much, and are being done with technology from the 1980s. Sablinski, a 30-year veteran of the drug development world with experience from Big Pharma to the virtual drug development arm of a private equity firm, co-founded Transparency Life Sciences with the intent of radically altering the costs of clinical trials.

Sablinski believes that by providing complete transparency on drug data, using crowdsourcing to shape clinical trials, and using digital tools wherever possible, Transparency will be able to produce better clinical data faster, and with greater convenience to patients and others involved in the clinical trials process. In fact, his goal is to cut clinical trials expenses by as much as 80 percent.

No doubt there is room for savings. In fact, a study presented in June at the Drug Information Association’s annual meeting found as much as $5 billion a year could be saved from the cost of clinical trials by eliminating unnecessary procedures. The study, conducted by researchers at the Center for the Study of Drug Development at Tufts University, found that as much as 25 percent of the procedures administered to patients during a clinical trial may be unnecessary, because they are not directly tied to the endpoint of the study.

Transparency thinks it can not only eliminate waste, but also improve efficiency through three elements critical to its approach to clinical trials.

The company got a major boost in December when the FDA gave a go-ahead for a mid-stage trial of hypertension drug lisinopril as a treatment for multiple sclerosis.

These include making available all of the information about a drug and sharing data; turning to the researchers, physicians, patients, and patient advocates to participate in providing ideas on clinical trial design through crowdsourcing on its website; and using digital tools to reduce the need to bring patients to clinics on a regular basis, minimizing transportation, waiting, and the use of healthcare workers.

Initially, Transparency is pursuing a portfolio of repurposed drugs to establish a proof of concept for its approach. Once it can demonstrate its approach passes regulatory muster and produces robust results and savings, it plans to in-license promising drugs in development that have stalled in the pipelines of pharma and biotech companies for a variety of reasons.

The company got a major boost in December when the United States Food and Drug Administration gave a go-ahead for a mid-stage trial of lisinopril as a treatment for multiple sclerosis. Lisinopril is an ACE inhibitor that has been used for years in millions of patients worldwide as a safe and effective treatment for hypertension. Animal models of MS have suggested that ACE inhibitors modulate the immune response and could have benefit in MS patients, where the body’s immune system attacks the protective coating of nerve cells. Because the drug has a different mechanism of action than existing MS therapies, Transparency believes it could be used in combination with other drugs.

By reaching out to the 15,000 users on the Transparency website, the company believes it will be able to focus the trial on matters that are important to patients.

MS trials have traditionally used what’s known as the Expanded Disability Status Scale as their primary endpoint. Neurologists score eight functional systems, generally measuring the function of different parts of the brain on a scale to score patients. But Transparency’s community instead argued the company should use the Multiple Sclerosis Functional Scale, saying that it is more important to patients and a better endpoint to use for the trial. That scale has generally been used as a secondary endpoint or not at all, said Sablinski. The scale measures leg function and the ability of the patient to walk, arm and hand function, and cognitive function.

Typically in MS trials, sponsors also perform costly MRI scans in mid-stage trials and advance compounds based on the results of radiological images of the brain, even though the MRI scans say nothing about function, which Sablinski notes is what patients care about.

“For internal decision making, pharmaceutical and biotech companies are using an end-point that, if you look at the correlation between it and clinical outcomes, is questionable to the point that FDA doesn’t really care about it,” he said, referring to the MRI scans. “We are trying to move to, pretty bluntly, something that matters to patients, and matters to physicians who treat them, and forget the MRI.”

The use of digital technology to monitor patients during the trial rather than having them travel regularly to clinical trial sites to be examined by health workers will be a major source of savings. Transparency will ask patients to come to a clinic for the first visit at the start of the trial and the last visit at the end of the trial, but everything else will be done digitally. To monitor patients, Transparency is working with the New York-based telemedicine provider AMC Health, which will provide everything from two-way video monitoring to tools that use GPS-based devices to measure patient movements.

“We know first-hand how effective at-home patient monitoring can be, providing significantly improved care at a much lower cost,” said John Holland, senior vice president for research and business development at AMC Health. FDA clearance of this lisinopril protocol, which primarily relies on telemonitoring-patient assessments, is an encouraging breakthrough.”

Sablinski said the initial goal is to perform clinical studies at 50 percent of current budget. The ultimate goal, though, is to get that down to 80 percent. Based on budgets the company has received from clinical research organizations for the lisinopril trial, he believes the savings will be closer to the 80 percent mark.

Sablinski launched Transparency in part because of the barriers of implementing his model within Big Pharma, where he did try to implement parts of the approach he is now using, but came up against resistance. Among the objections, he said, were concerns about IP, disbelief that the crowd would come up with better ideas than the thought leaders and experts within the company, and insistence that regulators would never go along with it. “The common denominator,” he said, “is protecting the system.”

For that same reason, he decided it would be best for Transparency to pursue its own drugs rather than operate as a contract research organization, since in almost all cases, companies would want to dictate trial protocols and be very protective of physicians who treat them, and forget the MRI.”

“I realized my life is too short to try to change corporate culture,” he said. “It’s just too big of a task.”
The Institute plans to access funds from government and non-government sources. Revenues derived from licenses will be shared between Calibr and the collaborating institutions. Calibr investigators will work collaboratively with academic scientists to advance new discoveries to preclinical proof-of-concept at which stage commercial partnerships will be sought for further development. Project proposals from the scientific community will be chosen on the basis of novelty, biomedical impact, and technical feasibility, and reviewed by a scientific advisory board headed by Harvard University professor and neurologist Christopher Walsh. In addition, an independent board of directors headed by 5AM Ventures founder and managing partner John Diekman will oversee the activities of the institute. “Effective translation of basic biomedical research is essential to advancing the next generation of novel therapies,” said Peter Kim, president of Merck Research Laboratories and member of the Calibr scientific advisory board. “Calibr will provide an important venue where basic research and drug discovery scientists may leverage each others’ strengths in the fight against disease.”

Janssen Research & Development is taking a different approach. It launched a pay-as-you-need-it lab space for 18 to 20 emerging biotech companies in San Diego. Janssen Labs is offering space and lab equipment on short-term renewable leases, all with “no-strings-attached,” said Jansen’s Diego Miralles, site head for the west coast research center. That means Janssen takes no stake in the companies it will house, nor are the companies guaranteed any affiliation with Janssen, though clearly there’s potential for such relationships to develop. “We need to figure out how to help the biotech industry be very healthy and thrive,” said Miralles. “The success of the biotech industry, in the long run, will be our success because that’s where a lot of our products come from.”

The 30,000 square-foot set-aside housing the labs, equipment, and administrative space was intended to provide a capital efficient, flexible lab environment for start-up companies pursuing new technologies and research platforms to advance medical care, Janssen said. If the experiment is successful in San Diego, the company may roll it out in other cities in the future, said Miralles. “This is one of many experiments as an industry we should be conducting. We’ll learn from it. It’s not going to be perfect because obviously, not all ideas are good ideas,” he said. “So we have to figure out, what is good about the idea? What is bad about the idea? We’ll adjust. But from the response, it seems like there was a tremendous need in the community for it.” [8] in September 2012 said it was going to establish similar centers in San Francisco, Boston, London, and China to accelerate early innovation.

Miralles said the arrangement allows companies to focus on the development of the science instead of setting up and managing the labs. He believes this will minimize cost and time and represents an effective way for companies to develop and focus on research. Janssen Labs’ management team is evaluating applicants based on criteria such as compelling science and demonstrated financial solvency.

Expanding opportunities
While improving the translation of discovery to products is seen as one path to improving the efficiency of the industry, so too is increasing the

2012 TIMELINE

**September 21:** Ten big pharmaceutical companies form a non-profit organization called TransCelerate BioPharma, with the goal of making clinical trials more efficient.

**September 22:** The European Parliament’s legal committee recommends that research involving human embryonic stem cells should not be funded in the European Union’s 2013-2020 research program.

**September 27:** A new analysis finds that federal research and development funds in the United States could be slashed by $57.7 billion over the next five years under an across-the-board budget cut set to come into effect in January 2013.

**October 2:** First conceptual debate is held in Denver, Colorado, and raises Mitt Romney’s chances in the polls.

**October 3:** First conceptual debate is held in Denver, Colorado, and raises Mitt Romney’s chances in the polls.

**October 5:** U.S. unemployment rate drops to 7.8 percent, its lowest point since 2009.

**October 8:** John Gurdon and Shinya Yamanaka win the Nobel Prize in Physiology or Medicine for their work on reprogramming mature cells into their embryonic states.

**October 10:** Kythera Therapeutics is the first life sciences company to go public via JOBS Act.

**October 11:** Hurricane Sandy becomes a super storm as it hits the east coast causing billions of dollars of damage and leaving millions without power for days thereafter.

**October 12:** European drug regulators recommend against approving Vivus’ obesity drug over concerns about cardiovascular and nervous-system side effects.

**October 18:** New drug approval: Fycompa Indication: myoclonic epilepsy

**October 19:** New drug approval: Stivarga Indication: colorectal cancer

**October 22:** Third and final 2012 Presidential debate is held in Boca Raton, Florida.

**October 26:** New drug approval: Synribo Indication: leukemia

**October 30:** IPO Regulus Therapeutics

$45 M

**November 1:** IPO TransCelerate BioPharma

$70 M

**November 2:** IPO InterCEPT Therapeutics

$37.5 M

**November 3:** IPO Regulus Therapeutics

$45 M

**November 4:** IPO TransCelerate BioPharma

$70 M

**November 5:** IPO InterCEPT Therapeutics

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**November 6:** IPO Regulus Therapeutics

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**November 7:** IPO TransCelerate BioPharma

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**November 8:** IPO InterCEPT Therapeutics

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**November 14:** IPO InterCEPT Therapeutics

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**November 15:** IPO Regulus Therapeutics

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**November 18:** IPO Regulus Therapeutics

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**November 19:** IPO TransCelerate BioPharma

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**November 25:** IPO TransCelerate BioPharma

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**November 26:** IPO InterCEPT Therapeutics

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**November 27:** IPO Regulus Therapeutics

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**November 28:** IPO TransCelerate BioPharma

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$37.5 M

**December 30:** IPO Regulus Therapeutics

$45 M
mileage companies get out of the drugs they have already developed, or at least demonstrated as safe, even if they have not proved effective in the indication for which they are being developed. In one sense, this means forging clinical development strategies aimed at finding multiple uses for a drug and maximizing the potential market opportunities. “While a lot of management attention is rightfully dedicated to getting a new drug approved and launched, the majority of value creation arguably depends on lifecycle initiatives that build and expand the clinical profile of the brand,” wrote the consulting firm McKinsey in an August 2011 report on optimizing clinical strategies. McKinsey points to the case of Cymbalta, Lilly’s anti-depressant launched into a “crowded and competitive” market. McKinsey notes that it “might have been destined to a mediocre end as just another SSRI for mood disorder,” but instead, thanks to the company’s generation of a stream of clinical data after the drug won initial approval, Lilly was successful in expanding the market for the drug from major depressive disorder to diabetic neuropathy, generalized anxiety disorder, maintenance therapy for relapse of depression, fibromyalgia, chronic depressive disorder to diabetic neuropathy, genital warts, and vasovagal syncope. Lilly repurposed Cymbalta into a “crowded and competitive” market. McKinsey notes that it “might have been destined to a mediocre end as just another SSRI for mood disorder,” but instead, thanks to the company’s generation of a stream of clinical data after the drug won initial approval, Lilly was successful in turning failure into success for the company from 2005 to 2012.

Turning failure into success

Taking advantage of unintended effects of drugs that might be desirable is another way drug companies have sought to capture additional value. Allergan did this with its glaucoma drug Lumigen, which had the side effect of causing eyelashes to grow long and full. Seeing a potential market in the drug for women interested in the cosmetic benefits, Allergan won approval for “Lattice,” which is used to promote eyelash growth by women who want long, lush eyelashes. Lattice is not the only drug in this category. The AIDS drug AZT first failed as a cancer therapy, Pfizer’s erectile dysfunction drug Viagra began its life as a drug intended to improve blood flow to the heart in patients with angina, and Rogaine, a failed drug to treat high blood pressure, is now used to promote hair growth in men battling baldness. A new emphasis on repurposing drugs that may be known to be safe, but may have failed in the indication for which a drugmaker was developing it or been abandoned for strategic reasons, is an area of growing efforts with the hope of wringing value out of an investment already made in R&D.

Repurposing a drug known to be safe, but that may have failed in the indication for which a drug maker was developing it, offers the hope of wringing value out of an investment already made in R&D.

that had been set aside for whatever reason. In many cases, these efforts have come through academic-industry alliances or public-private partnerships.

The National Institutes of Health’s National Center for Advancing Translational Sciences or NCATS in May 2012 launched a collaborative program with leading pharmaceutical companies to find new uses for drugs that failed to work in the indications for which they were being developed. The program, Discovering New Therapeutic Uses for Existing Molecules, focuses researchers on a pipeline of experimental drugs that has been difficult for them to access: compounds that already have cleared several key steps in the development process, including safety testing in humans. In 2013, about $20 million will be used to support grants of up to three years for pre-clinical and clinical feasibility studies to test more than 20 compounds from industry partners for their effectiveness against a variety of diseases and conditions. The companies will provide the researchers with access to the compounds and related data. Pfizer, AstraZeneca, and Eli Lilly initially joined the program, but that list was expanded just a month later to include Abbott, Bristol-Myers Squibb, GlaxoSmithKline, Janssen, and Sanofi. “Each company participating in this innovative collaboration has made substantial research and development investments to advance these compounds to the point where they can be used in clinical studies,” said Kathy Hudson, NCATS acting deputy director. “If researchers funded through this effort can demonstrate new uses for the compounds, they could significantly reduce the amount of time it takes to get a treatment to patients in need.”

Such efforts are not limited to the United States. The United Kingdom’s Medical Research Council in November 2012 said it is providing a total of $11 million (£7 million) in funding to 15 research projects that will seek to find new uses for 22 AstraZeneca compounds that had already been studied but shelved for a variety of reasons. The funding follows Prime Minister David Cameron’s 2011 announcement of the collaboration between AstraZeneca and the MRC as part of the U.K. Life Sciences Strategy. The MRC, through a peer review process, selected the 15 projects based on their scientific quality and importance. The scientists will test the AstraZeneca compounds on a broad range of diseases including Alzheimer’s disease, cancer, and a variety of rare diseases. Eight of the projects will involve human clinical trials, while the other seven will focus on laboratory and animal studies. The MRC received a total of 100 applications of interest in the funding and 23 full proposals. “Partnering across government, academia and industry is a critical way to spur additional scientific innovation and the delivery of new treatments for people who desperately need them,”
said Martin Mackay, president of AstraZeneca Research & Development. The drug giant is providing free supplies of 22 compounds to scientists through the MRC collaboration.

AstraZeneca had conducted early work on the compounds and validated their use for future research, but had put further development on hold. The rights to intellectual property generated using the compounds will vary from project to project, but will be similar to those currently used in academically-led research. AstraZeneca will retain its existing rights relating to the compounds, but academic partners in the collaboration will own any new research findings. "Not only will this bring benefits for patients in the form of more effective medicines and a better understanding of disease," said Patrick Johnston, chair of the MRC’s Translational Research Group, "but it has also allowed academic researchers to forge new partnerships with industry, which will give rise to future collaboration across the life sciences sector.”

A larger set of compounds will be looked at through a collaboration between Roche’s Translational and Clinical Research Center and the Broad Institute. The multi-year effort will seek to find new uses for development-stage compounds that failed to meet the goals of clinical trials in the indications for which they were developed, or had been shelved for strategic reasons. “Over the last 20 years of drug discovery we have created many drug candidates that did not make it to market,” said Karen Lackey, head of medicinal chemistry at Roche. “By compiling these compounds into an annotated set and collaborating with the Broad Institute to put to use its technologies and disease expertise, we hope to discover ways to repurpose these compounds that will be beneficial for patients.”

Under the agreement announced in November 2012, Broad will use its screening technologies to work through the Roche Repurposing Compound Collection, a library of more than 300 compounds intended for a wide variety of indications. Broad will screen the entire collection and link advanced compounds to novel patient populations through common biochemical pathways. This approach is expected to reveal unique targets for new drug discovery projects. Additionally, the companies said novel disease associations may be found that will lead to new clinical evaluations in which the compounds may have a higher probability of success. “The compounds in Roche’s collection are compelling starting points,” said Brian Hubbard, director of the Broad Institute’s Therapeutics Discovery and Development Platform. “If we can find new applications for them, we may be able to accelerate the process of finding the right drug for the right patient.”

**Market disappointments**

The difference between creating value and capturing value is sometimes a painful lesson for drugmakers, who may be successful at bringing new drugs to market only to find for a variety of reasons they fail to realize the profit potential of their work. Consider Human Genome Sciences, which won approval in March 2011 for Benlysta, its treatment developed with GlaxoSmithKline for systemic lupus erythematosus. Lupus is a chronic, autoimmune disease that can damage major organs, as well as the nervous system. Benlysta represented the first new drug approved for the disease in more than 50 years. It is the first in a new class of drugs called

### Figure 1.8

**Pharma Partnering With Payers**

<table>
<thead>
<tr>
<th>Date</th>
<th>Pharma</th>
<th>Payer</th>
<th>Focus</th>
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<tbody>
<tr>
<td>10/27/11</td>
<td>Pfizer</td>
<td>Medco Health Solutions</td>
<td>Pfizer established a research collaboration with Medco Health Solutions and its wholly owned subsidiary, United BioSource Corporation, aimed at more effectively matching patients with treatments that will benefit them the most, thereby improving patient outcomes. The collaboration is intended to enhance Pfizer’s precision medicine approach, which integrates genomic and phenotypic information, to help understand the underlying biology of disease and identify patients likely to benefit from a new drug. Under the terms of the agreement, Pfizer and Medco will collaborate to identify and evaluate patient subgroups in which investigational drugs and marketed drugs are shown to be most effective in improving patient care and health.</td>
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<tr>
<td>6/23/11</td>
<td>Sanofi</td>
<td>Medco Health Solutions</td>
<td>Sanofi and Medco Health Solutions’ wholly-owned subsidiary United BioSource entered into a global, multi-year agreement to improve patient care in real-world settings. The partnership will leverage several capabilities, including personalized medicine and pharmacogenomics, health economics, safety research, and clinical adherence support. The goal of the collaboration is to enable Sanofi to precisely identify patient populations with the greatest unmet medical needs. The partners also will attempt to determine those populations in which drugs are most effective; generate real-world comparative effectiveness data to support product value that meets stakeholder evidence requirements; and facilitate the development and implementation of novel care models to improve practice of care, adherence, and patient outcomes.</td>
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<tr>
<td>10/14/11</td>
<td>Pfizer</td>
<td>Humana</td>
<td>Pfizer and Humana announced a five-year research partnership to explore new ways to improve the quality, outcomes, and costs of the healthcare delivery system for senior citizens and other populations. The two will bring together researchers and healthcare experts from both organizations to study key issues and deliver interventions to reduce inefficiencies in the management of chronic conditions such as pain, cardiovascular disease, and Alzheimer’s disease.</td>
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<tr>
<td>2/2/11</td>
<td>AstraZeneca</td>
<td>HealthCore (WellPoint)</td>
<td>AstraZeneca and HealthCore, the health outcomes research subsidiary of WellPoint, entered into a collaborative agreement to conduct real-world studies designed to determine how to most effectively and economically treat disease. The research, which will include prospective and retrospective observational studies on disease states as well as comparative effectiveness research, will analyze how medicines and treatments already on the market are working in a number of disease areas, with a special emphasis on chronic illnesses.</td>
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BlyS-specific inhibitors and works by binding to BlyS, a B-cell survival factor discovered by Human Genome Sciences. By binding and sequestering the BlyS cytokine, the drug inhibits survival of the immune system’s B-cells and reduces the differentiation of these cells into immunoglobulin-producing plasma cells.

The approval generated praise for Human Genomes Sciences and excitement about the prospects for the drug. The Lupus Foundation of America president Sandra Raymond called it “a historic day for the millions of people with lupus and their families around the world who have waited more than 52 years for a treatment breakthrough.” Mark Schoenebaum, an analyst with ISI Group in New York told Bloomberg that the approval was a “landmark achievement for Human Genome Sciences and a testament to what well-managed, productive biotech companies can achieve.” Stifel Nicolaus analyst Maged Shenouda forecasted that sales of Benlysta could reach $2.3 billion a year in the United States and $3.6 billion worldwide in 2015. Shares of Human Genome Sciences moved toward $30 in the weeks following the approval. But by the third quarter of 2011, disappointing sales of Benlysta took a toll on Human Genome Sciences’ earnings and Wall Street’s expectations shrank [See Figure 1.5]. By the end of 2011, Benlysta generated just $52.3 million in sales. In fact, in October 2011, TheStreet.com reported results from an ISI Group survey that found 65 percent of buy-side investors expected sales of the drug would fail to reach $1.5 billion by 2018. The 2012 JP Morgan Healthcare Conference in San Francisco should have been a victory lap for Human Genome Sciences CEO Thomas Watkins. Instead, he stood at the podium announcing the company would eliminate 150 jobs while making "steady progress" toward

Scientific breakthroughs of 2012

Research has led to advancements in knowledge and new techniques that may change the approach to some disease treatments.

**Gut-on-a-chip**
Wyss Institute for Biologically Inspired Engineering at Harvard University
A miniature research device that mimics complex 3-D features of the intestine, including barrier and peristaltic functions.

**Bariatric surgery and diabetes**
480 primary health care centers and 25 surgical departments in Sweden
Studies show long term protective effect of stomach reduction surgery for Type 2 Diabetes risk.

**Genetically modified H5N1 virus**
University of Wisconsin–Madison and Erasmus Medical Center in Rotterdam, the Netherlands
Identification of determinants of mammalian transmission of H5N1 influenza virus. Led to unprecedented voluntary one-year moratorium on research.

**Stem cell-derived oocytes and mice pups**
Kyoto University and Japan’s Science and Technology Agency’s Exploratory Research for Advanced Technology Program
Creating complicated female sex cells, oocytes, from embryonic stem cells. Researchers then created a live, fertile mouse and pups from one of those eggs.

**Single-stranded library preparation**
Max Planck Institute for Evolutionary Anthropology, Germany
Reconstruction of the genome of a Denisovan ancestor by sequencing DNA from frozen finger fragments advances knowledge of our evolutionary past. Provides evidence that Denisovans and early humans interbred.

**Mouse models of autism spectrum disorder**
(1) McGill University in Montreal, Quebec, (2) Harvard
First transgenic mouse model of the social behavioral symptoms of autism (1) and first drug target identified for social behavioral symptoms (2).

**FLASH, Fast Ligation-based Automatable Solid-phase High-throughput, system**
Massachusetts General Hospital
Development of a rapid and cost-effective method for large-scale assembly of TALENs, enzymes that can be directed to cut DNA at specific locations.

**X-FEL, X-ray Free-Electron Laser**
SLAC National Accelerator Laboratory, Menlo Park
Straight-shot linear accelerator for difficult to crystalize protein structure determinations using X-ray diffraction.

**Practical application of whole genome sequencing**
Sanger Institute, Britain and Addenbrooke’s Hospital, Cambridge
First case of rapid whole genome DNA sequencing to lead to intervention of an infectious disease outbreak.
adoption of Benlysta. “With Benlysta, we are working to change the paradigm of treatment for systemic lupus,” he said. “This involves significant education on clinical data that are still unfamiliar to many lupus-treating physicians, followed by physicians’ initial trial of Benlysta in a few of their real-world patients.” With its share price battered down to a little more than $7, Human Genome Science’s long-time partner GlaxoSmithKline made an unsolicited $2.6 billion, or $13-a-share bid for the company, which the company rejected as inadequate. That sent human Genome Sciences in search of a white knight, a difficult prospect given GSK’s shared ownership of key assets. In the interim, prospects for Benlysta grew grimmer as both the United Kingdom’s National Institute of Clinical Excellence and Germany’s Institute for Quality and Efficiency in Health Care rejected the drug as too costly for what it delivers. In the end, GSK reached terms with human Genome Sciences in a sweetened $3 billion, or $14.25-a-share offer. Soon after GSK’s sweetened offer was made public, Reuters reported that human Genome Sciences had rejected a $3.5-a-share offer in August 2010, according to regulatory filings. Reuters reported that Amgen was the unnamed bidder, something neither Amgen nor human Genome Sciences would confirm—a lesson in the transience of value.

Insectible Colon-Imaging Tool
Product name: Check-Cap
Developer: Check-Cap
Non-invasive X-ray radar device creates a 3-D reconstructed image of the colon with minimal radiation exposure. No prior bowel cleansing is needed because it uses X-rays, which can see through the intestinal content that traditional optics cannot. The capsule transmits data to a wrist-worn device, where it is stored for a physician’s analysis.

Ingestible Sensor Pill and Skin Patch
Product name: Digital health feedback system
Developer: Proteus Digital Health
Ingestible sensor does not contain a battery, but rather two conductive materials, one on either side. When these get wet in the stomach, they power the sensor long enough to transmit patient compliance, heart rate, and other physiological measurements to the skin patch. A smartphone app receives the data for viewing and analysis.

Cellularized scaffold sheet
Product Name: Gintuit
Developer: Organogenesis
First approval of an allogeneic, or unrelated to the patient, cell product by the Center for Biologics Evaluation and Research arm of the FDA, and the first FDA-approved cell-based technology for use in the dental market. The product is a cellular sheet of cultured keratinocytes and fibroblasts in bovine collagen that is topically applied to a surgically created wound for treatment of adult gum diseases.

Payers say they would like to see clinical trials of new medications against standard of care to establish superiority.

But some payers wondered about the benefits of an MS drug that wasn’t disease modifying. Ampyra is a potassium channel blocker that essentially restores the ability to conduct electrical signals to nerve fibers that have lost their protective myelin insulation. In retrospect, Ron Cohen, CEO of Acorda, said if the company knew what it was going to encounter, it likely would have added elements to its clinical development program that would have been geared toward managed care acceptance, but might not necessarily have improved its chances of regulatory approval. “This is not your grandfather’s Buick anymore. If you grew up in biotech any time prior to the last five years, you need to reexamine your assumptions about the world of reimbursement. It has changed dramatically and it is continuing to change at really stun-
Innovative Products of 2012

**Sample-to-answer miniaturized point-of-care blood analyzer**

*Product name:* HDR and Axspring Technology  
*Developer:* Radisens Diagnostics

Point-of-care device and analysis software integrates measures of quality of life—immunoassay, chemistry and hematology—into a single device and replaces the ten or more stand-alone instruments a physician might require for routine blood testing.

**ProCellEx recombinant protein expression system in plant cells**

*Product name:* Elelyso  
*Developer:* Protalix Biotherapeutics, Pfizer

The first FDA-approved plant cell-based, rather than animal cell-based, recombinant therapeutic protein. The technology uses carrot and tobacco plant cells and is cost effective, safe and provides users entry into patent-protected markets. Elelyso, Protalix’s first therapeutic, is a protein that works as a long-term enzyme replacement therapy for treatment of Type 1 Gaucher disease.

**iPhone heart monitor**

*Product name:* AliveCor Heart Monitor  
*Developer:* AliveCor

First snap-on, coin cell battery-powered recorder with iPhone app for health screening to be used for rapid screening of ECG cardiac rhythms and heart rates. Enables screening of silent atrial fibrillation.

**Blood-brain barrier drug shuttle**

*Product name:* G-Technology  
*Developer:* to-BBB

Novel technology enables drugs to cross the blood-brain barrier for treatment of brain cancer, neurodegenerative diseases, lysosomal storage diseases, Alzheimer’s disease, and multiple sclerosis. Glutathione and the tag-along drugs within PEGylated liposomes cross the protective endothelial cell layer between the brain and the circulation via natural glutathione transport proteins.

“**This is not your grandfather’s Buick anymore. If you grew up in biotech any time prior to the last five years, you need to reexamine your assumptions about the world of reimbursement. It has changed dramatically and it is continuing to change at really stunning speed.**”

Ron Cohen, CEO of Acorda

In the absence of comparative effectiveness data, or data on offsets and actual use, developers are certainly moving toward taking into account payer concerns in clinical trials designs, the data pays most care about are...
still questions answered only after an approval. For instance, said Longman, the better drug developers can identify specific populations for drugs in their pipelines, the more receptive payers are likely to be to reimburse for the drug’s use. “That would be a very payer-focused way of thinking about this. Is this going to change how that payer does business? Is he suddenly going to have a product that is going to change the health of his population?” he asked.

Smaller biotechs have also begun focusing on the issues of reimbursement early in the drug development process. Executives say companies that focus only on the regulatory hurdles before them without an eye toward satisfying payers’ questions about new therapies have until they hit their registration trials. “It was a very different time,” he said. “Some people will argue that we’ve always done intense payer research. My impression is if it was done, it was always done late.”

Capturing value outside the product

The cost of healthcare around the globe continues to rise as growing populations, increasing longevity, expanding numbers of people over the age of 65, and the rise of chronic disease take a toll on the ability of governments and payers to wrestle with efforts to contain costs. As pricing pressures continue to intensify for pharmaceutical companies and the opportunity for drug companies to capture value directly through the sale of their products diminishes, they will increasingly look to the examples set by other industries to find ways to capture value outside of their products. High technology companies, retailers, and Internet companies have all provided examples of this.

Consider New York’s Museum of Modern Art, which in fiscal 2011 generated $2.2 million through admissions and $15 million through membership fees. That sum was dwarfed by the $50.5 million in revenues produced by what it calls “auxiliary activities.” This includes sales from the Museum’s stores (on- and off-site), e-commerce, mail order, publishing, restaurant, and other operations. Then there’s the online retailer Amazon.com, which has moved beyond generating revenue just from retail sales, but has also capitalized on the platform it created to build a major new business in cloud computing. Analysts have estimated that revenue from the cloud computing business could exceed $2.5 billion in 2014, according to Computer Reseller News. Grocery stores have learned to capitalize on the data they gather from customers to sell to marketers. Facebook now allows users of its social network to send gifts through major retailers, and the search engine giant Google generates its revenue not from it users but by selling advertising.

Lifesciences companies have also learned to capture value outside of their products. The personal genomics company 23andMe, which helps individuals understand their own genetic information through DNA analysis and well-equipped interactive tools, derives its revenues from selling genomics analysis to individuals and providing information to help people understand its meaning, as well as subscriptions to ongoing access to new information as it becomes available. But 23andMe has also created 23andWe, its research program. It allows customers to participate in research projects and help discover new genetic associations with diseases. Those efforts led in 2012 to 23andMe winning its first patent, which relates to identifying a genetic mutation associated with Parkinson’s disease. This could eventually lead to licensing revenue for the company. The company is also capitalizing on its customer base by helping drug-
If pharmaceutical companies think of themselves as being in the business of preventing and treating illness, new possibilities open up to provide services alongside the drugs they sell.
ers, and social networking support. If successful, the program will be expanded to as many as 1,000 patients in different countries.

In a separate agreement, in July 2012, Merck said it is collaborating with the integrated health services organization Geisinger Health System in an effort designed to improve patient outcomes by facilitating shared decision making between patients and physicians, increasing adherence to treatment plans, and improving clinical care. “We believe that healthcare is most effective when patients are active partners in their care,” said Glenn Steele, president and chief executive officer of Geisinger Health System. “Our collaboration with Merck will allow both organizations to leverage our individual expertise and joint resources to improve patient engagement, including finding new interventions to increase the likelihood that patients will adhere to their treatment plans.”

The first tool being developed is an interactive web application designed to help primary care clinicians assess and engage patients at risk for cardiometabolic syndromes, a clustering of various risk factors that put an individual at risk of developing type 2 diabetes and cardiovascular disease. The web application and other care management tools that Merck and Geisinger develop will initially be tested within the Geisinger system.

In 2010, Pfizer launched a pharmacy-based service in the United Kingdom that provides health screenings to prevent heart attack and stroke. By running cardiovascular tests in community pharmacies and then referring at risk patients to primary care physicians, the company provides a cost-efficient approach to preventing heart attacks and strokes. This ensures that physicians treat high-risk patients and address diet and lifestyle issues to help people stay healthy. A pilot program found that the approach was particularly successful in reaching patients who rarely consulted a doctor. A pilot test of 338 patients at seven community pharmacies throughout the United Kingdom found 26 percent of those patients had not visited a primary care doctor in more than a year and two-thirds said that they were unlikely or very unlikely to have made a similar screening appointment with their doctor. In all, 15 percent of those screened were determined to be at an elevated risk of a heart attack or stroke.

The Pfizer Vascular Health Check Service came in response to the U.K.’s National Health Services efforts to implement a program to provide cardiovascular disease risk screening to an estimated 25 million people 40 years to 74 years of age. Pfizer said it is providing primary care organizations with a comprehensive solution they need to deliver these screenings in a variety of settings by supplying all the equipment, consumables, training, information technology, and support services. Provided software guides pharmacists and clinicians through the evaluation and calculates patient risk factors, suggests courses of action, and relays information about the test to the patient’s physician.

The moment is now

The pharmaceutical industry has for much of the past decade been bracing for the very moment in time it now finds itself. The patent cliff, long on the horizon, is now at its steepest point. The end of the one-size-fits-all blockbuster era, marked not only by expiring patents, but also by scientific complexity, regulatory embarrassments, and payer frustration, has arrived as well. And the day of reckoning for bloated and ineffective R&D operations has come.

A bioreactor at an AstraZeneca plant in the UK. Innovative biotherapeutics will not be immune to the same pressures that traditional small molecule drugs have faced, but they are better positioned to withstand the assault that’s ahead.

What is Value?

Value is not a derivative of:

• Sales
• EBITDA
• Cash flow

Value, real and perceived, is dependent on:

• Technology
• Stage of development
• Indication/market
• Geography
• Payer

The pharmaceutical industry has watched approach brings new opportunities as well. The global economic crisis has seen new demand and growth in emerging countries where spreading prosperity is giving rise to an emerging middle class. With longer life spans and changing lifestyles, prosperity is also bringing with it a growing incidence of chronic disease that will drive demand for treatments for cancer, heart disease, diabetes, and other conditions in markets such as China, Russia, Brazil and elsewhere.

The pharmaceutical industry has been involved in a variety of efforts to both create value by reducing costs, increasing efficiency, and improving the value of what it produces, while at the same time seeking ways to capture value by focusing on drugs for unmet medical needs, rare diseases, and targeted therapies where value propositions are clear and pricing and competitive pressures are mitigated. A push to externalize research has accelerated. Pharmaceutical companies are forging deeper ties with academic institutions, disease advocacy groups, and independent research institutes. They are reaching further into the early-stage pipeline to partner on discovery-stage research with what, for now, are uncertain results. More than anything, these activities reflect an acknowledging that what has historically driven the industry is no longer producing adequate results and that it must find new ways to work. Consider Agen’s announcement in December 2012 that it would acquire the pioneering deCODE Genetics for $415 million. The Icelandic company has worked to identify links between genes and disease. Terry McGuire, general manager of Polaris Venture Partners and a deCODE backer, said in a blog post following the announcement of the deal that it may not fit analysts expectations of drugmakers buying companies for promising mid-stage or late-stage drugs, but that there’s a simple answer as to why Agen did so. “There is a great need by large biotechs and pharma companies to show change and more predictable innovation,” he wrote. “And Agen’s leaders know that the future of healthcare is laid on the foundation of producing truly innovative medicines and technologies.”

The challenges the industry faces are multi-dimensional and its collaborations will need to extend beyond traditional partners in order to drive its pipeline. Collaborations must build new relationships with patients, payers, providers, and non-traditional healthcare organizations that will be essential to a company’s future if it is to both create value for its customers and capture value for itself and its shareholders.

The moment is now. This brings good news for biotech companies that can both distinguish their pipelines with drug candidates that demonstrate value, as well as provide products that can command premium pricing even at a time that pressure grows to use generics, impose price controls, and employ other mechanisms to drive down the cost of drugs. Innovative biotherapeutics will not be immune from the same pressures that traditional small molecule drugs have faced, but they are better positioned to withstand the assault that’s ahead in a healthcare world that is rapidly transitioning to value-based models. A new world of biosimilars is emerging, and these players and providers have already demonstrated that they are unwilling to pay for new therapies that are too pricey, and a growing number of countries are moving toward Germany’s example in requiring some type of comparative effectiveness to justify pricing and use. That will make it harder for companies to pass off overpriced drugs or find substantial markets for ones that provide little or no improvement over existing therapies. But it will also bring a needed level of discipline to both investors and drug developers, and will provide rich rewards for those who can produce true innovation.
As payers increasingly demand proof of value of new therapies and regulators seek greater certainty about the safety and efficacy of drugs, drug developers are focusing more on targeted therapies as a better route to clinical, regulatory, and economic success. They are also finding that the blockbuster era is not dead, only that the era of the one-size-fits-all blockbuster is coming to an end. Beyond precision medicine, targeted therapeutics, and treatments tailored to individual patients, the greater promise of personalized medicine lies in radically transforming medicine. Through improved diagnostics, new understanding of the human genome, and an array of new monitoring devices in the emerging world of digital health, healthcare is on the cusp of realizing the deeper vision of precision healthcare—defined by its focus on personal, predictive, and preventive care.
CHAPTER 2:  
A Quest for Precision

Personalized medicine, rare disease, and the need to establish value

Michael Snyder envisions one day rolling out of bed, brushing his teeth, and sticking his finger for a blood sample to analyze perhaps thousands of measures of his health and to warn him of developing disease. Though this may sound like a long-standing personalized medicine fantasy by a geneticist, the difference is that Snyder has, in a sense, already lived it.

Snyder, a professor in genetics at Stanford University and the director of the Stanford Center for Genomics and Personalized Medicine, has gotten to know himself better than most people. Since arriving at Stanford in the summer of 2009, he’s been the center of his own personalized medicine research project that began with sequencing his entire genome and has since routinely drawn blood to measure the changes in 40,000 variables including RNA, proteins, metabolites, and antibodies the body produces against itself known as autoantibodies. The data forms what Snyder has dubbed an integrative Personal Omics Profile, or iPOP.

Snyder’s surprise, his whole genome scan revealed an elevated risk for diabetes. He was not aware of any family history of the disease and as someone with a medium build, he hadn’t considered himself at risk. However, he watched the disease develop at a molecular level following the development of a viral infection. He and his team believe his body’s stress response to the virus triggered the onset of his type 2 diabetes. Normally, he said, he would get a physical every two to three years so the disease could have gone undetected for some time, but Snyder said by catching the disease as it developed, he was able, through diet and exercise, to reverse it and restore his blood sugar to normal levels. Today he exercises more deliberately and forgos desserts, which he said he doesn’t really miss, except for ice cream.

Though Snyder’s intensive biological monitoring approach may not yet be ready for prime time because of the cost, the challenges of managing the massive amounts of data generated, the 50 to 60 milliliters of blood required for each draw, and the expense of conducting the various tests. But Snyder and his team believe it serves as a proof of principal of the transformational power of personalized medicine. He believes the number of variables monitored, the amount of blood required, and the cost of testing can all be reduced to a level appropriate as part of a regular doctor’s office visit or, he hopes, a consumer self-test. “When you go to a doctor’s office and they draw blood, they measure 15 different things,” he said. “We knew from the work we were doing that you could measure thousands, if not tens of thousands, of components in blood. That should give you a much better picture of what’s going on for measuring healthy and disease states.”

Using the integrated Personal Omics Profile, Snyder said the changes of various biological pathways could be seen at a level no one has ever seen before by measuring so many different elements. While it’s a great way to see when something goes wrong, the challenge now is to determine which of those measures are most valuable to monitor as robust indicators of health and disease. “If you can catch diseases early, you can usually correct them, as occurred in my case,” said Snyder. “If you catch them late, whether its cancer or anything else, it’s very difficult to reverse the symptoms or the problems.”

Snyder is now embarking on an expanded study by enrolling people who are at risk for type 2 diabetes and following them for five years, a period of time that should see about a third of them develop the disease. Snyder hopes to see the triggers of the onset of the disease as well as the molecular changes that occur. But he believes we are moving to a standard of care where patients will routinely have their whole genomes scanned to identify their risks for disease and use detailed monitoring on thousands of measures to indicate the changing status of their health.

As for his own blood draws and analysis, Snyder has no plans to stop. “I plan to do it all the way until I die. I guess that’s the endpoint. If I die of something acute and fast, it will probably be the person after me who will figure out what markers are associated with that. If it’s a slow, chronic thing, perhaps I’ll figure it out, what some of those markers might be.”

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Chasing Laplace’s demon

Snyder, in a sense, is chasing Laplace’s demon in the world of personalized medicine. The French mathematician, astronomer, and physicist Pierre-Simon Laplace offered a seductive view of the world. Building on the advances made by Sir Isaac Newton, Laplace in 1814 postulated in *A Philosophical Essay on Probabilities* what has come to be known as “Laplace’s Demon.” The idea is a simple one of scientific determinism. It suggests that if someone had the intellect to at once know the precise location and movement of every atom in the universe, they would be able to know the past as well as the future. “We may regard the present state of the universe as the effect of its past and the cause of its future. An intellect which at any given moment knew all of the forces that animate nature and the mutual positions of the beings that compose it, if this intellect were vast enough to submit the data to analysis, could condense into a single formula the movement of the greatest bodies of the universe and that of the lightest atom; for such an intellect nothing could be uncertain and the future just like the past would be present before its eyes.”

Laplace’s demon offers a certain elegance that in modern times has had to yield to notions of chaos. Laplace, of course, was concerned about the movement of celestial bodies, but today, scientists remain at as early a stage of the exploration of the genome as the astronomers of the Enlightenment were at in developing an understanding of the physical universe. Nevertheless, in a sense, personalized medicine is a chase of Laplace’s demon. The deepening understanding of the human genome continues to reveal new layers of complexity as researchers grapple with the need to understand not only what our DNA reveals—but how the metabolism, the proteome, and various other omics, along with diet and the environment—interact with our genes to alter wellness and disease. The question is, with enough information about the molecular changes in our bodies, can we know the future as well as we know the past? And casting aside the scientific determinism implicit in Laplace’s view, can we actually act on the information to intervene to preserve health and prevent or short-circuit disease before it takes a physical and economic toll?

An evolving vision

When people speak of personalized medicine they generally think about it in two ways. In simple terms, there is the notion of harnessing diagnostics and targeted therapeutics to attack the underlying molecular mechanism of a patient’s individual disease. In this sense, personalized medicine is, as the saying goes, about delivering the right drug, to the right patient, at the right dose, at the right time. It is here that personalized medicine has met with some of its most dramatic and earliest successes with early targeted therapies and companion diagnostics, such as Genentech’s breast cancer drug Herceptin, which radically altered the therapeutic landscape for cancer therapies by identifying patients appropriate for the therapy through an understanding of the molecular mechanism underlying the form of the disease against which the drug would be effective [See Figure 2.1]. Herceptin works on what actually drives the growth and spread of the HER2 positive breast cancer, overexpression of the HER2 gene, rather than using less discriminating toxins and hoping for the best. In this context, the term “personalized medicine” today is giving way to the newer term “precision medicine” as being more apt.

As pharmaceutical companies face increasing pressure from payers and regulators to establish the value of their products, they have come to embrace targeted therapies and companion diagnostics. In the old world, driven by a search for the next blockbuster drug, personalized medicine at first seemed like anathema. What drug company would go out of its way to marry a drug to a diagnostic that would guarantee eliminating a large number of potential customers,

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**Figure 2.1 Billion-Dollar Personalized Therapeutics**

Select approved therapeutic drugs with FDA/EMA required/recommended companion diagnostics

<table>
<thead>
<tr>
<th>DRUG</th>
<th>SALES</th>
<th>INDICATION</th>
<th>COMPANY</th>
<th>COMPANION DX TEST/MARKER</th>
<th>COMPANY</th>
<th>PEAK SALES FORECAST (USD B)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Xalkori</td>
<td>47</td>
<td>Lung cancer</td>
<td>Pfizer</td>
<td>Vysis ALK Break Apart FISH Probe Kit</td>
<td>Abbott Molecular</td>
<td>2.5</td>
</tr>
<tr>
<td>Zelboraf</td>
<td>35</td>
<td>Melanoma</td>
<td>Roche Flexikin</td>
<td>COBAS 4800 BRAF V600</td>
<td>Roche Molecular Systems</td>
<td>1.2</td>
</tr>
<tr>
<td>Kalydeco</td>
<td>N/A</td>
<td>Cystic-fibrosis</td>
<td>Vertex</td>
<td>COBAS 4800 BRAF V600</td>
<td>Roche Molecular Systems</td>
<td>3.5</td>
</tr>
<tr>
<td>Herceptin</td>
<td>5,940</td>
<td>Breast cancer</td>
<td>Genentech</td>
<td>PATHWAY ANTI-HER2/NEU HER2 FISH Pharm Dx Kit</td>
<td>Ventana Medical Systems</td>
<td>5.9</td>
</tr>
<tr>
<td>Erbitux</td>
<td>1,882</td>
<td>Anti-colorectal cancer</td>
<td>Bristol-Myers Squibb Eli Lilly</td>
<td>KRAS RGG PCR</td>
<td>Qiagen</td>
<td>1.9</td>
</tr>
<tr>
<td>Iressa</td>
<td>554</td>
<td>Lung cancer</td>
<td>AstraZeneca</td>
<td>EGFR+ Mutation</td>
<td>Giagen</td>
<td>1.0</td>
</tr>
<tr>
<td>Perjeta</td>
<td>N/A</td>
<td>Breast cancer</td>
<td>Genentech</td>
<td>HERCEPTIN HER2 FISH Pharm Dx Kit</td>
<td>Dako</td>
<td>8.5</td>
</tr>
<tr>
<td>Tarceva</td>
<td>1,415</td>
<td>Non-small cell lung cancer</td>
<td>OSI Pharmaceuticals</td>
<td>COBAS 4800 w/ EGFR IP</td>
<td>Roche Molecular Systems</td>
<td>1.8</td>
</tr>
<tr>
<td>Tasigna</td>
<td>716</td>
<td>Leukemia</td>
<td>Novartis</td>
<td>Philadelphia Chromosome positive Responders</td>
<td>Multiple</td>
<td>2.5</td>
</tr>
<tr>
<td>Spryclel</td>
<td>803</td>
<td>Leukemia</td>
<td>Bristol-Myers Squibb</td>
<td>Philadelphia Chromosome positive</td>
<td>In-house</td>
<td>1.0</td>
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<tr>
<td>Tykerb</td>
<td>370</td>
<td>Breast cancer</td>
<td>GlaxoSmithKline</td>
<td>HER2 overexpression</td>
<td>Monogram Biosciences/LabCorp</td>
<td>1.5</td>
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<tr>
<td>Gleevec</td>
<td>4,659</td>
<td>Cancer</td>
<td>Novartis</td>
<td>DAKO C-KIT Pharm Dx</td>
<td>Dako</td>
<td>4.7</td>
</tr>
</tbody>
</table>

Source: Burrill & Company, Evaluate Pharma, FDA
even if they would never benefit from using the drug? But as payers increasingly demand proof of value of new therapies and regulators seek greater certainty about the safety and efficacy of drugs, drug developers are focusing more on drugs that address unmet medical needs as a better route to clinical, regulatory, and economic success. They are also finding that the blockbuster era is not dead, only that the era of the one-size-fits-all blockbuster is coming to an end.

In 2012, newly approved personalized therapies included Vertex Pharmaceuticals’s Kalydeco for cystic fibrosis and Roche’s Perjeta for the treatment of a certain form of breast cancer that has spread. The U.S. Food and Drug Administration in June 2012 approved Roche’s Perjeta for HER2 positive metastatic breast cancer in combination with Herceptin and docetaxel chemotherapy. The approval was based on data from a late-stage clinical trial that showed previously untreated HER2-positive metastatic breast cancer patients who received the combination of Perjeta, Herceptin, and docetaxel chemotherapy lived a median of 6.1 months longer without their cancer getting worse compared to patients treated with Herceptin plus docetaxel chemotherapy. Progression free survival in patients that received Perjeta in combination with the other therapies had a median of 18.5 months compared to 12.4 months for patients that received just Herceptin and docetaxel.

As with Herceptin, Perjeta is a personalized medicine that targets the HER2 receptor, a protein found in high quantities on the outside of cells in HER2-positive cancers. But Perjeta is believed to work in a way that is complementary to Herceptin, as the two medicines target different regions on the HER2 receptor. “Perjeta attacks HER2-positive tumors differently than Herceptin. Based on the way the two medicines work together, the combination plus chemotherapy can prolong the time before this aggressive cancer worsens compared to Herceptin and chemotherapy alone,” said Hal Barron, chief medical officer and head of global product development for Roche’s Genentech subsidiary.

In the case of Kalydeco, the FDA approved the drug for cystic fibrosis patients with a specific genetic mutation known as G551D, which drives the disease in roughly 4 percent of patients, or about 1,200 people in the United States. Mutations of cystic fibrosis, a life-threatening disease that damages the lungs, causes a cell surface protein to function incorrectly, preventing proper flow of sodium and fluid in and out of cells. Kalydeco works by restoring the function of that protein. “Kalydeco addresses the underlying cause of CF and the science behind the drug has opened exciting new doors to research and development that may eventually lead to additional therapies that will benefit more people living with CF,” Robert Reul, president and CEO of the Cystic Fibrosis Foundation, said when the drug was approved. Cystic Fibrosis Foundation Therapeutics, the nonprofit drug discovery and development affiliate of the Cystic Fibrosis Foundation has long been in an R&D partnership with Vertex supporting the development of Kalydeco. Despite the small market for the drug, Vertex sales stand to be substantial. The drug carries an annual price tag of $294,000, according to Dow Jones Newswires.

Changing economics

In fact, a 2012 study in Drug Discovery Today from Thomson Reuters and Pfizer makes a strong economic case for pharmaceutical companies to develop drugs for rare or orphan disease, diseases that afflict less than 200,000 people in the United States. The financial incentives put in place to encourage the development of drugs for rare diseases, such as the Orphan Drug Act of 1983, provide tax breaks, R&D offsets, R&D grants, waived FDA fees, accelerated approval, and extended period of exclusivity. Orphan drugs also generally command higher prices than drugs for non-orphan diseases. As personalized medicine redefines diseases by their underlying molecular mechanisms rather than their outward manifestations, it is breaking disease groups into smaller sub-populations, turning one-time broad diseases into subtypes of those diseases that by definition constitute rare disease. [See Fig. R2 2.2 and 2.3]

“We’re not just talking about the typical rare disease, what we are also talking about are the emerging sub-diseases. You can take something like lung cancer; whereas before it might have been regarded as one cancer, typically pharma would try something to stick into lung cancer, now’s being talked of as 15 or 20 individual, small sub-disease,” said Kiran Meekings, life sciences consultant at Thomson Reuters and lead author of the Drug Discovery Today study. “So if we look at crizotinib (Xalkori), approved last year, that is an orphan drug because it is targeting a very small population of a large disease. This type of patient stratification or more personalized medicine approach is actually opening up new markets, which are smaller populations of larger diseases.”

Pfizer’s Xalkori was approved in 2011 to treat certain patients with late-stage, non-small cell lung cancers who express a mutated anaplastic lymphoma kinase, or ALK, gene. About 5 percent of patients with non-small cell lung cancer, or about 9,000 people a year with the disease, have the mutation. The drug costs $9,600 a month or $115,000 for patients who use it for a year, according to Forbes. Xalkori was approved with a companion diagnostic test that will help determine if a patient has the abnormal ALK gene, a first-of-a-kind genetic test called the Vysis ALK Break Apart FISH Probe Kit. The companion diagnostic is a result of the drug’s 2011 approvals. “The trend in oncology research continues towards targeted therapies,” said Alberto Gutierrez, director of the Office of In Vitro Diagnostic Device Evaluation and Safety in the FDA’s Center for Devices and Radiological Health. “This test is an example of the important role companion diagnostics play in determining that the safest and most effective treatments are promptly delivered to patients living with serious and life-threatening diseases.”

The Thomson Reuters study found that orphan drugs represent “an increasingly important component of the pharmaceutical market and have equal revenue-generating potential to non-orphan drugs.” The authors said orphan drugs make up 22 percent of total drug sales, and the cumulative annual growth rate of the orphan drug market totaled 25.8 percent between 2001 and 2010. That compares to only 10 percent for the matched non-orphan control group. In fact, the study found that the mean annual economic value of orphan drugs, in 2010 terms, reached $637 million compared to $638 million for non-orphan drugs. While the present value of orphan drugs remained roughly constant between 2000 and 2010, the present value of orphan drugs nearly doubled during that period. “This analysis suggests that the impact of a smaller treatable patient pool is offset by the higher pricing of many orphan drugs, the increased market share, the longer exclusivity period, and faster uptake rate that orphan drugs often garner as a result of the high unmet medical need in many of these diseases,” the authors wrote.

Like Xalkori, Kalydeco and Perjeta are also paired with companion diagnostics, but a growing list of personalized medicines are not necessarily paired with a diagnostic. Rare disease drugs, by their very nature, are personalized in the sense that they are addressing the

![Figure 2.2 Growth Rate of Orphan vs. Non-Orphan Drugs](image-url)
Is Big Pharma Serious About Orphans?

Signs that some companies are ready to make a bigger commitment

By Elmer Piros

Big Pharma supplied a steady stream of drugs for orphan indications over the last two decades. Between 1993 and 2012, the FDA approved drugs for 100 rare disease indications (200,000 patients or less in the United States) that listed Big Pharma companies as sponsors. The number of approvals remained relatively steady, at five indications per year, since 1993 [See Figure 2A]. In contrast, biotechnology companies, along with specialty pharma, brought more than twice as many orphan drugs to the market during the same period.

While the number of product approvals has increased by only 15 percent for the last decade over the previous 10-year period, the number of orphan designations paint a much more bullish picture for 2013 and beyond. There were only 650 orphan designations between 1993 and 2002. This number increased to 1,500 during the last ten years. Nowadays, the FDA issues 150 to 200 such designations annually [See Figure 2B].

Just by observing actual development, there is no evidence that Big Pharma is playing an increasing role in the field. However, there are subtle and some very visible signs of the interest and tangible commitment to rare diseases. Sanofi’s purchase of Genzyme is a clear indicator that some pharmaceutical companies are ready to take the plunge, as opposed to dabble into the field by selective licensing deals. Will BioMarin and Alexion, orphan-focused biotech companies with marketed products and deep pipelines, also find Big Pharma suitors in 2013?

Others, such as GlaxoSmithKline, use orphan drugs as buffers for downturns during the business cycle—at least for now. Mike Diem, director of business development at GSK's rare disease unit was quoted as saying that the company has integrated rare disease research into all of its R&D, according to Mark Fishman, president of the Novartis Institutes for Biomedical Research.

Not surprisingly, the unit is keenly interested in chaperones and other modifiers of protein trafficking, misfolding or degradation, as these mechanisms appear to be common amongst a number of orphan diseases. Finding a method to reverse the course of one condition may lead to a solution for another. Pfizer sees a potentially larger benefit. Hypothetically, by tackling Huntington’s disease for example, a disease-modifying therapy may be found for Alzheimer’s, a condition far from being orphan—over five million Americans suffer from it. This line of reasoning is not entirely hypothetical. Pfizer has tried, but unfortunately failed to achieve success with Dimebon, licensed from Medivation, a drug that was in development for both conditions simultaneously. As an aside, Prana Biotechnology is currently in phase 2 clinical testing with a drug that could address both Huntington’s and Alzheimer’s.

Pfizer made a formal commitment to rare disease drug development by signing a deal with Protalix Biotherapeutics for an enzyme replacement therapy in 2009. Subsequently, their orphan medicine Xalkori was approved in mid-2011 for genetically defined subsets of non-small cell lung cancer patients. This approval followed by two more in 2012. Elelyso, licensed from Protalix, was given the green light for Gaucher disease, followed by Bosulif for treating chronic myelogenous leukemia or CML. It is interesting to observe that neither Gaucher’s nor CML are truly orphaned indications. There were already drugs available for both conditions. In addition, Pfizer has embarked on a collaborative research initiative that would indicate that the company sees significant potential in orphan drugs down the road. The company’s Orphan and Genetic Disease Research Unit is actively seeking academic or commercial collaborations in at least eleven target areas.

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Novartis knows how lucrative an orphan drug can be. Gleevec was first approved in 2001, following a 2-month review cycle, for CML. Over the next 11 years, Gleevec was approved for an additional six rare oncologic indications. How lucrative? Novartis recognized $4.6 billion in Gleevec revenue in 2011. For Novartis, orphan drugs do not appear to just represent revenue buffers or something fashionable to do nowadays. The company has integrated rare disease research into all of its R&D, according to Mark Fishman, president of the Novartis Institutes for Biomedical Research.

"There is no distinction between how we approach medicine for a rare disease or for more prevalent disease," Fishman said in an interview with The Scientist. Novartis is currently targeting more than 40 rare diseases. Discoveries made in the orphan setting are expected to pay dividends for indications that are more common. Fishman cited the example of Afinito, which was approved in 2009 for treating advanced kidney cancer. Similarly to Gleevec, Novartis secured approval for a number of other indications since: prevention of organ rejection in 2010, astrocytoma associated with tuberous sclerosis in 2010, progressive or metastatic pancreatic neuroendocrine tumors in 2011, and hormone-receptor positive, HER2-negative breast cancer in 2012.

The number of orphan drug approvals or designations does not yet imply a shift in leadership for orphan drug development—the biotechnology industry is still in charge. However, there are tangible signs that Big Pharma is making a sizable investment.
genetic or molecular mechanism of a patient’s disease. And the growing pipeline of antibody-drug conjugates—drugs that marry a therapeutic payload to an antibody and deliver it in a highly targeted way that minimizes the toxicity of a drug that might otherwise be too toxic to use, a new push within personalized medicine.

Approval of Seattle Genetics’ Hodgkin’s lymphoma drug Adcetris in 2011 represented the first of a new wave of antibody-drug conjugates with a growing pipeline advancing behind it.

Making smaller markets attractive

Helping encourage the pharmaceutical industry’s embrace of rare disease drugs and targeted therapies are new incentives contained in the FDA Safety and Innovation Act, which reauthorizes the FDA to collect user fees from industry to fund drug reviews. The big winner in this fifth incarnation of the Prescription Drug User Fee Act may have been the rare disease community, which saw a list of pending bills forged by patient advocates folded into the final legislation. Rare disease advocates succeeded in getting five separate pieces of legislation aimed at creating incentives for drug companies to develop new therapies for rare diseases, speed the regulatory review process, and allow a greater role for patients in FDA discussions about the review of medical products.

The success of the rare disease community in its legislative push is credited to a well-coordinated grassroots campaign involving a wide range of organizations advocating for specific rare diseases and the involvement of a large number of people from the patient community. The effort included an email campaign from patients to members of Congress as well as a lobbying day organized by the collaborative group Rare Disease Legislative Advocates, that brought 70 patient advocates to the nation’s capital in support of the legislative initiatives. “The inclusion of so many rare disease provisions in FDASIA is a testament of the power of the grassroots patient community,” said John Crowley, a parent advocate and CEO of Amicus Therapeutics. He credited the “united voice of the patient community” for ensuring the success of the rare disease provisions (See Figure 2.4).

The provisions folded into the legislation included the creation of an incentive for drugmakers to pursue rare disease drugs by granting companies that bring a rare disease drug to market a voucher that provides accelerated FDA review of another drug, an incentive that could be worth hundreds of millions of dollars for large-market drugs. The legislation also included language to provide for accelerated approval of treatments for rare diseases by allowing the FDA to use surrogate endpoints for determining the efficacy of a drug. In addition, it directs the FDA to ensure that rare disease experts have greater input into the FDA review process and makes it easier for FDA staff to access such experts to help them understand the risks and benefits of therapies under review.

At the same time, the legislation pushes the FDA to increase its engagement with patient advocates in reviewing medical products. “If you think about all of it together,” said Emil Kakkis, president of the EveryLife Foundation for Rare Diseases, “it sends a very strong statement to the FDA from Congress that said we need to do better on rare disease drug treatments and I think that message will be heard by the FDA.”

1,000 Genomes Project Maps Genetic Variation

Project data should help guide drug developers

The 1,000 Genomes Project, an effort to identify rare variants in the human exome, the part of the genome that codes for proteins, has produced a map that will enable researchers to zero in quickly on variants, speeding efforts to use genetic information to develop new strategies for diagnosing, treating, and preventing common diseases.

Researchers sequenced the exons of 1,000 genes in each genome of 1,092 individuals from Europe, the Americas, East Asia, and Africa. Although most of these genetic variants cause little if any effect, some contribute to disease, and others are beneficial.

Consortium leader Gil McVean, professor of statistical genetics at Oxford University, said that the “single most important result” is that common mutations are shared by people across the globe, while rarer ones are confined to certain ethnic groups or nations. Variants that could strongly increase one population’s risk of a disease might be non-existent in another group of people.

The results could help drug developers understand why during a clinical trial a drug seems to benefit some patients, but not others. It could also help identify subgroups of patients for which a particular therapeutic might be beneficial, and rescue a drug otherwise doomed to clinical failure by providing insight into the population on which it is used.

In addition to the DNA sequences, the 1,000 Genomes Project has stored cell samples from all the people it has sequenced, to allow future investigations into the biological effect of the DNA variations. Use of the cell samples will be critical to translate the information contained in the 1,000 Genomes datasets to valuable, actionable, information.

“The results could help identify subgroups of patients for which a particular therapeutic might be beneficial, and rescue a drug otherwise doomed to clinical failure.”

A greater promise

Beyond precision medicine, targeted therapeutics, and treatments tailored to individual patients, the greater promise of personalized medicine lies in radically transforming medicine away from treating symptoms of illness, to not only addressing the underlying causes of disease, but also attacking disease at its earliest stages before it blossoms into a costly, chronic, or deadly threat. That’s exactly what Stanford’s Snyder was able to do with his own developing...
diabetes through his costly monitoring of the biological changes within his own body. Through improved diagnostics, new understanding of the the human genome and biomarkers, and an array of new monitoring devices in the emerging world of digital health, healthcare is on the cusp of realizing the deeper vision of personalized medicine—or perhaps more accurately personalized healthcare—defined by its focus on personal, predictive, and preventive care.

One of the primary drivers of that change is the rapidly falling cost of genome sequencing and the move of the genome from a costly and cumbersome research tool to a diagnostic tool with clinical utility. In 2012, the cost of sequencing was expected to fall below the $1,000 mark, blowing away Moore’s law [See Figure 2.5]. Though the Human Genome Project took 13 years and $3 billion dollars, the actual time and cost of sequencing the first human genome exclusive of other parts of the project has been estimated to have taken a year and cost about $500 million, according to officials at the National Human Genome Research Institute. In September 2012, Life Technologies began shipping its Ion Proton sequencing system. The company said the chip-based system cost about $500 million, according to officials at the company. Complete will continue to be operated as a separate company with headquarters and operations remaining in Mountain View, California. Though Roche failed to succeed in its hostile bid to acquire the sequencing company Illumina in 2012, its attempt gave a glimpse into how the biopharmaceutical giant viewed the role sequencing would play in the future of medicine. Roche in January 2012 initially offered $5.7 billion for the San Diego-based company, a 64 percent premium to the price of Illumina’s stock on December 21, 2011, the day before rumors of the deal first surfaced. Roche then sweetened its bid to $6.7 billion at the end of March 2012, but dropped its pursuit less than a month later with the expiration of its tender offer. The company said it was unable to engage in a meaningful dialogue and investors expressed growing concern about what Roche would do if it ever did pay a sequencing technology only to find in the rapidly changing landscape an alternative would emerge to dominate the market.

At the time Roche first announced its bid for the company, it said the acquisition would strengthen its position in the diagnostics market and accelerate the transition of sequencing into clinical and routine diagnostic use. Is this the next market for super-fast, cheap gene sequencing?” wrote Paul Howard, senior fellow and the Life Technologies plans to release a second-generation chip for its Ion Proton sequencing system that will be able to, in a few hours, sequence the human genome for $1,000.

### Figure 2.4 Rare Diseases Get Boost in PDUFA V

Life Technologies said it will develop and offer lab-developed tests as well as commercialized kits that have been approved by the FDA and other regulatory authorities. It also plans to build partnerships with pharmaceutical companies for companion diagnostic development, including participating in clinical trials, which it said is enabled by the CLIA lab acquisition.

“Life Technologies’ entry into the clinical diagnostics market, coupled with the scope of their clinical and research applications and their successful personalized medicine is no longer a distant future promise, but today’s reality,” Vance Vanier, president and CEO of Navigenics, said when the acquisition was announced.

In September 2012, China’s sequencing powerhouse BGI-Shenzhen agreed to buy the financially troubled next-generation sequencing company Complete Genomics for $117.6 million or $3.15 a share, a 54 percent premium over the company’s closing price the day prior to its June 2012 announcement that it was seeking strategic alternatives. Complete, which had been working to provide whole genome sequencing through a service-based business model, said that it was running out of cash and needed to explore strategic alternatives. At that time, it had less than six months of cash.

Cliff Reid, chairman and CEO of Complete Genomics, said the BGI deal represented the best alternative, providing stockholders with “liquidity and a premium value.” “The combination of the companies’ resources provides an opportunity to accelerate our vision of providing researchers and physicians with the genomic information needed to prevent, diagnose, and treat cancers and other genetic diseases,” Reid said. Complete will continue to be operated as a separate company with headquarters and a CLIA-certified lab that it plans to use to design and validate new diagnostic assays.

### Figure 2.5 The Falling Cost of Genome Sequencing

Life Technologies in July announced plans to acquire the personal genomics company Navigenics, part of an effort by the sequencing tools company to build its molecular diagnostics business. The companies did not release terms of the agreement. Life Technologies, though, gains Navigenics’ experience at communicating complex genomic information to physicians in simple and relevant terms. Under the plans for the company, Navigenics will focus on providing technology and informatics to pathologists and oncologists. It also provides Life Technologies with a CLIA-certified lab that it planned to use to design and validate new diagnostic assays.

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Source: National Human Genome Research Institute
director of the Manhattan Institute’s Center for Medical Progress on the organization’s blog in response to Roche’s bull.” “It’s hospitals, doctors offices - heck, maybe even the CVS drug store down the street. That’s the future of genome sequencing: fast enough and cheap enough to become a consumer commodity.”

Dan O’Day, Roche’s diagnostics division COO, speaking on a conference call with analysts in February 2012, said he expected sequencing to move from the research arena to the clinic faster in Europe than in the United States because of regulatory hurdles, but noted that sequencing is already finding its way into the clinic in some cases, such as matching donors to recipients in bone marrow transplants. “I don’t think this is something that is five or ten years out in Europe in particular,” he said, according to a Seeking Alpha transcript of the call. “I think it’s something we see already and that we can foster and begin to drive. It won’t be a black-and-white situation. There won’t be one day it’s in the research world, the next day it’s in the clinic world. But it will evolve and it will evolve quicker in Europe than it will in the United States.”

An accelerating pace

The evolution of personalized medicine is already evident and it is accelerating. In part, this is due to improvements in technologies, such as whole genome sequencing, being employed to address the problems of actual patients. Already there is anecdotal evidence of the impact sequencing can have on treatment and outcomes of patients in the clinic.

Consider the case of Lukas Wartman, a Washington University researcher stricken with the deadly cancer he had spent his career studying. Gina Kolata in The New York Times in July 2011 reported how, without any viable treatment for his adult acute lymphoblastic leukemia, Wartman’s colleagues decided to fully sequence the genes in both his normal and cancer cells, and interpret data from genetic sequencing. “I think it’s something we see already and that we can foster and begin to drive. It won’t be a black-and-white situation. There won’t be one day it’s in the research world, the next day it’s in the clinic world. But it will evolve and it will evolve quicker in Europe than it will in the United States.”

The case reflects the new medical realities of personalized medicines as doctors shift from focusing on the part of the body where cancer arises to the actual genes driving it and employing therapies tailored to the specific mutations of each cancer patient. “Researchers differ about how soon the method, known as whole genome sequencing, will be generally available and paid for by insurance—estimates range from a few years to a decade or so. But they believe that it has enormous promise, though it has not yet cured anyone,” wrote Kolata. “With a steep drop in the costs of sequencing and an explosion of research on genes, medical experts expect that genetic analyses of cancers will become routine. Just as pathologists do blood cultures to decide which antibiotics will stop a patient’s bacterial infection, so will genome sequencing determine which drugs might stop a cancer.”

New initiatives announced in 2012 should accelerate this move of whole genome sequencing out of the lab and into the doctor’s office. As not only researchers, but payers, providers, and diagnostics companies work to hasten the integration of personalized medicine into clinical practice and realize the promised benefits it brings to care. The University of Texas MD Anderson Cancer Center’s announced in September 2012 an ambitious $3 billion Cancer Moon Shots Program, which seeks to develop new diagnostics, devices, drugs, and policies to detect, prevent, and treat cancer by capitalizing on the convergence of low-cost sequencing, artificial intelligence, and other emerging technologies. The Moon Shots program is initially focusing on eight cancers including acute myeloid leukemia/myelodysplastic syndrome; chronic lymphocytic leukemia; melanoma; lung cancer; prostate cancer, and triple-negative breast and ovarian cancers. “If we fire across the whole beachfront—prevention, detection, prognostication, and treatment—we feel confident that in this decade we can dramatically reduce cancer mortality and set the stage in the years ahead to have this disease controlled,” said Ronald DePinho, president of MD Anderson.

As whole genome scanning moves to the clinic, the challenge will be to make the tremendous amount of information it provides not something that overwhms doctors, but provides actionable information. To that end, the genetic sequencing tools company Illumina entered into a strategic alliance in September 2012 with Partners Healthcare, the non-profit healthcare system founded by Brigham and Women’s Hospital and Massachusetts General Hospital, to provide geneticists and pathologists networking tools and infrastructure to report and interpret data from genetic sequencing. The companies did not disclose financial terms of the agreement, but said that they will integrate the functions of Illumina’s MiSeq sequenc- ing system with Partners’ Genes Insight Suite, a platform that streamlines the analysis, interpretation, and reporting of genetic test results. GeneInsight software has supported the interpretation and reporting for more than 24,000 complex genetic tests across multiple diagnostic reference laboratories since 2005, the companies said.

It’s not just genomic data that providers are seeking to harness to improve care. The University of Pittsburgh Medical Center in October 2012 announced a new five-year, $100 million enterprise healthcare analytics initiative that will foster personalized medicine. Along with its technology partners Oracle, IBM, Informat, and dbMotion, UPMC is working to create a data warehouse that brings together clinical, financial, administrative, genomic, and other information that today is difficult to integrate and analyze. Such information would enable doctors to better predict which treatments would be most effective and least toxic for individual patients based on their genetic and clinical information.

UPMC expects that advanced analytics and predictive modeling applications for clinical and financial decision-making will produce better patient outcomes, enhance research capabilities, and lower costs.
A Race to Unlock the Power of DNA

Norway, U.K. seek to integrate genome sequencing into healthcare systems

In the past year, Norway and the United Kingdom have led the world in establishing large-scale, genome-wide sequencing efforts within their National Health Services. The goal for both countries is to accelerate personalized medicine and lower healthcare costs.

In Norway, the long-term objective of the effort is to contribute to a national diagnostic service for all Norwegian cancer patients with researchers eventually sequencing all of the 20,000 or so protein-coding genes, known as the exome, in these patients. The entire effort falls within the National Research Council’s strategy for biotechnology under the BIOTEK 2021 program, successor to The Programme on Functional Genomics in Norway, which concluded in 2011. The current collective, known as the Norwegian Cancer Genomics Consortium, will establish not only technical and clinical guidelines for the project, but will also facilitate the exchange of information between clinicians and researchers, and analyze the health economic impact of national, standardized implementation of targeted therapies.

In its three-year pilot phase, the Norwegian Cancer Genomics Consortium will sequence the tumor genomes of 1,000 patients in the hope of influencing their treatments. It will also look at another 3,000 previously obtained tumor biopsies to better understand mutations in different cancers and how those mutations influence a patient’s response to a drug. It will be up to physicians and their patients to decide on the appropriate course of action.

In the second phase, depending on funding, the project will build the laboratory, clinical, and computing infrastructure needed to support this standardized approach for the 25,000 Norwegian diagnoses with cancer each year. In an example of academic-industry-government collaboration, academic medical center partners in the first grant will be supported by industry partners in the second grant, including the Oslo Cancer Cluster (Amgen, Pfizer, Astra-Zeneca, Sanofi, Aventis, and Bristol-Myers Squibb), Pubgene, Clavis Pharma, Arctic Pharma, BergenBio and the government-appointed Norwegian Biotechnology Advisory Board.

Cancer Research UK is a London-based charity that spearheaded the equivalent British pilot program, the Cancer Research UK Stratified Medicine Programme. Currently in year two of the first two-year phase of the project, 9,000 people with breast, colorectal, lung, prostate, ovarian, and skin cancer will have their tumors sequenced. Data on the tumors and the patients will be analyzed in a national database that is open but protected, similar to the existing General Practice Research Database, a huge set of anonymized primary-care records used by many British scientists.

Due to the pilot’s on-going success, the United Kingdom’s National Health Service announced late in 2012 that it will map the exomes of up to 100,000 patients with cancer and other rare diseases over the next three to five years at a cost of $162 million (£100 million). Prime Minister David Cameron expects Britain to become the first country to introduce genetic sequencing to its mainstream health service.

It’s a race not only to improve treatments, but also to spark innovation. “By unlocking the power of DNA data, the NHS hopes to lead the global race for better tests, better drugs, and better care,” Cameron said. “If we get this right, we could transform how we diagnose and treat our most complex diseases not only here but across the world, while enabling our best scientists to discover the next wonder drug or breakthrough technology.”
The industry has focused on nuts and bolts issues of building viable business models, forging regulatory pathways, establishing the case for reimbursement, resolving uncertain intellectual property questions, and considering questions such as privacy rights and protections in an age of genomics.

For practical reasons, the industry has focused on nuts and bolts issues of building viable business models, forging regulatory pathways, establishing the case for reimbursement, resolving uncertain intellectual property questions, and considering new questions created by the implications of technological advances, such as privacy rights and protections in an age of genomics. These are substantial issues that are being addressed, even though more work remains to be done.

The Genetic Information Nondiscrimination Act of 2008 provided a baseline of protections to individuals from insurance companies and employers requesting or requiring genetic information from themselves or family members. It also prevents the use of genetic information from being used to make insurance coverage decisions, set rates, or deny coverage because of a preexisting condition. Under the law, employers are prohibited from using genetic information for hiring, firing, or promotion decisions, and for any decisions regarding terms of employment. Of the 99,947 employment discrimination charges filed with the U.S. Equal Employment Opportunity Commission in fiscal 2011, just 245 alleged violations relating to GINA. That compared to just 201 complaints in 2010. The number of complaints is expected to grow as awareness of the law and genetic information about individuals proliferate.

But as the rapidly falling cost of whole genome sequencing moves toward clinical applications, there are concerns that new privacy protections are needed to ensure its medical benefits are realized. At the state level, new legislation has been put into place to provide new protections not offered by GINA, such as prohibitions on testing an individual’s DNA sample without his or her knowledge and declaring that DNA is the property of the individual from whom it comes.

Reflecting the concern about issues raised by the growing ease and commonality of whole genome sequencing, the Presidential Commission for the Study of Bioethical Issues in an October 2012 report said that in order to realize the benefits of whole genome sequencing, widespread public participation and a willingness among individuals to share genomic data and relevant medical information is necessary. In order for this to happen, though, there must be confidence among the public that there are adequate privacy protections. To that end, the commission offered a host of recommendations relating to such issues as informed consent, data security, accountability, and the exchange of information.

The dilemma, said the committee, is that while society as a whole will benefit from the information gleaned from whole genome sequencing, it is individuals who stand to bear the risk of misuse of their information without enjoying likely benefits. “The Commission’s goal was to find the most feasible ways of reconciling the enormous medical potential of whole genome sequencing with the pressing privacy and data access issues raised by the rapid emergence of low-cost whole genome sequencing,” said commission chair Amy Gutmann. “The life-saving potential of genome sequencing depends on gathering genetic information from many thousands (perhaps millions) of individuals, most of whom will not directly benefit from the research.”

Gutmann said people who are willing to share intimate information about themselves to advance medical progress should have confidence that private medical information, such as their risk for developing a specific disease, will be protected as confidential. In the absence of that, she said, individuals will be less likely to supply data that could lead to life-saving treatments for genetic diseases. With variation in protections from state to state, the commission called for the establishment of a “consistent floor of protections covering whole genome sequence data regardless of how they were obtained.” That means whether someone willingly provided a sample to researchers or medical professionals, or simply left saliva behind on an abandoned cup of coffee, people should be protected against unauthorized whole genome sequencing without their consent.

While much has been made about the need to address regulatory issues surrounding personalized medicine, the renewal of PDUFA is expected to enhance the environment relating to such issues as informed consent, data security, accountability, and the exchange of information.
Diagnostic companies are going to have to confront the natural—in this case the correlation between laws of nature, natural phenomena, and abstract ideas that have long been held by the court as more than laws of nature—in this case the correlation between thiopurine metabolite levels and the safety and efficacy of the dosage of the drugs. The federal circuit court on appeal reversed the ruling saying that the patent involved not only the natural correlations between thiopurine metabolites and the safety and efficacy of the drugs, but also processes for administering thiopurine drugs to patients and determining the metabolism level. These steps, it reasons, involve the transformation of the human body or of blood taken from the body. This, the appeals court said, satisfies the “machine or transformation test,” a standard used to determine the patentability of an invention. The Supreme Court sent the case back down to the appeals court following its ruling in Bilski v. Kappos, a case that involved an algorithm used in hedging strategies in commodities markets. The court in Bilski ruled that the machine or transformation test, while useful, should not be the sole determinant of whether an invention is patentable. The federal circuit reaffirmed its decision and Mayo appealed again.

Laws of nature, natural phenomena, and abstract ideas have long been held by the court as patent-eligible. Suppose a patient is taking thiopurine drugs, but also processes for administering thiopurine drugs to patients and determining the metabolism level. These steps, it reasons, involve the transformation of the human body or of blood taken from the body. This, the appeals court said, satisfies the “machine or transformation test,” a standard used to determine the patentability of an invention. The Supreme Court sent the case back down to the appeals court following its ruling in Bilski v. Kappos, a case that involved an algorithm used in hedging strategies in commodities markets. The court in Bilski ruled that the machine or transformation test, while useful, should not be the sole determinant of whether an invention is patentable. The federal circuit reaffirmed its decision and Mayo appealed again.

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As implicitly outside of the realm of patentable inventions. As Justice Stephen Breyer notes in the Supreme Court’s Prometheus ruling, Newton could not have patented gravity or Einstein his E=mc² formula. Justice Breyer wrote that the claimed processes are not patentable unless they have additional features that provide practical assurance that the processes are genuine applications of those laws rather than “drafting efforts designed to monopolize the correlations.” The claims instruct a doctor to administer the drug to his patient, tell the doctor to measure the resulting metabolite levels in the patient’s blood, and describe the metabolite concentrations above where there is a likelihood of harmful side effects. In his view, it is likely that the drug dosage is ineffective, and inform the doctor that metabolite concentrations above or below these thresholds “indicate a need” to decrease or increase respectively, the drug dosage. The additional steps in the claimed processes in Prometheus’ case, Breyer wrote, are not themselves natural laws, but they nevertheless fall short of being enough to transform the nature of the claims.

John Conley, a professor of law at the University of North Carolina at Chapel Hill and of counsel to the law firm Robinson Bradshaw & Hinson, said that he expects the decision to have little impact on diagnostics companies. He notes that, with regard to gene patents, the ruling said nothing directly or indirectly. The biggest impact, he said, is the uncertainty it creates, rather than any meaningful change to the patent landscape. “One thing the people in the industry are complaining about is a little bit that regardless of what the rule is, we’ve gone from a certain rule to one where the Supreme Court has called for a lot more case-by-case discretion,” he said. “To the extent that certainty is a business value for better or worse, we’ve backed off a little bit from the certainty we’ve had and the patent office and the courts are now called upon to exercise more discretion.” Over the next several years, he expects patent attorneys faced with intellectual property similar to Prometheus’ will seek to use clever drafting to see what they can get away with. If the Supreme Court is correct, they won’t be able to draft their way around the decision. Nevertheless, patent lawyers are certain to try.

The other major ruling in this area came from a federal appeals court in August 2012 in a challenge to patents held by Myriad Genetics. The litigation raised fundamental questions about the patentability of genes. The U.S. Supreme Court instructed the appeals court to revisit its decision in light of a subsequent ruling in a related case. After weighing the court’s instructions, the judges delivered a 2-1 ruling that the company could patent isolated DNA, but not the methods for comparing those gene sequences.

The United States Court of Appeals for the Federal Circuit found that Myriad’s isolated DNA for two genes associated with certain forms of breast and ovarian cancer are patentable. The decision overturns a district court’s ruling that found that isolated DNA was not patent eligible as a product of nature. The appeals court, though, said each of the molecules claimed in the Myriad patents represent “non-naturally occurring composition of matter.”

The case had been closely watched among investors and the life sciences industry because of the potential that a ruling invalidating Myriad’s patents could have consequences that extend well beyond the company’s products as life sciences companies rely on nearly 2,000 gene-related patents. “It’s certainly the best result for Myriad,” said Foley & Lardner’s Brinckerhoff. “Because I don’t think it was a very unexpected result, I think ‘victory’ is a bit strong. There would have definitely been much stronger reaction if it didn’t come out this way.” She said the ruling maintains the status quo.

The American Civil Liberties Union and the Public Patent Foundation originally filed suit against Myriad in 2009 charging that the patents were unconstitutional, stifle research, and have a detrimental effect on women getting access to more affordable alternatives by giving Myriad a monopoly on the BRCA genes. Those points Myriad refuted in a press release announcing the ruling. It pointed to the work of 18,000 scientists who have published more than 9,000 research papers on the BRCA genes and noted about 95 percent of appropriate patients have access to its tests.

“Importantly, the court agreed with Myriad’s arguments that issues of constitutional law are not the methods for comparing those gene sequences.

As with Glybera, UniQure is developing a pipeline of therapies that use adeno-associated viral derived vectors as the delivery vehicle for therapeutic genes. The company has been able to design and validate what it believes is “the world’s first stable and scalable AAV manufacturing platform.” It said its platform can be applied to a large number of rare diseases caused by one faulty gene.

“Final approval of Glybera from the EC marks a major step forward in making gene therapies available not only for LPLD but also for a large number of rare diseases with a very high unmet medical need,” said Jörn Aldag, CEO of UniQure. “The EC’s approval is an important validation of our innovative product platform and offers strong support for our other advanced development programs, which focus on acute intermittent porphyria, Sanfilippo B, hemophilia B and Parkinson’s disease.”

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European Commission Approves First Gene Therapy

UniQure’s treatment will be used for rare metabolic disorder

The European Commission has approved UniQure’s gene therapy as a treatment for lipoprotein lipase deficiency, a rare inherited disease that prevents people from metabolizing fat and leads to recurring, painful, and potentially lethal inflammation of the pancreas. It is the first gene therapy regulatory authorities in the Western World have approved for commercial sale.

The Netherlands-based UniQure expects to begin selling the therapy, Glybera, in the second half of 2013. The approval covers all 27 European Union member states. The company said it is preparing to apply for regulatory approval in the United States, Canada, and other markets.

Lipoprotein lipase deficiency is caused by mutations in the LPL gene, resulting in highly decreased or absent activity of LPL enzyme in patients. This enzyme is needed in order to break down large fat-carrying particles that circulate in the blood after each meal. When such particles accumulate, they may obstruct small blood vessels and cause recurrent and severe acute inflammation of the pancreas. LPL deficiency affects 1-2 persons per million.

In the absence of an existing treatment, the only recourse patients with the condition have is to severely restrict the amount of fat they consume. Professor John Kastelein of the Department of Vascular Medicine at the Academic Medical Center of the University of Amsterdam

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After weighing the court’s instructions, the judges ruled that the company could patent isolated DNA, but not the methods for comparing those gene sequences.
The American Medical Association’s 2013 code set creates 116 new codes for molecular diagnostics. Previously, in the absence of specific codes to cover molecular diagnostics, test makers had to cobble together existing codes to cover various steps in their diagnostic process.

and scientists from exchanging their ideas and research freely,” said Chris Hansen, a staff attorney with the ACLU Speech, Privacy and Technology Project. “Human DNA is a natural entity like air or water. It does not belong to any one company.” The U.S. Supreme Court at the end of November 2012 said it will hear an appeal, but will only address the question of whether human genes are patentable, and will not take up other questions raised in the appeal.

Cracking codes

In September 2012, the American Medical Association released its Current Procedural Terminology or CPT codes set for use in 2013. The codes, maintained by the AMA, are used by providers to bill insurance companies for medical, diagnostic, and surgical procedures. The new code set is particularly significant because it expands on the 2012 codes for molecular diagnostics with the creation of 116 new codes. Previously, in the absence of specific codes to cover molecular diagnostics, test makers had to cobble together existing codes to cover various steps in their diagnostic process, a method commonly called “code stacking,”. But the process was often unsatisfactory to diagnostic providers because they felt the result fell short of the actual value the test provided. Code stacking also frustrated payers because it was often unclear what they were actually paying for.

To ensure that payments better reflect the value that diagnostic tests provide, the industry is backing new legislation, drafted in part by industry members and introduced in September 2012 by Illinois Republican Congresswoman Peter Roskam. The legislation would require the Centers for Medicare & Medicaid Services, when setting reimbursement rates for clinical diagnostic laboratory tests, to consider such things as the impact the new test has on patient care, treatment, and management. It would also require the agency to take into account what private insurers and individual patients pay for the same tests, as well as weigh the recommendations from a 19-member advisory panel that includes clinicians, patients, and representatives familiar with advanced clinical diagnostic laboratory tests. Andy Fish, executive director of the trade group AdvaMedDx, speaking during The 8th Annual Biomedical & Genomic Medicine Meeting in San Francisco right before the introduction of the legislation, said the value diagnostics bring are not reflected in reimbursement because the CPT code system, constructed in the mid-1980s, wasn’t designed to assess value, but was instead based on a cost-of-materials basis and didn’t take into account modern technology. “The system needs to be overhauled,” he said.

How a diagnostics company establishes the value of its product is unclear in today’s environment. Ed Abrahams, president of the Personalized Medicine Coalition, who shared the stage with Fish, said diagnostic companies are facing “moveable goal posts.” “The payers are not very clear about what they want,” he says. “They say you have a lot of evidence here, but just not enough no matter whatever it is,” he said. Abrahams said his organization would like to set up a summit between diagnostics makers and payers to develop coherent policies on the level of evidence needed to establish reimbursement. While he acknowledges the need to demonstrate clinical utility of diagnostics, he also expresses skepticism about payers’ willingness to pay for diagnostics and said the cost of randomized clinical trials make that an impractical solution for most diagnostic companies. “Ultimately, to get the traction we need, we need to demonstrate across the board that we can, as we say, improve outcomes and reduce systemic long-term costs,” he said. “We’re not going to get traction with payers because payers, like government officials, are rightly skeptical. We need, as a community, to develop the evidence that we can do what we say we can do, and unfortunately the development of evidence costs plenty.”

Lost in translation

But if business issues such as reimbursement, regulation, and privacy have been advancing to catch up to the emerging world of personalized medicine, other challenges have confronted both researchers and industry suggesting fundamental problems on the scientific front that threaten to undermine efforts to incorporate personalized medicine more broadly into daily medical practice. The scientific integrity of research underlying the personalized medicine and the validation of the biomarkers as indicators of disease has emerged as one area of significant concern. Despite biomedical researchers’ improved understanding of the molecular underpinnings of disease, it has been difficult to translate the growing information about genomics, proteomics, metabolomics, and other so-called “omics” into actual improvements in patient care.

The problem became a center of focus in 2011 over the validity of research underlying tests...
0.0 Population: 62.3 M National Health Service Personalized Medicine Initiatives: Individualized medicine is an independent field of activity in the Federal Government’s current framework program for health research. Regional and local initiatives, partially supported by the federal government, include the Greifswald Approach to Individualized Medicine, the National Center of Competence in Research (NCCR) of the BioM Botech Cluster in Munich, the education and training initiative Fighting Drug Failure of the Dr. Margarete Fisher-Bosch Institute in Stuttgart, and the PerMed NRW competition in North Rhine-Westphalia.

UNITED KINGDOM Population: 62.3 M National Health Service Personalized Medicine Initiatives: Programs include The Stratified Medicine Innovation Platform of the Technology Strategy Board and the Stratified Medicine Programme of Cancer Research UK. The Technology Strategy Board and Department of Health, through the Small Business Research Initiative innovation program, support business in identifying health and economic benefits of their technologies in order to sell their products to the National Health Service and other healthcare providers. In addition to Cancer Research UK, other charities involved in Personalized Medicine include the Francis Crick Institute and the Wellcome Trust. The Medical Research Council is active in the field with programs aligned to Technology Strategy Board’s policies.

FRANCE Population: 65.4 M Statutory health insurance; Assurance Maladie Obligatoire Personalized Medicine Initiatives: The main activities in France are focused on cancer and are published in the Cancer Plan 2009-2013. The plan is financed by the Ministry of Higher Education and Research and the Ministry of Health and Sports. Implementation of the plan is mandated to the National Cancer Institute in Paris. Regional initiatives, bioclusters, and diagnostics alliances are also active in the field. The Advanced Diagnostic and New Therapeutic Approaches, or ADNA, research and development program has an estimated budget of about $264.5 million (€200 million) and will receive government funding of $1079 million (€816.6 million) over 10 years.

ITALY Population: 59.5 M Servizio Sanitario Nazionale Personalized Medicine Initiatives: Italy has no national program on personalised medicine and few regional level initiatives. The Regional Center for Diagnostic, Prognostic and Predictive Biomarkers in the Veneto Region focuses its efforts in oncology and neurodegenerative, cardiovascular, and immune system pathologies, as well as outcomes analysis and production, dissemination, and adaptation of guidelines. Scientists from IBM Research are collaborating with the Fondazione IROCC Istituto Nazionale dei Tumori, a major research center, on a new decision support solution to personalize treatment based on automated interpretation of pathology guidelines and intelligence from past clinical cases that are documented in the hospital information system.

SPAIN Population: 45 M National Health System Personalized Medicine Initiatives: Development of the field is outlined in the Spanish National R&D Plan 2008-2011 with a focus on national and inter-regional collaborations. The Carlos III Health Institute in Madrid plays a central role in coordination and funding of the various initiatives. ENISA, the State-owned Enterprise of the Spanish government that delivers services to the health sector, is the central governing body which is updated on an annual basis. Current key issues include quality of cost and performance evaluation and standardization of processes so that evidence development can be aligned with technology assessment requirements.

SWEDEN Population: 9.5 M Some 17 county councils and four regional organizations Personalized Medicine Initiatives: The Swedish Foundation for Strategic Research 2012-2017 strategy includes personalized medicine with a focus on diagnostic markers. Three national programs are ongoing, including $2 million allocated to the Predictive Models and Biomarkers for New Therapies with a program time frame of 2010-2014. SciLifeLab, providing the technology needed for optimal usage of resources unique for Sweden and Scandinavia, including clinical material in the form of biobanks and medical records, and COMBINE, focusing on inflammatory diseases and inviting participation from patients and patient organizations in design and interpretation of research.

SWITZERLAND Population: 8 M Mandatory private health insurance Personalized Medicine Initiatives: Analyses and diagnostics must be included in the Positive Analyses List, which is updated on an annual basis. Current key issues include quality of cost and performance data, calculation of investment costs and prompt reimbursement of innovations.
A NEW DATING RITUAL?

Personalized Medicine Gets A Little Personal

OraSure in-home HIV test may find a bigger market than intended

ew diagnostics are allowing people to approach their own healthcare in way that allows them to be more predictive and preventive, even if that’s not entirely what they were intended to do.

Consider OraSure Technologies’ OraQuick In-Home HIV Test, which became available in October 2012 as the first rapid infectious disease test ever made available directly to consumers for in-home use.

Douglas Michaels, president and CEO of OraSure hailed the test as a “tremendous breakthrough in our fight against HIV and AIDS, saying that the test will empower people “to learn their HIV status in the comfort and privacy of their own home.”

A story in The New York Times, though, found that the market for the $40 test may be different than its creators intended. The newspaper reported that an unadvertised use of the test—checking whether potential sexual partners are infected—may prove to create unexpected demand for the test. According to The Times, 70 percent of the 4,000 participants in the clinical trials for the test said they would definitely or very likely use the test to screen partners. In fact, the newspaper said some clinical trial participants suggested the company package the test two to a box so couples could use it together.

Others, though, such as the National Institute of Allergy and Infectious Disease Director Anthony Fauci expressed concern that a negative test could lead to people having unprotected sex and not only leave them vulnerable to HIV infection, but other sexually transmitted diseases. The test is almost 100 percent accurate when testing someone who is not infected. However, it is only about 93 percent accurate when testing someone who is infected. That’s because newly infected people may not yet be producing antibodies detected by the test.

OraSure's Michaels told the newspaper that the company is supportive of such uses, “as long as it’s between consenting adults.” But he also noted that the label for the test warns it should not be used to make decisions that might put the user at risk of contracting H.I.V.

“The real value of this report is for people who don’t have the capital or capabilities to develop their own set of best practices. Now we can point those people to this guide. It’s incredibly useful,” he said, “from having more openness and more transparency about the nature of the data, the way the data are organized, how the analysis is performed, and the criteria for claiming yea or nay on certain types of correlations, associations or mechanisms.”

Peeling the onion

Beyond the questions of scientific sloppiness and scientific fraud, though, is the need to grapple with the growing complexity of the science underlying personalized medicine. Each new advance seems to reveal new layers that need to be unlocked. It has become apparent that the industry underestimated what it would take to translate the mapping of the genome into actionable information that could be used to better diagnose, treat, predict, and prevent disease.

Scientists reminded the industry of this point with the publication of a series of 30 research papers in September 2012 in Nature, Genome, the New York Times, and the American Journal of Human Genetics.
Biology, and BioMed Central as part of the ENCODE or ENCYclopedia Of DNA Elements Project, an ambitious international effort to characterize and publish all of the functional elements in the human genome. It found that the 80 percent of DNA, once thought of as “junk,” actually plays a critical role in regulating genes and can also play a part in the onset of disease. The research suggests a far more complex view of DNA and how it works, and for a new definition of a gene that includes RNA-coding regions, not just protein-coding regions.

The findings not only create a new understanding of what a gene is and the role of some 80 percent of DNA once thought to serve no function, but also provides a new source of potential targets for drugs, new insight into how genes are regulated, and how people become ill. “During the early debates about the Human Genome Project, researchers had predicted that only a few percent of the human genome sequence encoded proteins, the workhorses of the cell, and that the rest was junk. We now know that this conclusion was wrong,” said Eric Green, director of the National Human Genome Research Institute, a part of the National Institutes of Health. “ENCODE has revealed that most of the human genome is involved in the complex molecular choreography required for converting genetic information into living cells and organisms.”

The researchers found that non-coding DNA and RNA play an active role, acting as switches that modulate genes. This non-coding DNA is involved in everything from cellular differentiation to the onset of disease. “We’ve come a long way,” said Ewan Birney of the European Bioinformatics Institute and lead analysis coordinator for the ENCODE Project. “By carefully piecing together a simply staggering variety of data, we’ve shown that the human genome is simply alive with switches, turning our genes on and off and controlling when and where proteins are produced.”

Changes under way

There is broad agreement today that personalized medicine can address serious problems afflicting healthcare, moving doctors away from merely treating sickness to providing a new approach to healthcare that is focused on prediction, preemption, and personalization to the biology of individual patients. Enabling this change is not only the rapidly falling price of sequencing, but the convergence of other technologies, such as low-cost wireless monitors, ubiquitous Internet connectivity, cloud computing, artificial intelligence, and more.

Despite the healthcare technopolis’ enormous ability to generate and collect biological data—even in real-time—the challenge is to create value by translating the various data streams available into actionable information based on validated science. While there is a growing number of targeted therapies giving rise to new notions of precision medicine, the bigger promise to improve healthcare lies in the use of technologies that empower patients to take a greater role in their own health and wellness. These technologies will improve the ability of doctors to not only monitor patients’ condition, but provide a continuous stream of data outside of the lab that reflects the reality of their health in their daily lives and allows for interventions at the earliest indications of changes in their wellbeing. The use of technology such as smartphones, wearable sensors, embedded sensors, or even nano sensors circulating within the blood that one day will warn of the genesis of a cancer or an impending heart attack, is transformational. Already, nascent digital health technology is being deployed to improve health, to better monitor elderly people living independently, or to provide people with chronic diseases the opportunity for early interventions that can prevent the need for costly treatments and hospitalizations. Not only is the convergence of technologies driving personalized medicine deeper into the foundation of healthcare, the convergence of interests of drugmakers, regulators, payers, providers, and patients is doing that as well. They each see value in the promise of personalized medicine to address problems they face.
3
Digital Health

Inexpensive, ubiquitous computing is revolutionizing the delivery of healthcare. Opportunities for health interventions and advice once tied to limited moments and places are becoming ever more closely woven into everyday life as smart sensors, algorithms, and persistent connectivity enable new approaches to wellness. Data once locked in disconnected silos is now being pieced together to paint richer pictures of the dynamic forces shaping our understanding of complex human behaviors and biology. Realizing the advantages made possible in this new world of digital health will be difficult at times, but the potential payoffs are too great to ignore.
A woman reclines on a couch, tablet in hand. She reacts calmly to the on-screen notification: Two cases of whooping cough have been reported nearby, the message says, and her daughter’s vaccination against the childhood killer is out of date. A second message offers an open appointment with the family doctor. She confirms the time and moves on. This vision of ambient healthcare information integrated seamlessly into everyday life is part of a futuristic scenario envisioned in a video created by the California-based design firm IDEO for the digital health company Scanadu. The vision the companies foresee is less distant every day. Already, tablets and smartphones running Google’s Android operating system are automatically presenting bleary-eyed commuters with predictions of how much traffic to expect before leaving for work and using location information to recommend the best-rated dishes at nearby restaurants. A growing array of data collected by mobile sensors, analyzed by algorithms, and presented just in time is giving rise to a new era in which technologies responsive to our environments, habits, and health surround us with ambient intelligence.

As companies such as Fitbit and Nike make tracking metrics, such as calories burned, flights of stairs climbed, or sleep patterns easy, there is room to create rich new experiences, suggests Brian Solis, a principal at the social media research and consultancy firm Altimeter Group. Speaking at the French technology conference, LeWeb, in December 2012, Solis challenged product designers and software developers to create technologies that employ the data people are collecting about their own activities and health to shape the online social presentation of that same data in ways that drive behavioral changes to improve people’s health and overall lives. “What I’m talking about is developing technology and products that push you outside of your comfort zone, to help you move beyond the quantified self and quantify aspirations and goals,” said Solis. “As sensors improve over time, you begin to see a convergence between health, data, behavior and lifestyle. Eventually technology just fades into the background, bringing disparate people, services, and outcomes together.”

People in developed economies are beginning to engage with an ever-broader array of networked computing platforms—from tablets to Ford’s 5-million-strong fleet of cars featuring its voice-controlled SYNC system. As the number of channels delivering information expands, it seems only natural that the mediums of delivery will begin to fade in importance relative to the messages carried. Indeed, much like personalized medicines, the right messages delivered at the right times, in the right dose, or format, could be just what the doctor ordered.

**Financing the future**

Despite the growth of financing activity in the digital health sector, venture investments in the space still account for just a fraction of the $12.4 billion in venture financing raised by life sciences companies globally in 2012. Total disclosed venture financings in the digital health sector rose 51 percent to $722.8 million in 2012, from $477.8 million in 2011. Digital health companies attracted venture financing in 83 deals during 2012, as compared to 54 financings in 2011 [See Figure 3.1]. Companies in the healthcare management information technology sector, those that are creating electronic medical records systems and other software for managing patient data, led the way, garnering 33 percent of the money raised. Kinnser Software landed $39.9 million to finance its web-based home health management software, while Practice Fusion’s ad-supported free electronic medical records system attracted $34 million, and Valence Health drew $30 million to fund its population management and reimbursement risk management technology.

**Figure 3.1 Digital Health Venture Financings 2011 vs. 2012**

<table>
<thead>
<tr>
<th>Category</th>
<th>Amount Raised USD M</th>
<th>2011</th>
<th>2012</th>
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<tbody>
<tr>
<td>Health Data</td>
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<tr>
<td>Information</td>
<td>$250</td>
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<tr>
<td>Information</td>
<td>$125</td>
<td>125</td>
<td>150</td>
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<tr>
<td>Monitoring</td>
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<tr>
<td>Population</td>
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<td>200</td>
<td>225</td>
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<tr>
<td>Reimbursement</td>
<td>$225</td>
<td>225</td>
<td>250</td>
</tr>
<tr>
<td>Service</td>
<td>$200</td>
<td>200</td>
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<tr>
<td>Telemedicine</td>
<td>$250</td>
<td>250</td>
<td></td>
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<tr>
<td>Total</td>
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<td>1975</td>
<td>2500</td>
</tr>
</tbody>
</table>

Source: Burrill & Company
Castlight Health’s $300 million Series D round, drew $152.2 million in disclosed 2012 venture funding. Meanwhile, patient monitoring tools drew $84.6 million, making it the third biggest sector in digital health by disclosed deal size.

Castlight’s funding is meant as a step toward an initial public offering for the company, said Castlight CEO and co-founder, Giovanni Cøella. Castlight has spearheaded the move for more transparency in healthcare pricing—employers have asked employees to pay a larger portion of their healthcare costs. Castlight’s platform offers employees of self-insured companies the tools to shop for procedures based on cost and quality. In San Francisco where Castlight is based, the difference between the highest and lowest charge for a procedure was $172,000, according to a study published by the University of California San Francisco.

Other big winners of 2012 financing among digital health companies were Best Doctors, a company seeking to bring together the best medical minds in the world to help people find the right diagnosis and treatment, which raised $45.5 million; the telehealth company America- Can Well, a provider of on-demand and sched- uled online doctor consultations, which raised $37.1 million; and Telecare, creator of a cellular-enabled blood glucose meter that provides instant feedback and coaching to patients with diabetes.

Feeding the pool of new companies are startup accelerators, such as Rock Health and Blueprint Health, which are backing clever products and services to reshape and disrupt traditional modes and models of healthcare delivery with seed money, mentorship, and support from healthcare heavyweights such as Kaiser Perma- nente, Qualcomm, and GE, as well as venture investors trying to keep their fingers on the pulse of the rapidly growing opportunities in digital health.

Despite this excitement, the sector is still in its early days. Just one digital health company, Green- way Medical, managed to go public in 2012. The healthcare management company’s focus on interoperability of electronic health records likely made it an attractive target for investors tuned in to government rules—first laid out in Octo- ber 2009’s Health Information Technology for Economic and Clinical Health Act—mandating health providers establish secure, confidential, electronic exchange of health information by 2014. Castlight may be next on the runway. But between now and the day when a greater number of digital health companies go public, there will be many innovations that fly (and flop) on their way to investor acceptance.

Embracing the revolution

digital health technologies will become ubiquitous as doctors and patients grow com- fortable with using their everyday digital devices to manage health. As comfort levels grow, increasing sophistication will be layered on to monitor patients and share information with doctors. The convergence of wireless tech- nologies, social media, and low-cost monitor- ing devices and sensors will provide consum- ers with new ways to take control of their own health and wellness.

Diagnostic tools are also moving from the clinic to the patient with rapid speed [See FIGURE 3.3]. Four high-profile digital health products won 501(k) clearance from the U.S. Food and Drug Administration in 2012: Proteus Digital Health’s ingestible sensor, Alive-Cor’s heart monitor, Sanofi’s iBGStar, and Sotera Wireless’ ViSi Mobile.

Proteus won clearance for its ingestible sen- sor in August 2012, clearing the way for it to commercialize and sell its digital health platform in the United States. Powered by stomach fluid, the company’s digital pills when swallowed, report heart rate, body position, and activity to a body patch that relays the information to a mobile phone via Bluetooth and ultimately on to caregivers and doctors to help guide treatment. “The FDA validation represents a major milestone in digital medicine,” said Eric Topol, director of the Scripps Translational Science Institute. “Directly digitizing pills, for the first time, in conjunction with our wireless infrastructure, may prove to be the new standard for influenc- ing medication adherence and significantly aid chronic disease management.”

The approval opened the door for sale of what Proteus calls “digital medicines” in the United States, yet Pro- teus didn’t go public today, but now containing a tiny sensor that can communicate vital information about medica- tion-taking behaviors and physiologic responses to drugs. “We had a great interaction with FDA, particularly in the last year or so while they were figuring out how to clear it,” said George Savage, Proteus’ co-founder and chief medical officer. “On the drug side at [the Center for Drug Eval- uation and Research] we had a good experience with regulators who helped us figure out how to streamline integration with already-approved drugs. We have clearance to go to market right now and we’ll get into pharmaceuticals within the next year.”

In addition to working with pharmaceuti- cal partners Novartis and Otsuka to integrate...
Figure 3.2  **HOSPITAL ON A SMARTPHONE**

Devices that turn smartphones into diagnostic tools

**Heart Monitor**

AliveCor’s Heart Monitor snaps onto an iPhone to take and record a person’s heart rate and rhythm instantly. It can display an electrocardiogram on the phone’s screen, store it in memory, or transmit it wirelessly. The device has received FDA clearance and is available starting in 2013 for $199. www.alivecor.com

**Glucose Monitor**

Sanofi’s iBGStar blood glucose monitor (below) can be used on its own or connected directly to an iPhone to display, manage, or share a person’s blood glucose level. A pinprick of blood is applied to a test strip and inserted into the device for analysis. Cleared by the FDA in December 2011, the iBGStar sells for anywhere from $50 to $75 plus the cost of test strips, which are covered by most insurers. www.ibgstar.us

**Vital Signs Monitors**

Scanadu’s Scout (above) is a handheld device that is touched to the temple to record five vital signs—blood pressure, blood oxygen level, heart rate, respiratory rate, and heart rhythm or ECG—which are wirelessly transmitted and stored in a smartphone. The product is still in testing. www.scanadu.com

LionsGate Technologies’ Phone Oximeter leverages smartphone audio jacks to connect a light sensor capable of reading blood oxygen levels from a person’s finger. Such readings are important for detecting hypoxemia, a condition in which blood is insufficiently oxygenated due to compromised ability of the lungs to absorb oxygen. The product is not yet available for sale. www.lgtmedical.com

**Detecting Disease**

CellScope’s attachable devices turn a smartphone into a microscope that allows patients to transmit high-magnification, diagnostic-quality images to their doctor for remote diagnosis and treatment. The Smart Otoscope for ear infections and the Smart Dermascope (shown at right) for skin infections, are in development. www.cellscope.com/devices

Stanford University’s OScan is an oral cavity scanner that attaches to any smartphone’s camera and allows users to take a high-resolution picture of the mouth cavity. It can be used to detect oral cancer, the most common cancer in India, at an early stage when the chance of survival is high. med.stanford.edu/ism/2012/april/vodaphone-0417.html

**Testing Eyes**

EyeNetra’s Netra-G (above) is a $2 clip-on eyepiece and a software app for a smartphone that allows anyone, anywhere to get an eye test for glasses, and access an eye care provider through the mobile network. It measures nearsightedness, farsightedness, and astigmatism. Research teams in 14 countries have already used prototypes. www.eyenetra.com

**Portable Ultrasound**

MobiSante’s MobiUS SP1 (above) is a hand-held ultrasound imaging system that plugs into a smartphone to generate and display the image, making it a portable point-of-care diagnostic tool. The device, which received FDA clearance in early 2011, is sold only to medical professionals and costs about $7,500. www.mobisante.com
its technology into their medicines, Proteus is developing its own branded digital drugs focused on chronic and neurological diseases, areas in which medication adherence can dramatically impact the efficacy of treatment. Proteus began selling its patch and digital pills through the U.K. pharmacy chain Lloyd’s pharmacy in fall 2012 under the brand Lifenote—a brand that replaces an earlier code-name for the platform, Helius. With the FDA approval in hand, the company is actively exploring partnerships with U.S. pharmacies too. “We need integrated treatment systems,” said Savage. “It’s complicated. But if you do it right, the value you create is huge.”

AliveCor received FDA clearance for its mobile heart monitor in December 2012, paving the way for it to ship its $199 iPhone-connected heart monitor in early January 2013. The device incorporates electrodes into a case that snaps onto the back of the Apple iPhone 4 and 4S smartphones. With a corresponding app, it can be used to record heart rate or the electrical impulses of the heart to create an electrocardiogram, or ECG.

In a presentation at the 2012 American Heart Association Meeting, a group of company and outside authors called the device “an ideal enabling technology for community screening programs to detect silent atrial fibrillation” and that screening programs using the device “could have a substantial impact on reducing ischemic stroke related to previously undiagnosed atrial fibrillation,” an arrhythmia that carries a five-fold increased risk of stroke. The heart rhythm records created by AliveCor’s monitor are stored on the user’s iPhone and securely on AliveCor’s website for later analysis, sharing, and printing.

The company is initially targeting sales to medical professionals. Doctors have embraced the iPhone in their practice according to statistics from Manhattan Research. More than two-thirds of physicians use an iPhone or other device running Apple’s mobile operating system, iOS, for professional purposes, according to the research firm’s 2012 online survey of 3,015 U.S. practicing physicians. Veterinarians are receiving their own message from the company, promising to connect the heart to create an electrocardiogram, or ECG.

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Sotera Wireless received clearance from the FDA for its full ViSi Mobile System and is commencing sales to hospitals nationwide. The ViSi uses WiFi to transmit patients’ vital signs, keeping hospital clinicians connected to their patients, whether patients are in bed or up and moving around. “The system is, the first to provide continuous monitoring of all the core vital signs on a patient worn platform. Researchers at Scripps Translational Science Institute are testing the device as a potential tool to use in monitoring the vital signs of future space tourists.

The institute won a $3.75 million grant from the Qualcomm Foundation in October 2012 to advance clinical trials of wireless biosensor systems, rapid pharmacogenomic diagnostic tests, apps and embedded sensors for tracking and predicting disease. The money will support additional staffing and other resources for a three-year program, called Scripps Digital Medicine, designed to move promising medical apps and devices more quickly to hospitals and clinics. The effort will now allow the institution to run four simultaneous digital health trials rather than just one at a time. “I recommend apps more than prescriptions these days,” said Topol. “I have them recording their blood pressure and other vital signs. Now they’re diagnosing themselves and seeing things they never saw before.” Clinical validation is an important part of the digital health movement, he said, but can be difficult for small innovative companies that don’t have the deep pockets to support trial personnel and other costs.

In May 2012, Sanofi’s iBGStar became the first blood glucose meter that can be used on its own or connected directly to an Apple iPhone or iPod touch to display, manage, and communicate information. It automatically syncs data with an accompanying app that tracks glucose, insulin, and carbs, and charts individualized glucose patterns over time.

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The institute won a $3.75 million grant from the Qualcomm Foundation in October 2012 to advance clinical trials of wireless biosensor systems, rapid pharmacogenomic diagnostic tests, apps and embedded sensors for tracking and predicting disease. The money will support additional staffing and other resources for a three-year program, called Scripps Digital Medicine, designed to move promising medical apps and devices more quickly to hospitals and clinics. The effort will now allow the institution to run four simultaneous digital health trials rather than just one at a time. “I recommend apps more than prescriptions these days,” said Topol. “I have them recording their blood pressure and other vital signs. Now they’re diagnosing themselves and seeing things they never saw before.” Clinical validation is an important part of the digital health movement, he said, but can be difficult for small innovative companies that don’t have the deep pockets to support trial personnel and other costs.

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US Unveils $200 Million Big Data Initiative
Activities will develop analysis tools for growing volume of digital data

The Obama Administration in March 2012 launched a Big Data Research and Development Initiative in conjunction with six federal departments and agencies, making a $200 million commitment to improve the tools and techniques needed to access, organize, and glean discoveries from the huge volumes of data generated around the world.

“In the same way that past federal investments in information technology R&D led to dramatic advances in supercomputing and the creation of the Internet, the initiative we are launching today promises to transform our ability to use Big Data for scientific discovery, environmental, and biomedical research, education, and national security,” says John Holdren, assistant to the President and director of the White House Office of Science and Technology Policy.

The National Institutes of Health and the National Science Foundation will be among the top recipients of funding, along with the Departments of Defense and Energy, and the U.S. Geological Survey. Besides advancing the development of technologies needed to collect, store, preserve, manage, and analyze the growing volume of digital data being generated on a daily basis, the initiative aims to glean the harnessed knowledge to advance scientific discovery, strengthen national security, and transform teaching and learning. Money will also be allocated to expand the skilled workforce needed to make sense of it all.

One of the first commitments is a joint solicitation supported by the NSF and NIH to advance the core scientific information from large and diverse data sets being generated by advances in sequencing and genomics that could accelerate scientific discoveries that improve human health. In conjunction with the Big Data Initiative, the NIH announced that its 1,000 Genomes Project, an international public-private attempt to build the most detailed map of human genetic variation available, is now publicly available on Amazon’s Cloud services.

“The explosion of biomedical data has already significantly advanced our understanding of health and disease. Now we want to find new and better ways to make the most of these data to speed discovery, innovation and improvements in the nation’s health and economy,” says NIH Director Francis Collins, who supports the Big Data Initiative.

Among the NIH components participating in the Big Data initiative are the National Human Genome Research Institute (NHGRI) and the NIH National Center for Biotechnology Information (NCBI), a division of the National Library of Medicine. NHGRI played a lead role in organizing and funding the international 1,000 Genomes Project. NCBI, along with the European Bioinformatics Institute, which is located in the United Kingdom, began making data from the project freely available to researchers in 2008. Besides the NIH, major supporters include the Wellcome Trust and BGI.

The project’s organizers hope to eventually analyze the genomes of 2,600 people from 26 populations around the world. It began with three pilot studies in 2008 that assessed strategies for producing a catalog of genetic variants that are present at 1 percent or greater in the population. The current 1,000 Genomes Project records are a prime example of big data that has become so massive that few researchers have the computing power to use them.

At 200 terabytes—the equivalent of 16 million file cabinets filled with text, or more than 30,000 standard DVDs—the current 1,000 Genomes Project records are a prime example of data so massive that few researchers have the computing power to use them.

To help solve that problem, Amazon Web Services agreed to post the data for free as a public data set, providing a centralized repository on its cloud. It lets any researcher access and analyze the data at a fraction of the cost it would take for their institution to acquire the needed internet bandwidth, data storage and analytical computing capacity.

“Improving access to data from this important project will accelerate the ability of researchers to understand human genetic variation and its contribution to health and disease,” says NHGRI director Eric Green.

Cloud access also enables users to analyze the data much more quickly, because it eliminates the time-consuming download of data and because users can run their analyses over many servers at once. “Putting the data in the cloud provides a tremendous opportunity for researchers around the world who want to study large-scale human genetic variation but lack the computer capability to do so,” says Richard Durbin, co-director of the 1,000 Genomes Project and joint head of human genetics at the Wellcome Trust Sanger Institute.

Wu Feng, associate professor of computer science at Virginia Tech, will participate in a project funded by the Big Data Research and Development Initiative that holds promising advances for genomics and metagenomics. Feng was recognized in 2011 for developing a research framework and toolkit of personal desktop supercomputing solutions for the analysis of genomic changes in next-generation sequencing data.
nity now to shift from a sickness model to a wellness model and use technology to monitor patients in the ambulatory environment so we can intervene earlier, or use it to teach them to stay healthier,” said Van Gorder. “Doctors and healthcare providers are going to be receptive to this if the technology is proven to be safe and reliable, and we can deal with patient confidentiality concerns.”

To ensure that both clinical and privacy concerns are adequately addressed, Scripps has a digital health committee that is exploring those issues. In the case of GE Healthcare’s Vscan, a flip phone-sized mobile imaging tool, the group is reviewing how the device is used, how the data it creates is kept private, and how the data is stored to both support future care and protect the hospital in cases where patients might challenge care decisions.

**Searching for health online**

While doctors are leveraging telemedicine tools, individuals are using the Internet and mobile technologies for health advice. Once wholly reliant on doctors as a primary source of medical information, patients are increasingly turning to each other on social networks and trusted sources on the Internet to find relevant and personalized health information.

One in three American adults has gone online to figure out what medical condition they or someone else might have, according to PatientsLikeMe. In July 2011, the Pew Research Center’s Internet & American Life Project released its Draft Guidance on PatientsLikeMe to work directly with Merck’s clinical researchers and epidemiologists to analyze and interpret psoriasis data reported by nearly 2,000 members of the site that report on their experience with the disease and what they do to treat it. “Effective use of health information provides the path forward to patient-centered care and personalized medicine,” said Sachin Jain, Merck’s chief medical information and innovation officer. “Our collaboration with PatientsLikeMe is an important part of Merck’s strategy to establish and apply innovative solutions that improve disease management and enhance the patient experience.”

The exchange of health information from doctor-to-doctor and doctor-to-caregivers is growing too. Already the specialty social network Doximity, a site for medical professionals, has attracted 20 percent of U.S. doctors. And as families struggle to coordinate and track their communications with caregivers and other family members, especially around elder care, niche management networks, such as CarePlanners and the SAP-backed CareCircles sites, are providing new online hubs for aggregating medical records, insurance information, and educational information to help keep caregiver networks in sync.

**Health at hand**

In addition to accessing and managing healthcare information from home, the rise of ubiquitous global mobile phone networks, fast- accelerating smartphone adoption, and open connectivity are moving a big part of online activity to mobile phones. An August/September 2012 Pew survey found that 31 percent of cell phone owners reported using their mobile phone to look for health or medical information online, up from 17 percent in September 2010. Smartphone owners led the way in this respect; 52 percent used their phone to search for health information versus 6 percent of other cell phone owners. In addition, a new wave of consumer-facing tools has potential to directly impact patients. Easy to distribute, cheap, and user-friendly, downloadable mobile health applica-
tions and wearable digital health devices are making their way into patients' lives. Health and wellness apps, carried from morning until night by many of the world's 1.1 million smartphone subscribers, stand to play a crucial role in changing patients from passive participants to active managers of their healthcare. The potential power of mobile apps as health and wellness tools has been embraced by both mobile phone developers and users alike. There are now more than 17,000 health and fitness apps and 14,000 medical apps in the iTunes store. The Google Play store boasts more than 15,000 health and fitness and 7,000 medical apps for Android-based devices. Apps addressing everything from access to medical records to blood glucose tracking are being downloaded faster than ever. In 2011, mobile health app developers doubled the number of health related apps in the market, generating an estimated $718 million worldwide according to Research2guidance. “In 2011, we saw the quality of the solutions has increased quite dramatically,” said Ralf-Gordon Jahns, Research2guidance. The rise of sensor-based applications capable of monitoring things like blood pressure, temperature, and blood glucose levels has raised the level of sophistication in the market, he said. The market’s model has also evolved. Once built mostly on paid downloads, it is now moving to consumer-purchased hardware paired with free apps or paid medical monitoring and analysis services, said Jahns [See Figure 3.3].

Despite growing recognition of the value provided by smartphone-based mobile health apps, don’t expect hospitals and insurers to pounce or to act any time soon. Patients remain motivated enough by the convenience of mobile health apps today that they’re willing to pay for products themselves. “How long that will last is hard to predict,” said Jahns. “One day or another, health insurers will see the benefits and then they will start paying for those solutions and then things will change. But that could take five years or more.”

Jahns is less optimistic about regulation of the mobile health applications industry. “I talk to quite a few players in the market and they tell me that regulators say, ‘You have to find out what is possible in the market and what is not,’” he said. “They’re not going to push having a framework of what’s allowed and what is not. They’ll do it case by case.”

During the next three years, Research2guidance expects that revenue from mHealth applications will continue to build strongly in the United States due largely to the sheer size and growth of the country’s smartphone market. But the unique character of non-Western markets may make them more like harbingers of the future of the mobile health market.

Africa’s sheer number of mobile devices and scarcity of fixed-internet connections are likely to drive innovative and life saving uses of mobile health applications. Already, African nations boast the highest percentage of mobile phone-based disease surveillance programs among those surveyed by the World Health Organization. Southeast Asia, where WHO found the highest proportion of member state initiatives geared to providing health information to mobile devices at the point-of-care, may also drive the creation of innovative mobile health apps. Jahns expects India could see tremendous growth in mobile phone apps because of its large population, strong IT industry, and limited number of doctors serving rural areas.

Despite high hopes, smartphone apps may provide limited impact, at least in their current form. A pair of reviews of the scientific literature evaluating the use of mobile health technology interventions published in January 2013 found modest benefits and a need for more high quality, adequately powered trials to evaluate outcomes. The two reviews, published in PLoS Medicine by authors from the London School of Hygiene Tropical Medicine and Imperial College, evaluated the impact of text messages and photos taken with mobile phones to improve diagnosis and health management outcomes.

Trials using mobile technology-based photos reported reductions in correct diagnoses when compared to “gold standard” care, the authors wrote—a finding aligned with a study disparaging the accuracy of smartphone applications for melanoma detection published in JAMA Dermatology. Text messaging was found to hold more promise, with studies included in the review showing that text-based interventions can increase adherence to antiretroviral regimens and smoking cessation plans while also improving communications between patients and medical providers. Medical appointment reminders sent by text message showed modest benefits too, the review found. Taken together, the reviews paint a picture of an active desire by public health and medical researchers across the globe to put mobile technologies to the test.

While the FDA has weighed in with a draft guidance suggesting how it might approach the emerging market for medical apps in the United States, nervous developers were still awaiting final guidance from the agency at the beginning of 2013. How the agency proceeds on app regulation will be important, both for U.S. and global app developers, since global regulators consider modeling their regulation of the space on the FDA’s framework.

In spite of such uncertainties, the tremendous benefits and convenience of access to health information, whenever and wherever it is needed, continue to drive the rollout of new health-oriented software and hardware.

“Acessing health information and care from mobile devices is quickly becoming a new norm for care,” said George Halvorson, the outgoing Kaiser CEO who led the company through the rollout of a $4 billion enterprise-wide electronic health record system. That system, the world’s largest, is accessible by smartphone with free Android and iPhone apps, giving nearly 9 million members anywhere, anytime access to their medical information from their mobile devices.

"Accessing health information and care from mobile devices is quickly becoming a new norm for care.”

George Halvorson Chairman and CEO, Kaiser Permanente

Seeing a bigger picture

All of this activity on smartphones, the internet, and intelligent monitoring devices is not only providing patients unprecedented ability to take control of their own health and wellness, it is also creating an enormous public health opportunity for anyone able to aggregate and analyze the collective activity. Consider the seemingly mundane activity of using a search engine, something many people do throughout the day.

The Google users sent millions of queries to the Internet search engine giant in the waning days of 2012 while killing time between spills, or feeling a little feverish. Each anonymized query, aggregated and analyzed, created a clear picture: The 2012-2013 flu season was growing worse in nearly every corner of the United States. The emerging pattern, painted by Google Flu Trends used the company’s search data to estimate flu activity in near real-time, highlighting the disease’s spread. While Google’s model eventually overestimated the severity of the U.S. flu outbreak in January 2013, it illustrates the potential value of big data collections, even as works in progress.

In every corner of healthcare, mountains of detailed data are being mined for new insights and information that can be used to improve the quality of care and make it more efficient. The proliferation of smartphones, ubiquitous connectivity, and low-cost monitors are converging to revolutionize the way healthcare is accessed and delivered. These tools, coupled with the infusion into the healthcare business of big data analytics, artificial intelligence, and Silicon Valley startup culture, are fueling the creation of a new breed of companies that are harnessing information and communication technologies to not only provide patients with a new kind of care, but also strike at fundamental drivers of...
“Studies have shown that people are more willing to share more private medical information in social media than they’re willing to share with their medical providers.”

Martin Kohn, Chief Medical Scientist at IBM

Despite the promise of data-driven advances in healthcare, many challenges remain. Simply obtaining massive quantities of detailed care and biometric data is only the first step toward understanding it. Integrating what is known about the best courses of care with health records remains daunting. And even when clinical information is successfully paired with payers’ records, the right path forward may not be clear. The incremental and sometimes backward development of digital health tools and health information technology makes plain how difficult it will be to impact population health trends, influence behavior, and assess the value of treatments. But the early evidence is in. A world of 1.1 billion smartphone subscribers and 2.4 billion global Internet users, interconnected and sharing more health and personal information than ever before, is providing an enormous resource of real-time health data waiting to be tapped.

Google, Facebook, and Twitter among others have sought to unlock the data captured through their websites. It is what Wired co-founder John Battelle coined “The Database of Intentions,” an aggregated collection of “desires, needs, wants, and likes that can be discovered, subpoenaed, archived, tracked, and exploited to all sorts of ends.” By analyzing search data, Google has been able to track not only the rise of the flu, but also discover peaks of interest in the dangers of norovirus, bird flu, and dengue. Facebook’s Open Graph, launched in January 2013, is giving people new ways to navigate their connections to people and shared interest groups while driving online and mobile app developers to encourage users to share more structured data to map out their online identities, including big life events, such as major illnesses. Facebook’s primary service focus is connecting people, but the byproduct of the conversations reviewed on this site is a rich portrait of individual tastes, habits, and movements that, when mined, can yield insights for advertisers and possibly health researchers. Describing the intimate connection people feel while on social networks, Martin Kohn, chief medical scientist at IBM, told the Financial Times that “studies have shown that people are more willing to share more private medical information in social media than they’re willing to share with their medical providers.”

Twitter, meanwhile, has seen tremendous growth in the number of health-related tweets on its global short messaging system. Tweets referencing personal health, health education, and health policy increased 51 percent between January and October 2012 according to the company, peaking with 13,000 tweets per minute during the Supreme Court’s announcement of its decision on the Patient Protection and Affordable Care Act in June 2012. Though Twitter hasn’t publicly released any health-related analyses of its data, computer scientist Mark Dredze and Michael Paul at Johns Hopkins University’s Department of Computer Science have already analyzed a collection of more than 11.7 million instances in which Twitter users posted tweets about their health, using it to generate a model that discovers meaningful descriptions of disease as well as information that can be used for health surveillance. Building on that work, Dredze has built a system using the microblogging network to track the spread of flu cases across the United States, separating out tweets that simply reference flu from those of people who actually became ill. The National Institutes of Health’s Models of Infectious Disease Agent Study, a group partly funding Dredze’s work, is supporting a number of other such efforts that adapt weather forecasting models to track the spread and dynamic ebb and flow of disease worldwide.

The bits of data logged with every search, Facebook “Like,” and tweet are creating new opportunities and are being used for such things as guiding pharmaceutical marketing campaigns. And the data individuals choose to share through specialty networks like the consumer genomics company 23andMe to learn more about their own ancestry and genetic health risks, can help lead to new understandings of diseases and inform the creation of intellectual property, such as 23andMe’s patent for polymorphisms associated with Parkinson’s disease.

Though drug and device makers have been cautious in their approach to embracing social networks due to regulatory concerns, they are making the shift from focusing on products alone to spotlighting measures of the value those products produce as reflected in electronic health records and economic benefits. “One could argue that manufacturing a pill is difficult, but it is not what differentiates an innovative pharmaceutical company,” wrote Craig Lipsit, Pfizer’s Head of Clinical Innovation in July 2012. “We generate data—data on the efficacy, safety, and quality of new and existing medicines. We analyze that data. And we communicate that data to many stakeholders and partners—regulators, payers, physicians, researchers, and patients.” As that happens, he said, “we are focusing a great deal of R&D resources on precision medicine and the ability to best target a medicine for the right patient. Our success in discovering this future hinges on our ability to use data to generate unprecedented scientific insights.”

Decoding big data

Despite the World Economic Forum’s 2012 annual meeting focus on decoding meaning from the deluge of data, big data remains a fuzzy concept for many people. Big data, as the consultancy IDC describes it, is a new generation of technologies and software architectures, designed to “economically extract value from very large volumes of a wide variety of data by enabling high-velocity capture, discovery, and/or analysis.”

We explore the particulars of big data storage, collection, and analysis bog down quickly in a
Extending Doctors’ Reach

Telehealth provides digital access to healthcare services

From connecting patients in rural areas to medical experts far away to extending the boundary of the doctor’s office into retail outlets for the sake of convenience, telemedicine is playing an important role in the future of healthcare.

In Billings, Montana, for instance, a telemedicine program at St. Vincent Healthcare saves some pediatric patients with head injuries a trip to Denver, where the nearest pediatric neurosurgeons are based. Instead, the children receive a computerized tomography scan in Billings and a trip to the nearest clinic. For a routine check-up in the past year, have cholesterol screening in the past five years, and visit a dentist in the past year, often because they either can’t afford it or they can’t spend the time to travel to the nearest clinic.

The Department of Veterans Affairs, already a trailblazer in the deployment of health information technology, is also betting on telehealth, a tool it believes will help it improve access to care for America’s 22 million veterans. In May 2011, the department awarded contracts totaling almost $1.4 billion to six information technology companies to run its growing telemedicine program, already one of the largest in the world.

Meanwhile, telehealth kiosks, such as HealthSpot’s Care4 Station, created by Cleveland-based Nottingham Spirk, are being rolled out across the country. The walk-in HealthSpot kiosk remotely captures height and weight and blood pressure measurements and will be in place in 1,000 locations in 2013 to provide acute care patients live access to doctors via high-definition videoconferencing. Doctors can remotely unlock digital medical equipment as needed, and when a patient’s visit is done, the booth is wiped down and automatically disinfected.

An expansion of the type of preventive health services that easy-access kiosks could help address is the rising threat of chronic disease in the United States, especially for U.S. adults. Those living in large-population areas are far less likely than residents outside those areas to utilize selected preventive health services. Residents outside large population areas were less likely to see a doctor for a routine check-up in the past year, have cholesterol screening in the past five years, and visit the dentist in the past year, often because they either can’t afford it or they can’t spend the time to travel to the nearest clinic.

As pressures mount to ensure U.S. citizens and populations across the globe receive adequate care, telehealth will play a key role in extending the reach of skilled healthcare providers.

Each day, individuals are contributing to the world’s rich but unstructured data stream with 2.9 billion Google searches, 7.8 years of video uploaded to YouTube, and 986 million items shared on Facebook. To make meaning from the din of new data points will take effort, not to mention, new spending.

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<tr>
<th>Preventive Service Use</th>
<th>Metropolitan Statistical Area in 2009</th>
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<tbody>
<tr>
<td>Wellness visit (past year)</td>
<td>81%</td>
</tr>
<tr>
<td>Cholesterol screening (past 5 years)</td>
<td>65%</td>
</tr>
<tr>
<td>Dental visit (past year)</td>
<td>35%</td>
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Source: Agency for Healthcare and Quality
As healthcare systems around the world digitize medical records at an increasing pace, a small but important commonality is showing up in many of the most successful systems, according to a Commonwealth Fund review: unique identifiers that can be used to bridge otherwise disconnected records.

In Singapore, for instance, a 35-year-old housewife suffering from a drug overdose was saved when, armed with her name and national identity card number, a doctor discovered that she had just been discharged from another hospital and so was able to identify the drugs she had taken.

In New Zealand, a nation with the world’s highest rate of information technology use among primary care physicians, every person has a national health index number. Integrated and shared care plans coordinating the efforts of multiple health professionals there succeed in part because providers can access shared records keyed to that number.

In Denmark, top-ranked in Europe for its use of health information technology, uses unique personal IDs to unify patient records but goes a step further. Its national health information systems are dual-use, providing patients with general health information and personal medical records while also hosting medical handbooks, scientific articles, and treatment guidelines for use by medical professionals.

Acceptance and development of medical records systems and accompanying health information technology systems has been more halting in other countries. In Germany, national strategies to create unified electronic medical record systems have met opposition. Germany’s electronic medical record system is a patchwork of incompatible services, according to the Commonwealth Fund’s review. Concerns about data safety and privacy have held back the adoption of a unique medical identifier.

In the United Kingdom, where every patient registered with the National Health Service has an NHS number, hospital and general practice records have not been integrated. Following a failed attempt to create patient records covering all services, the government is currently moving ahead with a more limited Summary Care Record that will store data on patients’ current medication, adverse reactions, and allergies.

The story is murkier in Switzerland, where hospitals vary greatly in the degree to which they have merged their internal clinic systems with an interoperable national patient record. Such integrations are not a priority for the national coordinator, eHealth Suisse, given the national emphasis on decentralization, privacy, and data protection.

In the end, government and institutional efforts to develop electronic health record systems will be crucial if technology is to make any dent in managing healthcare costs. As illustrated by the Commonwealth Fund’s review, securing national buy-in for unique IDs will be critical to tying together records that are not currently connected to create more complete pictures of patient health. Whether patients will put their trust in such systems remains to be seen.

As stores of biological data across the globe have grown, so too has the collaborative spirit initiatives to derive new insights. In January 2013, for instance, health insurance giant UnitedHealthGroup joined forces with Mayo Clinic to form Optum Labs, an open, collaborative research and development program with the goal of improving patient care. Working together in Cambridge, Massachusetts, the companies will comb through their combined and extensive troves of patient clinical records and health claims data to help create the most effective approaches to care. By leveraging what they believe to be the largest combined source of clinical and claims information, the companies plan to provide a comprehensive picture of patients’ diagnoses, progression of diseases, comparative treatments, and outcomes.

By working with academic institutions, life sciences companies, commercial and government payers, and other care providers, Optum Labs expects to be able to determine the best treatments for conditions in any given setting; better understand variations in care; and to examine the effectiveness of patient care programs and approaches. The group will work on projects, such as measuring the treatments for the blood cancer chronic myelogenous leukemia, developing applications that measure the relative cost effectiveness of medical devices, and analyzing how to improve the diagnosis of hepatitis C.

“Every patient is different; every patient has a unique story,” said Steven Shapiro, chief medical and scientific officer at the University of Pittsburgh Medical Center. In October 2012, UPMC launched a five-year, $100 million investment together with Oracle, IBM, Informatica and dbMotion, to create a comprehensive data warehouse that brings together clinical, financial, administrative, genomic and other information that today is difficult to integrate and analyze. The partners believe that advanced analytic and predictive modeling applications for clinical and financial decision-making will produce better patient outcomes, enhance research capabilities, and contribute to continual improvements in care while simultaneously reducing costs. With the rapidly decreasing cost of genetic sequencing, UPMC expects huge amounts of genomic information will be added to its database in the future.

In order to make the data useful, UPMC and its technology partners over the next two years will install the hardware and software needed to create a comprehensive data warehouse that will bring together more than 200 sources of information across UPMC, UPMC Health Plan, and outside entities, including labs and pharmacies. Clinicians, researchers, and administrators will have secure, real-time access to data and analytic tools that fit their particular interests and needs.

Early analytics projects are expected to improve quality reporting and measurement across UPMC hospitals and physician offices; provide insight into the effectiveness of treatments and cost variations in care; and offer predictive alerts that will improve disease prevention.

UPMC is just one of many institutions that have embarked on genomic medicine programs as time and technology improvements have eroded the costs of genotyping, and the whole genome and whole exome sequencing. But despite the progress made within such programs, parallel efforts by disconnected institutions are encountering infrastructure problems. Sometimes, they are even developing the same solutions, often independently, according to a review published in the journal Genetics in Medicine.

Groups sharing their experiences developing genomic medicine projects with the National Human Genome Research Institute described numerous difficulties. “Every project was different; every project was a unique story,” said Teri Manolio, director of NHGRI’s Division of Genomic Medicine.

More structured collaboration and sharing approaches are needed, participants in NHGRI’s Genomic Medicine Colloquium found, as well as the establishment of common infrastructure, such as a catalog of genetic variants observed across large numbers of sequenced patients, an updatable database of actionable variants, and evidentiary standards tailored to benefits and risks.

As stores of biological data across the globe have grown, so too has the collaborative spirit...
among public and private enterprises exploring it for new insights. New government initiatives in the United States and abroad have prioritized funding, set goals, and aligned policies in pursuit of big data payoffs. In March 2012, the Obama Administration announced its Big Data Research and Development Initiative to improve the nation’s ability to extract knowledge and insights from large and complex collections of digital data. By October 2012, two agencies involved in the program, the National Science Foundation and NIH had provided nearly $15 million to support new big data fundamental research projects.

“To get the most value from the massive biological data sets we are now able to collect, we need better ways of managing and analyzing the information they contain,” said NIH Director Francis Collins. “The new awards that NIH is funding will help address these technological challenges—and ultimately help accelerate research to improve health—by developing methods for extracting important, biomedically relevant information from large amounts of complex data.”

Billions of dollars are being invested with the hope of transforming healthcare. The goal is to create an ideal system in which individual health profiles and histories inform individualized approaches to treatment—addressing Wanamaker’s dilemma by making clear the “half” of our health spending that’s wasted. Despite the successes achieved through the collection and analysis of massive new amounts of clinical data, the results of broader healthcare information technology adoption in the United States have been mixed. The rapid adoption of health information technology, estimated in 2005 by RAND Corporation researchers to hold promise to trim $81 billion from annual healthcare savings, has instead contributed to the United States’ healthcare expenditure, which rose nearly $800 billion between 2005 and 2012. Furthermore, suggests a new RAND assessment, published in the journal Health Affairs in January 2013, although the use of health information technology has seen a significant increase, the quality and efficiency of patient care are only marginally better.

The shortfall can be largely attributed to several factors, according to RAND’s Arthur Kellermann and Spencer Jones. These include slower than anticipated adoption of healthcare information technology systems, the adoption of systems that are neither interoperable nor easy to use, and a failure by healthcare providers to reengineer care processes to gain the full benefits health information technology can provide. In the end, they write, the necessary “revamping of healthcare delivery is unlikely to happen before payment models are realigned to favor value over volume” [see Figure 3.4].

To the original RAND team’s credit, its projections were based on the assumption that the shortcomings holding back real cost-savings progress would be addressed. Instead, even as modern health records have become increasingly sophisticated, especially in large integrated health delivery systems, such as the Department of Veterans Affairs and Kaiser Permanente, progress within those systems hides a problem that can arise when patients seek care outside the system, said RAND’s Kellermann and Jones. Instead of allowing patients to access needed health information anywhere and at any time like automated teller machines, current systems function more like frequent flier programs, they note, reinforcing brand loyalty. Kaiser members, for instance, can go online to view lab results and diagnos-
Digital health is already transforming healthcare. It is providing patients with tools to take greater control over their own health and wellness. It is providing a means to attack costs in the system by improving compliance, by providing real-time and real-world insights into the status of their health, and by helping patients modify unhealthy behaviors. But the proliferation of health gadgets and apps, often with unproven benefits, obscures the transformation being brought about by the digitization of healthcare.

By taking advantage of the existing communications and computing technology, digital health is creating new means of access of delivery of care, moving the patient to the center of the healthcare world, and providing more personalized, preventive, and cost effective care. Though the smartphone is becoming a versatile tool connecting patient to provider and health data to both, it is information that lies at the heart of digital health.

The power and promise of digital health lies beyond hand-held devices on the front lines of healthcare. The ultimate benefit will only be realized by capturing, aggregating, and analyzing the rich data already available in the system and integrating it with new data, such as genomic, proteomic, and other biological data. Incorporating this with real-time changes in the biological states of patients could bring about custom-tailored healthcare based not on trial and error, but on new understandings of risk, early warnings of disease, and targeted interventions delivered when their impacts are greatest.

**Figure 3.5** ADOPTION OF EMR/EHR SYSTEMS BY OFFICE-BASED PHYSICIANS

<table>
<thead>
<tr>
<th>Year</th>
<th>Any EMR/EHR system</th>
<th>Basic system</th>
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<tbody>
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<tr>
<td>2006</td>
<td>70</td>
<td>60</td>
</tr>
<tr>
<td>2007</td>
<td>80</td>
<td>70</td>
</tr>
</tbody>
</table>

Source: National Center for Health Statistics, Centers for Disease Control and Prevention
At the heart of the Affordable Care Act is an ambitious and seemingly contradictory goal of expanding and improving care while cutting costs. The challenge is not unique to the United States. Healthcare systems around the world are struggling with the need to provide more for less and experimenting with ways to accomplish that, including value-based approaches that tie payments to outcomes, focusing on preventive care, and requiring proof that new products provide economic as well as health benefits. The hope is that by increasing efficiency, aligning incentives, and cutting waste, healthcare systems will be able to reverse long-term trends of rising costs, and if not cut spending, at least bring growth in spending under control to manageable levels.
CHAPTER 4:

Demanding Value

Healthcare moves from paying for procedures to paying for outcomes

On July 11, 2012, Republicans in the House of Representatives voted to repeal the Patient Protection and Affordable Care Act, the Obama Administration’s landmark healthcare reform legislation. It was the 33rd time that House Republicans voted to repeal the legislation since its passage in 2010 and this time they were joined by five Democrats. The vote came two weeks after the U.S. Supreme Court delivered a 5-4 decision to uphold virtually all portions of the law including the controversial individual mandate, which requires most citizens to have health insurance or face financial penalties. Though Chief Justice John Roberts rejected the administration’s argument that the individual mandate was within Congress’ constitutional authority to regulate interstate commerce, he voted with the court’s more liberal members to uphold the law based on it being within Congress’ constitutional authority to levy taxes.

Following a divisive presidential campaign in which Republican challenger Mitt Romney vowed to repeal the signature legislation on his first day in office if elected, President Obama’s re-election appeared to end the fights over repeal and bring most opponents to a grudging acceptance. After the election, House Speaker John Boehner, the de facto leader of the Republican Party, sat down to an interview with NBC’s Diane Sawyer in which she asked if Republicans can Party, sat down to an interview with NBC’s Diane Sawyer in which she asked if Republicans would continue efforts to repeal the legislation. “Obamacare is the law of the land,” he said. “I think there are parts of the healthcare law that are going be very difficult to implement. And very expensive. And at the time when we’re trying to find a way to create a path toward a balanced budget everything has to be on the table.”

The U.S. Supreme Court in November 2012 did order the 4th Circuit Court of Appeals to hear a challenge to the Affordable Care Act’s employer mandate, which requires companies with more than 50 employees to provide health insurance coverage to their workers. The challenge, filed by Liberty University, a Lynchburg, Virgina-based Christian college, argues that the requirement that employers provide coverage of contraceptives without requiring a co-payment makes the provision unconstitutional because it would violate the right to free exercise of religion, since it would force an employer to pay for birth control and abortions. The 4th Circuit is expected to hear the case in the spring of 2013. But while challenges may arise, the reality is that, as Speaker of the House John Boehner acknowledged, the Affordable Care Act is the law of the land. With the presidential election over, the shift from a fight about whether the law would stand has now moved to one about the details of its implementation, as well as addressing problems in America’s healthcare system not addressed by the Affordable Care Act. “To preserve and strengthen our nation’s economy, it is imperative that we take action now to create a new healthcare model for America,” said John Noseworthy, president and CEO of Mayo Clinic. “The current model is unsustainable. Care for patients is fragmented, reimbursement inequitable and imprecise.”
As implementation efforts accelerate, the initial focus has been on the creation of insurance exchanges and marketplaces for consumers and small businesses to access qualified health insurance programs. But other issues likely to take center stage in 2013 will focus on efforts to repeal or reform certain parts of the legislation. Top on that list for the biopharmaceutical and medical device industries are the establishment of the Independent Payment Advisory Board, an appointed 15-person body that has been given broad authority to reduce Medicare spending by $4 billion a year. The industry calls the level of cuts “arbitrary” and believes the board usurps the authority of Congress.

Industry has been concerned about the ability of the board to enact sweeping changes to Medicare with little check on its authority. The board can only be overruled by a supermajority of Congress. The industry believes it can win bipartisan support to repeal this part of healthcare reform. “In the end, what the drugmakers got may be precisely what they were bargaining against,” writes Gottlieb. “Sure, Medicaid pricing was kept out of the Part D benefit. But included in the new health reform was a provision that would allow the Medicare program to import this pricing by regulatory fiat—without the direction of Congress.” He argues such steps would hurt innovation by making investment in new therapies less attractive to investors and send capital elsewhere.

The medical device industry also has its sights focused on an excise tax on medical devices passed as part of the Affordable Care Act. The law, which took effect at the start of 2013, imposes a 2.3 percent tax on sales for medical device makers. The trade association AdvaMed said it sees bipartisan support for repealing the tax. Even though the tax was included in the Affordable Care Act, the $20 billion expected to be generated by it over 10 years goes to the general fund and does not specifically fund health care. Legislation to repeal the tax in 2012 passed in the House, but failed in the Senate. Obama threatened to veto it, but new faces in the Senate offered some encouragement that there is stronger support for the industry on the Democratic side of the aisle. However, it is unlikely that the industry will win an outright repeal of the tax. Instead, its best hope is to get a modification of the measure, which it says hurts young entrepreneurial companies that are not yet profitable and could have the effect of stifling innovation and dissuading investors from backing device companies.

At the heart of the Affordable Care Act is an ambitious and seemingly contradictory goal of expanding and improving care while cutting costs, a goal not unique to the United States. Healthcare systems around the world are struggling with the need to provide better and expanded care for less money than they currently spend and are experimenting with ways to accomplish that, including value-based approaches that tie payments to outcomes, focusing on preventive care, and requiring proof that new products provide economic as well as health benefits. The hope is that by increasing efficiency, aligning incentives, and cutting waste, healthcare systems will be able to reverse long-term trends of rising costs, and if not cut spending, at least slow growth in spending to a manageable rate [See Figures 4.1-4.3]. In the absence of achieving that through carrots, governments will likely wield sticks to impose price controls, shift a greater portion of costs to individuals, and ration care. “As far as I can see into the future, Congress is going to try to figure out how to make programs sustainable, and the natural first impulse is to just reduce reimbursement rates,” says Jim Greenwood, CEO of the trade group the Biotechnology Industry Organization. “It’s our job to explain why that is pennywise and pound foolish.”

Pressures on healthcare

In 2004, Ontario Premier Dalton McGuinty warned that “the baby boom is about to become...
a patient boom.” Around the world there are related trends that are driving costs and putting increasing pressure on healthcare systems [See Figures 4.4–4.7]. This includes aging populations, rising standards of living that are extending life expectancy, and increasing demands for healthcare services. While improved standards of living have brought lifestyle changes throughout the world, those changes have also fueled a growing incidence of chronic diseases that is taxing healthcare systems in both the developed and developing world.

Along with a welcome increase in longevity [See Figure 4.8], growing prosperity has also been accompanied by declining birth rates in many countries. The phenomena will add to the pressure on healthcare systems as the percent of the population over the age of 65—the largest consumers of medical services—grows. The problem is that as the population ages and people live longer, there are fewer people of working age to pay into government supported systems paying to support healthcare services. These shifting demographics spell potential financial problems for governments that will have to struggle with growing demand for healthcare services among the aged and a shrinking percentage of the population actually paying to support healthcare services.

The percent of the global population over the age of 65 rose to 8 percent in January 2011, up from 5.9 percent in 1980, according to Euro-monitor International. Growth in this segment is expected to rise an average of 3.1 percent through 2020, when it will reach 9.6 percent of the world population. Japan leads the world in having the largest portion of its population over 65, at 23.3 percent, with the other nine of the top ten nations with the largest percent of their population over 65 all in Europe, including Monaco (22.6 percent), Germany (20.6 percent), Italy (20.3 percent), and Greece (19 percent) [See Figure 4.10]. Western Europe represents the part of the world with the oldest population, with 16.5 percent of its inhabitants aged over 65 [See Figure 4.9]. That compares to just 3.2 percent of the population of sub-Saharan Africa. In the context of Europe’s debt crisis, these demographic pressures represent a growing financial burden. Overall, the old-age dependency ratio—the ratio of people over 65 relative to the working age population (15-64)—rose globally to 12 percent in 2010 from 10 percent in 1980, Euro-monitor International says.

Aging alone is not driving the rise in healthcare spending—a 2007 Health Affairs study found aging of the population accounted for just a 0.5 percent increase in total healthcare spending among OECD countries out of a 3.7 percent increase—but healthcare spending over an individual’s lifetime tends to be concentrated on end-of-life care. Diseases of aging are among the costliest and most intractable diseases faced. These include heart disease, stroke, cancer, neurological diseases, pulmonary diseases, and diabetes. Though estimates vary, the cost of treating chronic diseases is associated with about 75 percent of total healthcare spending in the United States. Healthcare spending in the United States is concentrated. In 2009, just 1 percent of the population accounted for about 20 percent of healthcare expenditures with an annual mean cost of a little more than $90,000, according to The Agency for Healthcare Quality. A total of 5 percent of the population accounted for nearly half of all healthcare expenditures that year. Not surprisingly, the elderly make up a disproportionate share of that concentration of healthcare spending.

![Figure 4.6](image1.png) ![Figure 4.7](image2.png)
While elderly people, defined as those 65 and older, represent a little more than 13 percent of the population, they account for nearly 43 percent of the top decile of healthcare spenders. Aging populations and the diseases they face are a growing source of pressure on healthcare systems around the world. While policymakers across the globe have sought ways to restrict spending, others are turning to innovative approaches that can keep people healthy and allow them to live independently. Changing approaches to care can improve the quality of life while helping control the demands the elderly put on the healthcare system. There’s also hope that scientific breakthroughs in treatments can address the ravages caused by diseases of aging, and if not reverse the aging process, at least slow and halt the damage that we’ve come to view as part of it.

“Reforming the healthcare financing system is an essential part of dealing with an aging population.”

Julio Frenk, Dean of Harvard School of Public Health; former health minister of Mexico

A United Nations report on aging populations that looked at the period from 1950 to 2050 called population aging trends now underway “unprecedented” and “without parallel in the history of humanity.” The United Nations forecasts that the percent of the world population that is over the age of 60 will grow to 21 percent by 2050, up from 10 percent in 2000 [See Figure 4.12]. The trend is happening in concert with a decline in the percent of people under the age of 15. By 2050, the United Nations said for the first time in human history, the number of older people in the world will exceed the number of younger people. In fact, this turn of events, it said, is already being seen in many developed countries today.

Though the impacts of these changes are being felt around the world, they pose particular challenges in lower- and middle-income countries as they not only have to face the financial pressures of caring for an aging populous, but must face the additional difficulties of doing so with a healthcare system that may be both inadequate and built to combat a different set of health problems, as Harvard School of Public Health Dean and former health minister of Mexico Julio Frenk said to the Economist Intelligence Unit in 2009 in discussing his homeland. He noted that previous health programs concentrated on addressing diseases that were widespread, but relatively inexpensive to treat. But with increasing longevity has come changing demands on the healthcare system. “You cannot deal with chronic diseases like cardiovascular disease and diabetes, thinking that you can continue to spend the same level of resources as for acute diarrhoea or other easily preventable childhood conditions,” he told the Economist. “Reforming the healthcare financing system is an essential part of dealing with an aging population.”

![Figure 4.8](image-url) **INCREASE IN YEARS OF LIFE EXPECTANCY BY COUNTRY FROM 1960 TO 2010**

Source: OECD Health Data 2012
A shifting disease burden

A September 2011 report from The World Bank, *The Growing Danger of Non-Communicable Diseases*, noted that heart disease, cancer, diabetes, chronic respiratory conditions, and other non-communicable diseases are growing problems in many lower- and middle-income economies. These countries have to confront higher levels of these diseases at “earlier stages of economic development, with fewer resources, and with less time to respond effectively” than their higher-income counterparts.

The World Bank warns that in Eastern Europe and Central and East Asia, the level of non-communicable diseases is above those in high-income countries. In 2010 in China, 580 million people had a least one modifiable risk factor for a non-communicable disease. In Sub-Saharan Africa, non-communicable diseases are expected to account for 46 percent of all deaths by 2030, up from 28 percent in 2008. During that same time period, South Asia will see deaths from non-communicable diseases rise to 72 percent from 51 percent. Nearly a third of those deaths will be premature and preventable, “The World Bank says [See Figure 4.11].”

“Attempts to ‘treat their way out’ of the NCD challenge will be too costly for most middle- and lower-income countries, and such a strategy would, in any event, constitute an inefficient use of resources,” says the report. Instead, it argues prevention programs have the potential to generate meaningful results as it notes a long list of modifiable risks including physical inactivity, unhealthy diet, tobacco use, alcohol, and exposure to environmental pollution.”


“A healthcare system in transition

The problem with non-communicable diseases is particularly acute in the Russian Federation, which, at 68.7 years in 2009, has among the lowest life expectancy rates of countries tracked by the OECD. It was the only country tracked by the organization to see no increase in life expectancy between 1960 and 2009. In fact, the OECD noted that premature death rates in the Russian Federation are more than four times the OECD average for males and three times the OECD average for females.

The healthcare system in Russia is undergoing a transformation from its historical state-run, state-funded, and centralized system where care was provided for free to a more market-based system in which employers are required to pay for workers health insurance. A 2010 Rand Corporation analysis found a crisis in healthcare continued in the Russian Federation. “Despite the large number of hospitals and a huge army of medical doctors, they [have] been unable to provide people with an acceptable level of healthcare services,” wrote Boris Rotenfeld, of the Institute for Economic Forecasting at the Russian Academy of Sciences.

“This is mainly due to a continued lack of funds, medical and technical equipment and supplies, and, finally, to the ineffective organization of healthcare delivery services. As a result, the quality of services and their accessibility remains quite low.”

In an effort to address the nation’s health problems, Russian President Vladimir Putin in May 2012 signed an executive order calling for strengthening healthcare policy with the goal of improving the health and longevity of its citizens. Among other things, the order instructed the government to ensure that the rate of deaths due to cardiovascular disease, cancer, tuberculosis, and road accidents, as well as infant mortality, decrease by 2018. The order also called for increasing domestic production of pharmaceuticals to ensure that 90 percent of the drugs on the nation’s list of strategically significant medicines and the list of vital and highly important pharmaceuticals are produced in Russia. In addition, the order calls for the creation of a strategy for developing medical science in the Russian Federation through 2025. And, it called for the establishment of measures to train healthcare professionals and modernize the Russian Federation’s drug service by the start of 2016.

In an acknowledgement of the role lifestyle Figure 4.11

Deaths from NCDs as a share of total deaths 2008 to 2030 (projected)

<table>
<thead>
<tr>
<th>Region</th>
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<th>2030</th>
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<td>All Ages, Percent</td>
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<tr>
<td>High-income countries</td>
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<tr>
<td>Europe and Central Asia</td>
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<td>81%</td>
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<tr>
<td>East Asia and Pacific</td>
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<tr>
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Sources: The World Bank, World Health Organization

Figure 4.12

Over-60 Population Growth Unprecedented

Proportion of world population 60 years old or over

<table>
<thead>
<tr>
<th>Year</th>
<th>Proportion</th>
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<tbody>
<tr>
<td>1950</td>
<td>8%</td>
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<tr>
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Source: United Nations

A healthcare system in transition

The problem with non-communicable diseases could be prevented through interventions that address such risk factors as physical inactivity, unhealthy diet, tobacco use, alcohol, and exposure to environmental pollution.”


“More than half of the burden from non-communicable diseases could be prevented through interventions that address such risk factors as physical inactivity, unhealthy diet, tobacco use, alcohol, and exposure to environmental pollution.”


“A healthcare system in transition

The problem with non-communicable diseases could be prevented through "a few key health promotion and disease prevention interventions that address such risk factors.”

In many cases, this involves actions taken outside of the healthcare system itself. For instance, in India the National Biomass Cookstoves Initiative has been working to avoid 570,000 premature deaths in women and children a year that result from cookstoves in Indian homes using biomass and coal that produce high levels of pollutants. Officials in Bogota, Columbia have built bike paths across the city and initiated an exercise program for bike riders and walkers that attracts 1 million people a week. Even in the developed world, policies are being instituted to address the costly problem of dealing with these diseases. For instance, in 2012, New York City, which previously banned smoking in bars and restaurants, prohibited the use of trans fats, forced fast food restaurants to disclose calorie counts of food on their menus, and added to its list of prohibitions a new law that restricts the sale of soda and other sugary drinks in larger than 16-ounce containers at restaurants and snack bars.

A healthcare system in transition

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In an acknowledgement of the role lifestyle

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Source: United Nations
plays in Russia’s healthcare problems, the executive order also called for the implementation of measures aimed at getting Russians to adopt healthy lifestyles. The OECD noted that premature death rates in the Russian Federation are more than four times the OECD average for males and three times the OECD average for females.

As part of these efforts, Prime Minister Dmitry Medvedev in October 2012 backed legislation intended to curb smoking in the Russian Federation. Smoking is a major public health concern in a nation that suffers more than 400,000 smoking-related deaths each year. Speaking on a video blog, Medvedev said one in three Russians is a smoker. “The government is not at war with smokers,” he said. “But we are making a stand against smoking.” Russia is second only to China in its use of tobacco. The proposed legislation, which would take effect in 2013, would ban public smoking including in restaurants, cafes, and stores. It would restrict advertising of cigarettes, the places where cigarettes can be purchased, and discourage smoking by taxing cigarettes heavily.

**An emerging opportunity**

Changing demographics, rising economies, and efforts to reform healthcare systems are creating opportunities for life sciences companies around the world. The most dramatic example of this is in China, where healthcare spending is expected to grow to $1 trillion a year by 2020, up from $357 billion in 2011, according to McKinsey & Company. The consulting firm notes that 13 of the world’s top 20 pharmaceutical companies since 2006 have announced plans to open R&D centers in China. As companies have downsized their salesforces in the United States and Europe, China is becoming a more attractive market for drugmakers.

The average urban worker in China earned about $7,000 in 2011. Public health insurance doesn’t cover pricey outpatient drugs.

The report said Roche and Swiss Re are considering expanding the program to other parts of Asia. “We’re creating a market,” Roche CEO Severin Schwan told Bloomberg. “The biggest hurdle in emerging countries is access.”

**Roche Seeks Private Insurance for Chinese Market**

Drugmaker in alliance with insurer to keep expensive drugs accessible

Developers of a new generation of cancer therapies are eyeing potentially large growth markets in emerging economies, such as China, but are stymied by the reality that the high cost of their drugs put them out of reach of many people who might benefit from them. In a novel approach to addressing the problem, Roche is collaborating with the reinsurer Swiss Re to offer private insurance in China that would provide access to its cancer drugs, Bloomberg reported. Though China’s robust economy has fueled a rapidly expanding middle class, wages remain relatively low. The insurance policies are being offered starting at $50 a year and extend up to several thousand dollars a year depending on the extent of the coverage, according to the report. The average urban worker in China earned just less than $7,000 in 2011. Public health insurance in China covers about 70 percent of hospital costs, but doesn’t cover the use of the pricey outpatient drugs Roche provides.

And Roche’s cancer therapies are expensive. A year-long course of Herceptin can cost nearly $60,000 while a course of Avastin can cost more than $100,000. Bloomberg said Roche wouldn’t comment on pricing of its products in China, but said prices are comparable to what it charges in the United States.

The Roche policy serves as supplemental coverage and the move by Roche points to a new reality for drugmakers. They are attracted to emerging markets such as China because of its rapid growth and expanding middle class, but stymied by health systems that won’t pay for their drugs and populations that can’t afford them. As biopharmaceutical companies seek to embrace new models to capture the value they create, Roche’s approach is unique.

The Roche policy was also seen as a way to keep a big drugmaker in the market as the country, it is also seeking to contain costs. But all of this growth comes with a note of caution for companies viewing emerging markets as opportunities. As China pursues an ambitious agenda to transform healthcare, modernize facilities, and extend care to everyone in the country, it is also seeking to contain costs. China has expanded its list of essential drugs to be another 142 million people from the countryside to cities, and the growing incidence of chronic disease. Already there are 92 million people with diabetes in China and another 150 million people with pre-diabetic conditions, according to a 2010 report in the *New England Journal of Medicine*. And, 85 percent of deaths in China today are caused by chronic diseases, according to China’s Ministry of Health. But also driving companies interest in doing business in China is the country’s commitment to invest in healthcare and build its life sciences sector. As a result of government reforms, more than 95 percent of the population now has some form of health insurance and China’s goal is to establish universal healthcare for basic services by 2020. The country’s 12th Five Year Plan identifies the life sciences as one of seven strategic industries.

**Controlling costs**

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include 700 from a little more than 300. Drugs on the list are deemed critical to the health of the population, are procured by the government, and are subject to price controls.

India’s drug price regulators initiated efforts to expand their drug pricing controls to include retail pricing of imported drugs. The policy expands the number of so-called essential drugs subject to price controls in India to 348 from 74. The rules capped the price of drugs on the list to the average price of all drugs in the same category of medicines that have at least 1 percent market share. The previous pricing mechanism was tied to the manufacturing costs of a drug and a maximum profit allowance. The Times of India reports the nation has the highest share of out-of-pocket spending on healthcare at around 75 percent. Some 80 percent of that out-of-pocket spending goes for drugs. In addition to price controls, India controls costs by using its power to order compulsory licenses to address the high cost of novel cancer drugs.

Efforts to rein in the rising cost of drugs are taking place in developed economies as well. [See Figure 4.13 and 4.14]. In these countries, while there have been policies put in place to drive use of generic drugs, there has also been a move toward controlling the cost through a case-by-case review process when new drugs are introduced into the market. Germany’s AMNOG, which took effect in 2011, put into place a new system that requires pharmaceutical companies to introduce new drugs into the German market to demonstrate their value by comparing them to existing drugs on the market against which they will compete. The law is expected to save the German government at least $2.7 billion a year on drugs. The industry, which expressed concerns about the legislation’s harm to innovation prior to its enactment, has continued to criticize it after its implementation. In June 2012, the European Federation of Pharmaceutical Industries and Associations called on the German government to make changes to the legislation it characterized as “flawed” and “inflexible” as it warned it was jeopardizing Germans’ access to new medicines and the nation’s status as a “home for pharmaceutical innovation.”

Among the organization’s chief complaints is the choice of comparator drugs used by the Institute for Quality and Efficiency in Health Care, the German agency that performs the AMNOG analysis. The industry says comparators often differ from the ones chosen for the development program after consultation with the European Medicines Agency and that the selection of comparators is being used by the agency to push prices of new medications in Germany towards prices of generic drugs. “Forcing the price of innovative medicines that deliver clinical benefit to match that of much older products will undermine incentives to life-changing medical discovery,” the trade groups says. Instead, the industry argues that price comparisons should be made between new products and patented products and wants more consultation and discussion about the selection.

“We have found the set-up very rigid. Unfortunately, many of my member companies have been forced to announce that several new medicines will not be made available in Germany, because the model seeks to base the price for new medicines on what is paid for much older, generic medicines,” says Richard Bergström, director general of the European Federation of Pharmaceutical Industries and Associations.

India Imposes Compulsory Licensing

India’s Patent Office ruled in March 2012 that Bayer must license the intellectual property behind its kidney and liver cancer drug Nexavar to Natco Pharma, which will make an inexpensive generic version of the drug for the Indian market. The compulsory license was the first to be issued on a patented drug in India.

In issuing the ruling, India joined Thailand and Brazil as part of the small group of nations that have enacted compulsory licensing on drugs for public health reasons. The action by India raised the possibility that governments in other developing nations may begin to override other patents for costly but life-saving therapies they deem essential to national health. Such a trend could, though, could undercut the value of emerging markets for drugmakers even as they look to the same markets for growth.

“The drug is exorbitantly priced and out of reach of most of the people,” said India’s controller general of patents, designs, and trademarks in the ruling, which relied on provisions in multilateral international trade agreements to support its conclusions.

Natco said it was pleased with the ruling, which will allow it to sell the drug for no more than about $176 per month instead of the much higher price Bayer has charged in India, reported to be approximately $5,500 per month. Under the terms of the license, Natco will pay Bayer a mandatory royalty of 6 percent of its net sales of the drug each quarter and, like Bayer, will supply the drug free of cost to patients unable to afford it. It will, for now, be the only Indian company licensed to produce generic Nexavar, and will retain its license until Bayer’s Indian patent on the drug expires in 2021. Bayer has appealed the decision.

The Indian Patent Office took other actions throughout the year that further raised concerns among multinational pharmaceutical companies. It revoked Merck’s patent for an asthma drug following a challenge from domestic pharmaceutical company Cipla. In an order issued by the patent office, the drug’s patent was revoked on the grounds that it lacked invention. The patent office also revoked Pfizer’s patent on its cancer drug Sutent. And, it withdrew a patent on Roche’s hepatitis C virus drug Pegysus. Though the Pegysus challenge was based on an argument that it was not a new invention, the patent office cited its $8,000 cost for six months of treatment as a reason for revoking its patent.

The U.S. trade group PhRMA called issuance of compulsory licenses an inappropriate tool. “Legitimate health emergencies that require making exceptions to intellectual property rights can and should be accommodated under the international framework, but only after exhausting all other efforts and under extraordinary circumstances,” said John Castellani, the group’s president and CEO. “If countries begin to routinely use compulsory licensing, we could see a ‘race to the bottom’ in which governments in the developing world walk away from their responsibility to support research and innovation in public health.”

All this growth comes with a note of caution: As governments seek to control costs, drugs deemed critical to the health of the population are subject to price controls.

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Efficiency in Health Care board decided not to extend the contract for its director, Peter Sawicki. Sawicki, the institute’s founding director, was viewed as a critic of the pharmaceutical industry. But the end of his reign came with controversy as supporters say the agency’s decision not to keep him in place could risk weakening public perception of the institute as impartial and science-driven. Some 600 physicians and clinical researchers petitioned the board and the minister of health to keep Sawicki in place. In September 2012, Jürgen Windeler, an expert on comparative effectiveness and a medical researcher, succeeded Sawicki.

In the United Kingdom, the National Institute of Clinical Excellence has been charged with making recommendations to the National Health Services about health technologies, clinical practice, and wellness. Concerned that NICE’s current approach to recommending whether NHS use or not use a drug too often required the service to either pay high prices that may not be justified by the therapy’s benefits or restrict access, the government instituted a value-based pricing system for new drugs starting in 2014 in the hopes of creating better access to innovative drugs. Under the plan, NICE will continue to assess the benefits of new drugs.

But as negotiations continued between the government and industry over how value-based pricing will work, the Association of the British Pharmaceutical Industry expressed concerns over the impact of new pricing rules when the current Pharmaceutical Price Regulation Scheme expires at the end of 2013. While the industry has agreed with the U.K. Department of Health that the new pricing scheme should consider the value of new drugs, there is disagreement about how that should be weighted. “We are not convinced that value-based pricing will encourage innovation or reward the most effective medicines,” says Association of the British Pharmaceutical Industry head Stephen Whitehead. “We are concerned that value-based pricing could in fact stifle innovation because it will struggle to accurately reflect the inherent gradual and incremental nature of innovation.”

Throughout the world, healthcare systems have used a combination of price controls and comparative-effectiveness measures as both ways to control cost and improve quality, according to a 2012 Commonwealth Fund report that profiles healthcare systems in various countries. In Australia in 2012, the country’s Independent Hospital Pricing Authority, created by that country’s 2011 healthcare reform, began paying for hospital services in a way that rewards efficiency and increases transparency. In Canada, the province of Ontario, which mandated 50 percent cuts to the price of generics and 25 percent cuts to brand name drugs in 2010, extended those cuts to private plans in 2012. The provincial government also slashed fees in 2012 for a long list of physician services in an effort to save $3 million a year. In France, where the health insurance system has struggled with 20 years of deficits, 600 drugs have been removed from its public reimbursement list. The French system also requires the use of generic drugs whenever possible, and has cut the number of acute care hospital beds.

In the United States, where the nation’s outsized spending on healthcare hasn’t translated into superior performance (see Figures 4.15 and 4.16), several parts of the Affordable Care Act are aimed at driving value in the healthcare system. One way the legislation seeks to do this is through the creation of the Patient-Centered Outcomes Research Institute or PCORI. The institute is expected to fund $3 billion in research over ten years. In May 2012, PCORI released its National Priorities for Research and Research Agenda, the framework to guide PCORI’s funding of comparative clinical effectiveness research. The agenda came after the board made changes to its draft agenda in response to more than 450 public comments that extended across 15 major themes. Nevertheless, PCORI said it did not amend its national priorities for research because the comments did not identify any significant gaps in the five proposed priorities.

PCORI’s five priorities, shaped by the dictates of the Affordable Care Act, include assessment of prevention, diagnosis, and treatment options; improving the healthcare system; communication and dissemination of research; addressing disparities; and accelerating patient-centered outcomes research and methodological research. With the release of the priorities, the institute announced it would award $120 million for research projects in 2012.

Value-based pricing already here

While there are examples of healthcare plans in the United States engaging in value-based pricing arrangements with pharmaceutical companies for at least a decade, Deloitte’s Center for Health Solutions is shifting to a value-payment system for medical products by tying reimbursement...
for drugs and devices to criteria that emphasize patient outcomes. More broadly, CMS is also moving toward value-based payments for care. CMS has conducted pilot programs since 2003, according to Deloitte, recording improvements in the quality of care through the use of incentives to healthcare providers. It noted that half the participants in the Physician Group Practice demonstration program shared in 80 percent of the savings—some $25.3 million. Composite quality scores rose an average of 15.9 percent for acute myocardial infarction, coronary artery graft, heart failure, pneumonia, and hip/knee replacements by the end of third year of the program in a hospital pay-for-performance demonstration, the briefing said. The Affordable Care Act will expand the use of value-based purchasing with hospitals. Deloitte says the legislation will shift new emphasis to results-based measures of clinical safety and improvements, require collaboration across the delivery system, and add financial risk to providers as base payments will be reduced.

The rise of ACOs

The management consulting firm Oliver Wyman says that Accountable Care Organizations or ACOs are an important part of the transformation of healthcare under the Affordable Care Act. ACOs involve multiple providers that come together to deliver care and are paid based on quality. Oliver Wyman argues that as this new model takes hold, it will accelerate the movement toward value-based healthcare. “For many of us in the healthcare industry, the real potential game-changer in the Affordable Care Act was not the highly publicized provisions—the creation of insurance exchanges or its embrace of guaranteed issue, community rating, and regulated medical loss ratios. Rather, it was the way ACA opened the door to accountable care organizations in Medicare,” the firm writes in its report The ACO Surprise. “Here at last was a development in U.S. healthcare that would shift the focus to delivery and encourage provider organizations to compete on quality and price—something the traditional fee-for-service system has failed at rather spectacularly. We believed—and still do—that as this sort of competition is successfully introduced into the U.S. system, it will inevitably spread, enabling and accelerating a movement toward healthcare that is priced and paid for in terms of value, not volume of services rendered.”

Oliver Wyman notes that in a short period of time, ACOs have become a significant part of the healthcare landscape. The firm defines ACOs more broadly than provider organizations the IOM committee sees roles for regulators to clarify and improve the rules governing the ACO model can produce strikingly better value for Medicare dollars to lure providers into making the switch. And we’ve already learned that the ACO model can produce strikingly better value than fee-for-service.”

As competition (in quality and price) is successfully introduced into the U.S. system, it will inevitably spread, enabling and accelerating a movement toward healthcare that is priced and paid for in terms of value, not volume of services rendered.”

“A boost for retail clinics

With the addition of an estimated 32 million Americans to the health insurance ranks through the Affordable Care Act and the shift towards value-based healthcare, retail clinics are expected to grow in number after a brief stall during the downturn in the economy and uncertainty surrounding healthcare reform [See Figure 4.17]. The retail medicine research and consulting firm Merchant Medicine expects the number of retail clinics to grow to 3,000 by 2016, up from about 1,400 in 2006. CVS CareMark’s Figure 4.17 RETAIL CLINICS GROWING AGAIN

“Transformation of time, ACOs have become a significant part of the healthcare landscape. The firm defines ACOs more broadly than provider organizations enrolled with one of the Medicare programs. Instead, it includes providers participating in population-oriented, value-based care delivery and reimbursement models. It calculates that between 25 million to 31 million Americans get care today through ACOs and 45 percent of the population lives in areas served by at least one ACO. Though the report notes that few organizations have achieved the full potential of the model, the top performers are already generating savings and delivering improved care. “The real issue is to get healthcare providers competing on cost and quality, something that the fee-for-service model has never been able to do,” says Rick Weil, partner with Oliver Wyman.
Other leading retail clinic providers have also been entering into alliances with hospital systems. The Affordable Care Act is expected to help drive the trend as accountable care organizations proliferate and seek out retail clinics to be part of their organizations. “Once accountable care organizations start to be a major deal in 2014, the healthcare industry is no longer going to be counting patients’ visits but looking to get people the right care,” Thomas Charland, CEO of Merchant Medicine told The New York Times in January 2012. “It’s going to be about cost, quality, outcomes, and they are going to be measuring everything.”

Carrots and sticks
One driver of healthcare costs in the United States is that the person being treated is often disconnected from the full cost of that care. That’s due, in part, to the fact that many people in the United States receive health insurance through employer-sponsored programs. While 61 percent of companies in the United States still offer healthcare plans to employees—the same in 2012 as in 2011, according to the Kaiser Family Foundation—fewer Americans have healthcare coverage through an employer and those that do are paying more for it. A 2011 Gallop study found that the percent of Americans with employer-sponsored healthcare fell to 44.6 percent in 2011 from 49.2 percent in 2009 [See Figure 4.18]. Increased unemployment is likely a factor in declining levels of employer-based care, both illnesses which lead to blindness. Preliminary data published in The Lancet showed significant improvements in vision which has lasted up to 4 months after cell therapy and no unabated proliferation of the cells.

Cardiovascular disease continues to be an area of intense progress. Over the past several decades, pharmacological and interventional therapeutics have significantly enhanced the quality of life for patients with heart disease. That said, stem cell therapeutics are emerging as a strategy to decrease ventricular remodeling, combat inflammation, and potentially reverse scar formation. While preclinical models have been largely suggestive of both the safety and efficacy of stem cell therapy, the definitive proof from placebo-controlled randomized studies has remained elusive. Cardio 3, Athesys, Cytori, and Neostem are but a handful of companies working to tackle the number one cause of mortality in the United States.

Finally, in 2012, the Nobel Prize in Physiology or Medicine was given to John Gurdon and Shinya Yamanaka for the discovery that fully differentiated cells could be reprogrammed to become pluripotent. Several companies now are advancing the field of induced pluripotent stem cells, or iPSCs.

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health insurance, but is not the sole cause," Gal-
lup says. "It appears that even Americans who are in the workforce—both full- and part-time employees—are becoming less likely to get their health insurance from their employer."

Those employees that are receiving health-
care through their employer are paying more. As premiums have risen steadily [See Figure 4.19], workers have faced a steep increase in the cost for employer-sponsored healthcare. Since 2002, average premiums for family coverage have increased 97 percent [See Figure 4.20]. That's outpaced the 33 percent growth in wages during that time and the 28 percent rate of inflation. "In terms of employee insurance costs, this year’s 4 percent increase qualifies as a good year, but it still takes a growing bite out of middle-class workers’ wages, which have been flat or falling in real terms," says Kaiser Family Foundation President and CEO Drew Altman.

Employers have turned to wellness pro-
grams as one way to address the rising cost of healthcare and improve the health of their employees. Some 63 percent of companies that provide health benefits offer some kind of wellness program, according to the Kaiser Family Foundation/Health Research & Educational Trust Employer Health Benefits 2012 Annual Survey. These wellness programs vary widely, but can include such things as weight loss programs, smoking cessation programs, gym memberships or on-site fitness facilities, nutrition classes, online resources for healthy living, or a wellness newsletter [See Figure 4.21]. Companies with at least 200 employees are more likely to offer wellness programs; 94 percent of them offer at least one wellness benefit. The survey found that 73 percent of firms offering health benefits that included at least one wellness program believe that the programs are effective at improving employees’ health. A little more than half—52 percent—say the wellness programs are effective in cutting the cost of healthcare for them.

In order to get employees to participate in these programs, employers use a combination of incentives and penalties. The incentives can include such things as gift cards, cash, and lower healthcare costs. Employees who fail to par-
ticipate or achieve certain health related goals, such as lower weight, blood pressure, or chole-
sterol, may face financial penalties in the form of higher premiums on their health insurance. The

**Figure 4.18  EMPLOYER-BASED HEALTH INSURANCE DECLINING**

![Graph showing average percent coverage of adults 18 and older](image)

**Figure 4.19  INCREASE IN WORKER CONTRIBUTIONS**

![Graph showing average annual health insurance premiums and worker contribution for family coverage, 2002 to 2012](image)

**Figure 4.20  AVERAGE ANNUAL PREMIUMS FOR COVERED WORKERS WITH FAMILY COVERAGE 1999-2012**

![Graph showing average annual premiums for covered workers with family coverage, 1999-2012](image)

Kaiser Family Foundation survey found that at 11 percent of the companies surveyed, employ-
ees found to have a health risk factor were required to complete a wellness or health man-
agement program or activity. If they did not, they faced a financial penalty in the form of a higher premium contribution or greater patient cost sharing. At 9 percent of large companies, employees identified with health risk are penal-
ized or rewarded based on whether or not they meet a specific target, such as reaching a certain

body weight or reducing their cholesterol to a certain level.

How effective wellness programs are at achieving their goals is a little unclear. Health Affairs reported in a 2012 policy brief that one review of 36 peer-reviewed studies found that employers saved $3.77 for every dollar spent on a wellness program. They also
saved an average of $2.73 additionally for every dollar spent through costs for employee absen-
teesism. A separate study in 2005 of previous studies found employers of all sizes saved about 25 percent on sick leave, health plan costs, and workers compensation and disability, Health Affairs reported.

But while financial incentives and penalties do effect participation in employer wellness pro-
grams, evaluations of whether these carrots and sticks make any difference in health outcomes for employees is murky. Health Affairs noted that one study by researchers at Oxford Univer-
sity of 17 previous studies found no difference in outcomes among employees in a smoking cessation program between those who received financial rewards and those who did not. A separate study found similar results for employ-
ees in a weight loss program. A series of studies from the University of Pennsylvania, thought, found evidence that financial rewards signifi-
cantly increased the number of employees who lost weight or quit smoking through employer wellness programs.

Employer wellness programs are not with-
out their controversy. While they can be power-
ful tools for improving health, some say the programs can be used to make healthcare unaf-
fordable and drive employees from employer plans. They also say penalizing employees with certain health problems, as a result, can unfairly penalize low-income individuals and people with racial and ethnic backgrounds that may make them more susceptible to certain health problems.

**Benefits in the Affordable Care Act**

The Affordable Care Act is designed to end entirely by 2014," says non-
profit consumer advocacy group Families USA in a June 2012 issue brief. "Both practices result in people paying higher health insurance costs
Value Shopping

Medical tourism attracts travelers with promise of high quality at low prices

The search for value in healthcare has fueled medical tourism in recent years with countries now actively instituting economic development plans and policies to build a medical tourism industry within their borders.

A 2011 OECD report on medical tourism found a shift towards patients from richer, more developed nations travelling to less developed countries to access health services. That trend is being driven by low-cost treatments, and aided by increasing amounts of information available on the Internet as well as inexpensive flights. In 2009, medical tourists from the United States spent $600 million for medical care in other countries, according to the OECD. That’s up 13 percent from 2004.

Governments have sought to promote their countries as medical tourism destinations through international trade fairs, advertising, overseas press, and through their economic development and tourism policies.

In Singapore, the public-private partnership SingaporeMedicine has been promoting its medical hub nearly a decade as a destination for advanced medical care. India offers a special visa category for medical tourists. And Malaysia has long promoted medical tourism through its National Committee for Promotion of Medical and Health Tourism. In some locations, such as Dubai, governments have supported medical tourism efforts by encouraging hospitals to obtain international accreditation, the OECD report found.

Though cost savings have attracted some medical tourists to travel great distances for significant surgeries, some countries, such as Hungary and Poland, are attracting medical tourists from nearby European countries seeking dental and cosmetic surgery. The Medical Tourism Survey 2012 from Intuition Communications found. In fact, the survey of 1,000 European medical tourists found that Hungary was the leading destination for these travelers, followed by Poland, Turkey, Spain, the Czech Republic, and India. Nine out of ten travelers said they would “definitely” or “probably” go abroad for treatment again, and 85 percent said they were either “very” or “quite satisfied” with their experience.

Medical tourism is still more about regional medicine and cross-border healthcare rather than global healthcare, according to Keith Pollard, managing director of Intuition Communications, which publishes the International Medical Travel Journal. “As travel costs climb, the concept of long-distance medical tourism becomes less attractive,” he wrote. “The imposition of hefty departure taxes in countries such as the United Kingdom, Germany and elsewhere will continue to fuel growth, particularly if and when impediments are addressed.”

There are barriers that impede the growth of medical tourism. These include concerns about quality, challenges with follow up care once a patient returns home, legal recourse when procedures don’t work out, and other issues such as language. But the compelling cost savings and availability of quality care will continue to fuel growth, particularly if and when impediments are addressed.

“Ascension Health has been working with Dr. Shetty for two years to explore ways to adapt his success at providing high-quality healthcare at low cost,” said Anthony Tersigni, president and CEO of Ascension Health Alliance. “We’re excited to be part of this venture. Together, we are committed to bring first-rate healthcare provided in a world-class setting.”

The Health City Cayman Islands is an approximately $2 billion project that will be built in phases over 15 years on a 200-acre site. It will include a tertiary-care hospital, an educational facility, a biotech park, and an assisted living community. The first phase will consist of approximately 140 beds expected to open in early 2013. The multi-specialty hospital will provide services not widely available in the region such as open-heart/bypass surgery, angioplasty, heart-valve replacement, cancer treatment, bone-marrow transplant, nuclear medicine, organ transplant and orthopedics. Once complete, the hospital will house as many as 2,000 beds.

The prices for surgery take into account hospital and doctor charges, but do not include the costs of flights and hotel bills for the expected length of stay.

<table>
<thead>
<tr>
<th>PROCEDURE</th>
<th>US</th>
<th>INDIA</th>
<th>THAILAND</th>
<th>SINGAPORE</th>
<th>MALAYSIA</th>
<th>MEXICO</th>
<th>POLAND</th>
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<tbody>
<tr>
<td>Heart bypass (CABG)</td>
<td>113,000</td>
<td>10,000</td>
<td>13,000</td>
<td>20,000</td>
<td>9,000</td>
<td>3,250</td>
<td>7,140</td>
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<tr>
<td>Heart valve replacement</td>
<td>150,000</td>
<td>9,500</td>
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<td>13,000</td>
<td>9,000</td>
<td>18,000</td>
<td>9,520</td>
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<td>Angioplasty</td>
<td>47,000</td>
<td>11,000</td>
<td>10,000</td>
<td>13,000</td>
<td>11,000</td>
<td>15,000</td>
<td>7,300</td>
</tr>
<tr>
<td>Hip replacement</td>
<td>47,000</td>
<td>9,000</td>
<td>12,000</td>
<td>11,000</td>
<td>10,000</td>
<td>17,300</td>
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<td>Knee replacement</td>
<td>48,000</td>
<td>8,500</td>
<td>10,000</td>
<td>13,000</td>
<td>8,000</td>
<td>14,650</td>
<td>6,375</td>
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<td>11,000</td>
<td>15,000</td>
<td>20,000</td>
<td>13,000</td>
<td>8,000</td>
<td>11,069</td>
</tr>
<tr>
<td>Hip resurfacing</td>
<td>47,000</td>
<td>8,250</td>
<td>10,000</td>
<td>12,000</td>
<td>12,500</td>
<td>12,500</td>
<td>7,905</td>
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<tr>
<td>Spinal fusion</td>
<td>43,000</td>
<td>5,500</td>
<td>7,000</td>
<td>9,000</td>
<td>-</td>
<td>15,000</td>
<td>-</td>
</tr>
</tbody>
</table>

The prices for surgery take into account hospital and doctor charges, but do not include the costs of flights and hotel bills for the expected length of stay.

Source: OECD
based on their health risk factors, like high cholesterol, BMI, or blood sugar levels, and both can result in health coverage being unaffordable for those who need it the most."

Nevertheless, the Affordable Care Act codifies in the Health Insurance Portability and Accountability Act, or HIPAA, regulations on employee wellness programs and increases the potential size of both the incentives and disincentives employers can use. Those regulations spell out limits on rewards and penalties, require that employees be able to qualify for the reward at least once a year, and that an alternative standard or waiver be provided to employees who cannot achieve a health outcome because it is either unreasonable or medically inadvisable. Under the Affordable Care Act, employers in 2014 will be able to increase wellness program rewards to 30 percent of health benefit costs from 20 percent. They will also be able to charge covered employees who do not participate in the wellness program as much as $1,500 a year.

The Medicare Better Health Rewards Program Act of 2012, legislation introduced by Senator Rob Portman, R-Ohio, and Ron Wyden, D-Oregon, sought to bring the same kind of approach to improving care and cutting costs for patients in Medicare. The voluntary program sought to provide financial incentives to seniors to get and stay healthy. The rewards would be funded by savings generated by the program. The three-year wellness program would pay seniors for achieving improvements in six key areas of health: tobacco usage, body mass index, diabetes indicators, blood pressure, cholesterol, and up-to-date vaccinations and screenings. Medicare beneficiaries who participate in the program would be assessed in each of these areas and then work with their doctor to develop a plan to bring their indicators into a healthier range. The seniors’ progress would be measured during subsequent wellness visits in years two and three of the program. The legislation died in Congress in 2012 and had not yet been reintroduced at the time of this writing.

**Challenge of value**

The move to value-based systems and payments does not come without challenges. Not the least of these will be getting patients, providers, payers, regulators, and drug and device makers to come to some agreement on what value is and how to measure it. Michael Porter, professor at the Harvard School of Business, addressed the question of what is value in healthcare in a 2010 perspective in the New England Journal of Medicine. "Value—neither an abstract ideal nor a code for cost reduction—should define the framework for performance improvement in healthcare," he writes. "Rigorous, disciplined measurement and improvement of value is the best way to drive system progress. Yet value in healthcare remains largely unmeasured and misunderstood.”

Porter argues for a patient-centric definition of value, saying that it should be measured by outcomes achieved rather than the volume of services delivered. Outcomes measured against costs equals value. Such a formula would reward efficiency, but it is no simple task in a system that is fragmented and, particularly for patients with chronic conditions, outcomes will need to be measured over long periods of time. "The failures to adopt value as the central goal in healthcare and to measure value are arguably the most serious failures of the medical community," writes Porter. "This has hobbled innovation, led to slow diffusion of innovation, allowed pseudo-innovation with no meaningful value benefits, resulted in ill-advised cost containment, and encouraged micromanagement of physician practices, which imposes significant costs of its own. Failure to measure value is one of the principal reasons why reform in healthcare has been so difficult as compared with other fields.”

At the heart of value-based healthcare is the need for information and analysis that can track outcomes and costs. The challenge is significant and measures will need to be established, but some countries are well down the path to value-based healthcare. Sweden in the 1970s began to establish disease registries to track outcomes. The country has nearly 90 registries covering more than a quarter of the nation’s total national health expenditures, according to The Boston Consulting Group 2012 report Progress Toward Value Based Health Care. It says about a third of those registries collect patient data on more than 90 percent of all Swedish patients diagnosed with a specific disease or undergoing a particular procedure. The government in 2011 said it would increase its financial support of registries to $45 million a year by 2013 from just $10 million in 2011. The challenge, it adds, is for Sweden to work with providers and suppliers to tie reimbursement to outcomes so it not only impacts payments for adverse outcomes as it does today, but also provides incentives for performance and quality.

Singapore, too, has made great strides towards a value-based healthcare system. In 2001, the country established the National Registry of Diseases Office to collect and publish data. In 2007, it passed legislation to established standards for mandated reporting of outcomes for a set of diseases including cancer, stroke, and heart attacks among others. The report found that Singapore now needs to help clinicians analyze and use the data it collects to identify best practices and guide treatments. "It takes years and, perhaps, even decades for a country to make the transition to value-based healthcare,” wrote The Boston Consulting Group. “But the picture of what it takes to build an effective value-based healthcare system is becoming clearer. And the most advanced countries are already reaping benefits.”
Regulation and Policy

In a world of growing scientific complexity, regulators and policymakers are adapting. They are revising laws, reviewing programs, and raising expectations. Key legislation impacting industry was renewed in 2012, reshaping and reaffirming the ties between drugmakers and medical device companies, and the FDA. The mounting cost of innovative therapies and tightening national budgets has continued to shape policy decisions the world over. In this time of government budgets are under pressure while industry faces new fees and taxes. Meanwhile, comparative effectiveness research and value assessments are becoming more common and forcing industry to work in new ways with regulators and payers.
CHAPTER 5: Keeping Pace

As approval process is streamlined, payers demand proven value

The crowning U.S. regulatory achievement of 2012 came during the summer, when lawmakers sent the Food and Drug Administration Safety and Innovation Act of 2012 to President Barack Obama for his signature. After months of debate and negotiation between regulators and industry, the act, known as FDASIA, extended and improved two key agreements with industry, the Prescription Drug User Fee Act, commonly called PDUFA, and the Medical Device User Fee Act, MDUFA. The Innovation Act also added two entirely new user fee programs to support the review of generic drugs and biosimilars, and provisions to encourage the development of pediatric drugs, track-and-trace system for drugs or closer control of the pain medication hydrocodone, might trip up a final agreement. Without approval, by mid-July 2012, the agency would have had to begin issuing pink slips to employees supported by PDUFA funds, something both industry and the agency sought to avoid. Testifying on behalf of the Biotechnology Industry Organization, Richard Pops, chairman and CEO of Alkermes, stressed the need for a quick reauthorization of PDUFA that would “enhance the drug development and review process through increased transparency and scientific dialogue, advance regulatory science, and strengthen post-market surveillance.” To the delight of the majority of stakeholders, reauthorization brought together all those elements and more.

Industry agreed to pay the agency a base $693 million in fiscal 2013, 6 percent more than it paid in fiscal 2012, and higher amounts in the remaining four years of the authorization until 2017 to support resources to expedite the agency’s reviews. That money—nearly $2 billion per application requiring clinical data, plus establishment and product fees—plays a crucial role in overall funding for the agency. PDUFA fees accounted for 62 percent of the $932 million the FDA spent in fiscal 2010 conducting human drug reviews, while budget appropriations provided the balance of the funding. In recognition of the increasing complexity of modern therapies, drugmakers supported a two month extension of the review timelines for new molecular entities and new biologics [See Figure 5.2]. The FDA, in turn, committed to review and act on 90 percent of priority applications within six months and 90 percent of standard applications within 10 months. But more importantly to drugmakers, the agency also agreed to schedule pre-submission, mid-cycle, and late-cycle meetings with companies seeking drug approvals.

The new review program for applications for innovative drugs and biologics should improve the efficiency of the review process and reduce the overall time until new medicines become available to patients [See Figure 5.3]. Specific-
cally, said the Pharmaceutical Research and Manufacturers of America, earlier and more comprehensive communication between the agency and drug sponsors will improve the rate of “on-time, first-cycle” successes—the number of new medicines that are fully reviewed and approved within the target timeframe following initial submission.

The FDA had also agreed to standardize risk evaluation and mitigation strategies—the post-market monitoring and testing plans that help ensure the benefits of a drug outweigh its risks—with the intent of reducing the burden such programs place on healthcare providers, drugmakers, and patients, something for which industry groups like PhRMA advocated. Better monitoring will, in part, come from expanding the use of the FDA’s Sentinel system to track adverse events. Better efficiency will stem from the adoption of another component of the plan: standardized electronic data submission.

Faster reviews of drugs for rare diseases and breakthrough therapies that show substantial improvement over existing treatments in early trials found a place in the legislation, as did provisions supporting a renewed focus on patient-centered drug development and funding for regulatory science activities. The breakthrough therapies program, first backed by the Friends of Cancer Research, seeks to reduce the total development time and cost of the most promising treatments and to minimize the number of patients that would be given a control regimen or a currently available treatment that doesn’t work well. As 2012 closed, guidance for what sorts of experimental medicines might fetch a breakthrough designation was still in development. But, generally, it required the FDA to expedite the development and evaluation of those drugs and to establish an interactive real-time development process if the drug is intended to treat a serious or life-threatening disease or condition and preliminary clinical evidence indicates that it may demonstrate substantial improvement over existing therapies on one or more clinically significant endpoints.

Support for regulatory science—the science of developing new tools, standards, and approaches to assess the safety, effectiveness, quality, and performance of FDA-regulated therapies against colorectal cancer treatment capable of extending patient’s lives. Also in September, Pfizer delivered Bosulif for chronic myelogenous leukemia, a therapy that the FDA recognized as an improvement in the treatment of the leukemia based on a better understanding of the molecular basis of the disease.

The 20 percent of breast cancer patients with HER2 positive cancers gained access to Roche’s Perjeta in June 2012. It joined Vertex Pharmaceuticals’ Kalydeco, a targeted therapy for cystic fibrosis patients who have a specific gene mutation, on the roster of personalized therapies approved by the FDA during the year. Pfizer won approval for Xeljanz, the first oral disease-modifying drug for rheumatoid arthritis in more than a decade. There were also some notable innovations in 2012 in the way approved drugs were made. Pfizer, along with its partner Protalix Biotherapeutics, won approval for the Gaucher disease drug Elelyso, the first drug to be manufactured using genetically engineered plant cells. Novartis won approval for Flucelvax, the first seasonal influenza vaccine licensed in the United States produced using cultured animal cells instead of fertilized chicken eggs.

In a critical year for the U.S. Food and Drug Administration, when its policies and budget received close scrutiny, agency drug reviewers pushed through a raft of new drugs, raising 2012’s total approval count to 39—its highest level of approvals in one calendar year since 1996 [See Figures 5.3 and 5.10]. One-third of the drugs approved in 2012 had orphan drug status. Orphan drug status confers financial and other benefits to a drug’s sponsor to encourage the development of drugs to treat patient populations of 200,000 or less in the United States. The approvals included many new cancer therapies, as well as treatments for cystic fibrosis, HIV, macular degeneration, Alzheimer’s disease, blood disorders, meningitis, and Gaucher disease. Roche’s Erivedge, approved in January 2012, became the first FDA-approved drug for late-stage basal cell cancer, the most common form of skin cancer. January also brought approval of BTG International’s Voraxaze, an enzyme that lowers toxicity associated with the common chemotherapeutic drug, methotrexate.

Attacking a public health priority, Xandi was approved in August 2012 to treat men with late-stage castration-resistant prostate cancer. Medication and Astellas Pharma co-developed the drug. Meanwhile, Stivarga, Bayer’s therapy for late-stage colorectal cancer, joined Zaltrap in September 2012 in the arsenal of approvals included many new cancer therapies, as well as treatments for cystic fibrosis, HIV, macular degeneration, Alzheimer’s disease, blood disorders, meningitis, and Gaucher disease. Roche’s Erivedge, approved in January 2012, became the first FDA-approved drug for late-stage basal cell cancer, the most common form of skin cancer. January also brought approval of BTG International’s Voraxaze, an enzyme that lowers toxicity associated with the common chemotherapeutic drug, methotrexate.

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products—will color the agency’s approach to early toxicology studies, novel manufacturing methods for biologics, and its evaluation of personalized therapies, among other areas. Increased staffing will help validate the use of new scientific tools, such as pharmacogenomics and biomarkers that can help demonstrate therapeutic benefits more rapidly. Evaluating this aspect, PhRMA president and CEO John Castellani and BIO president and CEO Jim Greenwood called it “an exciting new era in regulatory science.” A reliable, science-driven regulatory environment fosters innovation, promotes economic competitiveness and helps maintain high patient confidence in the integrity of our medicines,” they said. “If implemented successfully, PDUFA V will refocus the program on its original intent—timely patient

FDA’s Woodcock Argues for Clinical Research Makeover

Regulator wants academia to help rethink drug development process

A cademic biomedical researchers should take a greater role in drug discovery and development to help transform clinical research in the United States, according to Janet Woodcock, director of the FDA’s Center for Drug Evaluation and Research.

The drug development enterprise in the United States is “floundering” in its efforts to translate innovative science and bring to market therapies based on that science, said Woodcock during a California Institute for Quantitative Biosciences seminar at the University of California, San Francisco in April 2012. “The academic medical center needs to help reengineer the clinical research enterprise. Currently, clinical research is very expensive, driving much of it overseas. You’re losing clinical research in the United States,” she said.

Clinical trials tend to be extremely expensive, unpleasant for most participants, inefficient, not totally reliable, and unavailable to most patients, she said. “The vast majority of clinical research is done by industry, and I think that’s probably wrong,” said Woodcock. A better model, she argued, would come from academia and industry building on each other’s strengths.

While the pharmaceutical industry has built expertise in clinical rigor, medicinal chemistry, lead optimization, and late-phase development, among other areas, academic researchers can bring to the table talent in molecular biology, in-depth understanding of disease, animal and in vitro testing capabilities, and relationships with relevant patients, said Woodcock.

By working more closely with industry, she proposed, academic researchers could fill an urgent need for new drug safety evaluation tools and help create hubs for clinical trial networks that incorporate sophisticated and standardized scientific tools.

At least some innovative partnerships already exist, Woodcock noted. One in which UCSF is already participating provides a very good prototype for future of clinical trials: the I-Spy 2, a biomarker-based adaptive trial investigating multiple breast cancer drugs. She also highlighted work done by the Foundation for the National Institutes of Health to help support scientific work on new endpoints for use in clinical trial design.

Current drug development often ends in late-stage clinical failure because of factors such as unexpected drug toxicity and failure to outperform existing therapies, she said, comparing the process to physics without engineering. “We build an airplane and see if it can fly,” she said. The application of new scientific knowledge in the clinical testing process, built with a central role for academic scientists, could provide a huge opportunity for improvement, she said.

access to new medicines—while strengthening FDA’s high safety standards and helping to establish a new system-wide approach to regulatory science that embraces the scientific tools used in 21st century drug development.

Another provision included in PDUFA V is a new initiative called Patient-Focused Drug Development, which sets the goal of obtaining the patient perspective on disease areas to help focus the FDA’s limited resources. In September 2012, the agency proposed 39 disease areas including heart failure, obesity, and lung cancer as potential candidates for the focus of one of 20 future public meetings. “Right now, we don’t have a systematic way of hearing from patients and how they feel about their disease,” said Janet Woodcock, director of the Center for Drug Evaluation and Research, at an October 2012 meeting to discuss the initiative. However, as more tools and techniques emerge allowing for the direct capture of patients’ health needs and desires, she said, that is rapidly changing.

“Some people don’t want to cross the San Francisco Bay Bridge. It’s too risky, right? Each person has a different assessment of risk and how much risk they’re willing to tolerate. Other people want to binge jump off the Bay Bridge, right? So yes, we’re all different,” said Woodcock. “We need to understand that spectrum of risk tolerance and how much any given person might be willing to trade off for improvement of various symptoms that they’re suffering.”

A renewed focus on rare disease

Taking the opportunity of the landmark regulation and Policy
ease are every bit as significant as the Orphan Drug Act, according to Emil Kakkis, president of the Everylife Foundation for Rare Diseases. “Taken together, it sends a very strong message to the FDA from Congress that said, ‘We need to do better on rare disease treatments,’” he said. “And I think that message will be heard by FDA.”

**A threat to public health**

The oft-neglected field of antibiotic drug development also got significant attention in FDASIA, in a component called The Generating Antibiotic Incentives Now Act or GAIN Act. Research and development for new antibiotic drugs has declined for decades, and the number of new FDA-approved antibiotic drugs has fallen steadily since the 1980s [See Figure 5.3]. Meanwhile, the persistent and sometimes indiscriminate use of existing antibacterial drugs worldwide has resulted in a decrease in the effectiveness of those drugs. More than 70 percent of the bacteria that cause hospital-associated infections are resistant to at least one type of antibacterial drug most commonly used to treat these infections. In the United States, nearly 2 million Americans developed such infections in 2002, resulting in about 99,000 deaths.

The GAIN Act creates new incentives to encourage the development of products to treat, prevent, detect, and diagnose antibiotic-resistant infections, while extending the length of time an approved drug is free from competition and clarifying the regulatory pathway for new antibiotics.

The act grants an additional five years of market protection at the end of the existing exclusivity for qualified infectious disease products, plus six months more with an approved companion diagnostic; requires FDA to grant priority review to drugs that are intended to treat, detect, prevent, or identify certain drug-resistant infections; calls for a review of clinical trial guidelines for antibacterial drugs and, as appropriate, to revise the guidelines; and calls for the Government Accountability Office to study the problem and report on the need for incentives to encourage the research, development, and marketing of qualified products.

Rib-X Pharmaceuticals was among the first companies to benefit from the qualified infectious disease product designation, winning the advantages conferred by GAIN. The antibiotics guidance—with a draft due in June 2013—will specify how preclinical and clinical data can be utilized to inform an efficient and streamlined pathway for antibiotic drug development program. It also needs to provide industry stakeholders with advice on approaches for the development of antibacterial drugs that target a more limited spectrum of pathogens than current antibiotics. By the end of 2014, following a

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**Figure 5.3** **Antibiotic Development Dwindling**

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“*If we want to address the issue of access, I think we have to spur innovation in manufacturing. We also need to create an environment in which international manufacturers are interested in manufacturing biosimilars in India.*”

**M.K. Bhan,**

Secretary of India’s department of biotechnology

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**EXPANDING AVAILABILITY**

**Biosimilars Hold Promise for India**

As demand grows, the country hopes to build on its strong generics industry and market will be greater than those in the generics market, said P.M. Murali, president of the Indian Association of Biotechnology and Pharmaceuticals. “Although sales of biosimilars in India are reduced or no delay altogether. They include cases in which no medicine is available, or in a national healthcare emergency. Bhan predicted that 2012 and 2013 would be a time of major reform in India’s drug regulatory system, with a focus on improving the process for approving medical devices and diagnostics. “The operation needs to be stronger and the process needs to be stronger,” he said.

P.V. Appaji, Director General of the Pharmaceuticals Export Promotion Council of India told The Economic Times that he believes biosimilar sales will rise as much as $10 billion by 2015, a possibility that has drawn significant interest from Indian companies. Companies such as Wockhardt, Zydus Cadila, Indian Immunologicals, Biological E, and Lupin have committed new resources to process development and analytics to prepare for the market.

In addition to the implications of biosimilars regulation for Indian patients, Indian drug-makers are also eager to leverage the opportunities to serve big pharmaceutical markets such as the United States and Japan.

Due to the complexity of manufacturing biosimilars, investments made in the nascent market will be greater than those in the generics market, said P.M. Murali, president of the Association of Biotechnology Led Enterprises in February. “Regulation is going to be the key for targeting and compelling growth in the next two years.”
public comment period, the U.S. Department of Health and Human Services is required to publish a final version of the guidance.

**New priorities, new programs**

In addition to extending and fine-tuning the longstanding user fee programs for drugs and medical devices, FDASIA also created important new fee programs to support the review of biosimilars and generic drugs. Biosimilars are therapeutics that are highly similar to already-approved biologics, notwithstanding minor differences in clinically inactive components. In the United States, while FDA has approved a few related biologics as new molecular entities, it has not yet approved any biosimilars pathway that became law as part of the Patient Protection and Affordable Care Act.

With the expectation that biosimilars will cut 20 percent to 40 percent from the price of innovator biologics, most payers are enthusiastic about the development of regulations that accelerate biosimilars’ adoption. The Obama administration is also eager to see biosimilars developed and approved. It has consistently sought to shorten the exclusivity period on brand name biologics to seven years from 12 years—a proposal that has found support in some quarters of Congress and that the president first advanced in a deficit reduction plan in September 2011. Reducing the exclusivity period would save federal health programs $4 billion over 10 years, the administration has estimated.

In February 2012, the FDA provided draft guidance on the abbreviated approval pathway created for biosimilars through the Patient Protection and Affordable Care Act. It also provided drugmakers an initial roadmap to guide their way to participate in what IMS Health estimates will, by 2015, become a global $1.9 billion to $2.6 billion market for copies of the biotech drugs. While the guidance provided detail on what the FDA will be looking for in applications for approval of new biosimilars, the Biosimilar User Fee Act that was signed into law as part of FDASIA put into place the user fee program to make it a reality. Drugmakers will pay $195,880 per application to support the agency’s review, plus further fees for final approval and evaluation of clinical data.

Though a program of support for biosimilars is rapidly developing in the United States—which has so far lagged Europe in this area—several speed bumps are likely to slow progress in the short term, with the issue of funding reviews leading the way. Despite the FDA having received numerous biosimilar meeting requests, it is likely that the biosimilars program will be under-resourced for the next few years as the program, which collects just a fraction of the fees collected under PDUFA, accrues sufficient funding, said Janet Woodcock at a joint DIA/FDA Biosimilars Conference, reported by FDA Week in September 2012. Arguments over naming, automatic substitution, and questions over how worthwhile it will be to use the biosimilars pathway may also slow the arrival of biosimilars to market.

The agency first set up foreign outposts after a series of contaminated imports from China triggered alarm over the safety of food and pharmaceutical products from there. The events made clear that the FDA’s lack of presence overseas impaired its ability to respond quickly and efficiently. It now has offices in China, India, Latin America, Europe, and as of June 2011, new offices in Jordan and South Africa. The FDA is using its staff in those locations to learn more about the local landscape and regulatory systems and to further strategies for better monitoring the safety of food and drugs product destined for importation to the United States, which it first outlined in its 2011 report, Pathway to Global Product Safety and Quality. To overcome the constraints of its resources and authority abroad, the agency is trying to get on the same page as other regulators to facilitate the exchange of information on quality, safety, and efficacy. It is also piloting programs to employ techniques such as data mining and pattern discovery technology to evaluate and rank FDA-regulated imports based on their potential health risk.

Progress was announced in November 2012 with the signing of two cooperative arrangements. A statement of cooperation with FDA’s counterpart in Brazil outlined procedures for enhanced collaboration between the nations on common regulatory issues at a time when Brazil is dramatically increasing its trade with the United States. A second arrangement, between the FDA and regulatory agencies in Australia, Brazil, and Canada provides for the creation of a single audit program for medical device quality management systems.

Nevertheless, Hamburg acknowledges the challenges are significant. “It still is a real problem,” she said, “to take enforcement action proactively in another country.”

**FDA Responds to Growing Challenge of Imports**

Hamburg said agency lacks resources are a problem for the agency with drug development becoming an increasingly global enterprise, the U.S. Food and Drug Administration has struggled to keep on top of monitoring global supply chains. Now the agency is working to strengthen ties with their foreign counterparts in China, Brazil, Australia, and beyond to better protect public health at home.

“The already difficult job of ensuring the safety of FDA-regulated products has grown exponentially due to two trends: the expansion of global trade, and the need for ever-greater expertise from regulators as innovations bring increasingly sophisticated products to market,” said FDA Commissioner Margaret Hamburg in a November 2012 post on the agency’s blog, FDA Voice.

The agency is dedicating $10 million from Congress to pay for additional staffing and drug manufacturer inspections in China and is developing new risk-based approaches to ensure product safety and quality to improve its results.

“The $10 million is a small part in the bucket of what our overall needs are,” wrote Hamburg. But coming to terms with globalization is “a huge priority,” she writes. “FDA is at the cutting edge of much of this in terms of responding to the challenges of globalization. And at the present time we don’t have the tools and authorities that we fully need to achieve that nor do we have the resources.”

What the agency is doing with the limited resources it does have was covered in April 2012 in its Global Engagement Report detailing its efforts and evolving responses to the growing complexities and dangers of imported food and drugs. According to the report, more than 80 percent of the active pharmaceutical ingredients and 40 percent of finished drug dosages sold in the United States are manufactured abroad. The rise in imports from China has been particularly steep. From fiscal 2007 to 2011, the number of shipments of FDA-regulated products from China increased by 62 percent, according to FDA statistics. During that time, problems with contaminated baby formula and heparin produced in China created international concern about the safety of products produced there.

“It’s very clear that the FDA’s lack of presence overseas impaired its ability to respond quickly and efficiently. It now has offices in China, India, Latin America, Europe, and as of June 2011, new offices in Jordan and South Africa. The FDA is using its staff in those locations to learn more about the local landscape and regulatory systems and to further strategies for better monitoring the safety of food and drugs product destined for importation to the United States, which it first outlined in its 2011 report, Pathway to Global Product Safety and Quality. To overcome the constraints of its resources and authority abroad, the agency is trying to get on the same page as other regulators to facilitate the exchange of information on quality, safety, and efficacy. It is also piloting programs to employ techniques such as data mining and pattern discovery technology to evaluate and rank FDA-regulated imports based on their potential health risk.”

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Nevertheless, Hamburg acknowledges the challenges are significant. “It still is a real problem,” she said, “to take enforcement action proactively in another country.”
The second new user fee program put into place in 2012 was the Generic Drug User Fee Amendments of 2012, or GDUFA. Designed to speed access to safe and effective generic drugs to the public and reduce costs to industry, GDUFA requires industry to pay user fees to supplement the costs of reviewing generic drug applications and inspecting manufacturing facilities. Prescription drug spending in the United States reached $367 billion in 2010, an increase of $135 billion since 2001, and comprised approximately 12 percent of all health care spending in the country, according to the Government Accountability Office, which in January surveyed the impact of the landmark Hatch-Waxman Act. Summarizing research on savings from generic drugs, the GAO reported mixed results in January 2012, saying that some studies found they raised healthcare costs, while others found they led to cost savings. Not disputed, however, was the enormous backlog of generic drug submissions at the FDA—a queue that in April 2012 had reached a record 2,500 applications—and was growing rapidly. The new fee program, sought by the generics industry in large part to solve the backlog problem, established a set of user fees to be paid by generic drugmakers that together will generate $299 million in funding for the agency in fiscal 2013, with annual adjustments thereafter. Additional resources supported by the fees are slated to help the FDA reduce its backlog of pending generic drugs applications, cut the average time required to review generic drug applications for safety, and increase risk-based inspections. GDUFA will also enhance global supply chain safety by requiring that generic drug facilities and sites around the world self-identify.

"User fees for generic drugs or GDUFA will add to our current generic drug review backlog caused by the increase in generic drug applications, their growing complexity, and the number of generic drug facilities now located overseas where inspections are more challenging," wrote FDA Commissioner Margaret Hamburg in a blog post regarding the program. "The added money from user fees will reduce this backlog and eventually ensure that FDA is able to inspect overseas facilities as often as it does domestic facilities." Ralph Neas, president and CEO of the Generic Pharmaceutical Association, called the new user fee program "the most important pharmacutical legislation since the 1984 Hatch-Waxman Act," and said that it would ensure all participants in the U.S. generic drug system, whether U.S.-based or foreign, comply with the United States' strict quality standards.

FDA Clears Path to Personalized Medicine Approvals

Agency works with industry to remove regulatory barriers

It has become increasingly clear that billions of dollars are wasted on treatments that don't work. By some estimates, 90 percent of drugs are ineffective for between 50 percent and 70 percent of the population. That realization is not just shaping industry, but also transforming the expectations of regulators.

Of the 39 innovative drugs approved by the U.S. Food and Drug Administration in 2012, two were approved based on a narrowing of the initial patient population. The FDA approved Kalydeco to treat a rare form of cystic fibrosis in patients age 6 and older who have the specific G551D mutation in the Cystic Fibrosis Transmembrane Regulator gene. But while few would argue with the promise of personalized medicine in refining our understanding of drugs' risks and benefits, there is also a widely held belief that lack of regulatory clarity has slowed progress in this area. "When you ask people in industry about this, some feel it is because there's no clear regulatory pathway or guidelines," said Issam Zineh, Director of the Center for Drug Research and Evaluation’s Office of Clinical Pharmacology.

To clear things up, the FDA has been moving to define a framework for the approval of more targeted therapies, by developing and publishing new guidances, communications that represent the agency’s current thinking on the subject. Recently published guidances and others in development have been created to help industry incorporate the concepts of personalized medicine into the needs of drug development, and then leverage that information to make decisions about patient selection or clinical trial designs in later phases of drug development, said Zineh.

The FDA published draft guidance on pharmacogenetics in early development in February 2011 and was, at the end of 2012, working to finalize that guidance. It is also worked to develop guidance on "enrichment strategies" for late-stage drug development, including a genomics component as one type of enrichment and has released a draft policy and definitional guidance on companion diagnostics, a document in the process of being finalized at the end of 2012.

To further its efforts to expand the regulatory resources in place to review personalized medicines, the agency convinced stakeholders to support increased staff at the CDER to review and develop guidance in the area of personalized medicine. The proposal also includes a provision for holding a public workshop to explore how FDA, industry, external scientists, and consortia can interact in a more flexible way to advance biomarker science, pharmacogenomics, and other areas critical to personalized medicine.

Powering up device reviews

The medical device industry also negotiated a crucial renewal of its own set of user fees and commitments as part of the FDASIA. The medical device category includes a wide range of products that are used to diagnose, treat, monitor, or prevent a disease or condition in a patient. Provisions of the third reauthorization of the medical device user fee program, the Medical Device User Fee Amendments of 2012, grant the FDA authority to collect a total of $595 million in user fees from medical device makers to support the review of those devices between 2012 and 2017, plus adjustments for inflation, doubling the $287 million collected during the previous five years.

The outline of MDUFA III was first established in February 2012, after more than a year of negotiations between the FDA and industry. Companies submitting medical devices for clearance to the FDA wanted the agency to be more transparent, predictable, and accountable. To reach those goals, MDUFA incorporates a more structured pre-submission process and a "leave no submission behind" provision, requiring FDA to meet with companies to create a plan for completing work on the submission if a performance goal on a pre-market application or 510(k) is missed. Additional applicants will now get a mid-cycle opportunity to meet with agency reviewers, giving them a chance to respond to any questions that arise early in the review process [See Figure 5.4].

The new funding was projected to cover FDA’s hiring of more than 200 new human resources by the end of the five-year program in September 2017. Additional human resources will be important if the agency is to reduce the average total length of its reviews, a goal at the heart of the program since the Medical Device User Fee and Modernization Act of 2002. Even though the FDA met all its medical device performance goals for 510(k), according to a February 2012 report from the GAO, the elapsing time from submission to final decision has increased substantially in recent years. [Figures 5.6 and 5.7]

Medical device makers have generally been less satisfied with FDA’s iterative improvement to its review processes than the biopharmaceutical industry has been. To improve the

The new user fee program was sought by the generics industry to solve the FDA’s backlog of generic drug submissions, which had reached 2,500 applications by April 2012.
The guidance, which finalized an August 2011 draft, outlines the systematic approach to regulating the sector during 2012 with the release of draft guidance. In March 2012, the agency published what it described as a “first-of-a-kind” guidance for medical device manufacturers, listing the factors it uses in evaluating the risks and benefits of medical devices during pre-market reviews.

Premarket approval is the FDA’s process for evaluating the safety and effectiveness of the highest-risk medical devices it reviews: those that support or sustain human life, are of substantial importance in preventing impairment of human health, or which prevent a potential unreasonable risk of illness or injury, typically called Class III devices. The agency’s de novo process is available for low- and moderate-risk devices that it finds aren’t substantially similar to existing devices.

The guidance, which finalized an August 2011 draft, outlines the systematic approach that FDA device reviewers take when making benefit-risk determinations during the pre-market review process, providing manufacturers a tool to explain the principal factors considered by the agency during the review of pre-market approval applications, and delineates the regulatory pathways for high-risk and novel, low- to moderate-risk medical devices. It describes an approach that “takes into account patients’ tolerance for risks and perspectives on benefits, as well as the novelty of the device,” the agency said. “This guidance clarifies this process for industry, which will provide manufacturers with greater predictability, consistency and transparency in FDA decision-making while allowing manufacturers and the FDA to use a common framework for benefit-risk determinations,” said Jeffrey Shuren, director of FDA’s Center for Devices and Radiological Health.

While medical device makers received new clarity from the FDA, they also got something they didn’t want from the Affordable Care Act—a new tax. The 2.3 percent excise tax on sales, one part of a package of new revenue sources meant to fund the act, took effect starting January 1, 2013, on nearly all FDA regulated medical devices, with few exceptions. It applies equally to imported and domestically produced devices. Devices produced in the United States for export are tax-exempt.

From the very start, the tax became the subject of tremendous industry backlash, with the Advanced Medical Technology Association, commonly known as AdvaMed, raising concerns that the tax would damage innovative start-up companies, threaten tens of thousands of jobs, and unfairly burden medical device makers. AdvaMed, together with Ernst & Young estimated in November 2012 that the tax would add another 29 percent per year in taxes to the amount the medical device industry already pays in federal income tax. Medical technology companies would pay about $8.7 billion in overall federal income taxes in 2013, and based on estimates from Congress’s Joint Committee on Taxation, the device tax would add another $2.5 billion to that tab, according to the report.

“A dramatic tax increase on a job-creating industry like medical technology makes no sense,” said Stephen Ubl, president and CEO of AdvaMed and a leading voice in urging Congress to repeal the tax. “A tax bill this big will only lead to fewer jobs, reduced investment in tomorrow’s treatments and cures, or higher health care costs for the consumer,” he said. The Congressional Budget Office has projected the tax would collect $20 billion during the temporary period it will be in force.

The Joint Committee on Taxation has estimated that repealing it would cost $29 billion over the 2013-2022 period. AdvaMed, with the Medical Device Manufacturers Association and the Medical Imaging & Technology Alliance, in November launched a major lobbying push urging Congress to repeal the tax. While the House had voted to repeal the tax, the group had not yet convinced the Senate by the end of 2012.

**Safety concerns emerge in Europe**

European markets presented their own special headaches for medical device makers. Driven first by the scandal over ruptured breast implants and metal-on-metal hip joint replacements, concern about the device industry in general grew in Europe throughout the early part of 2012. “Just a few months ago, everybody was shocked by the scandal involving fraudulent breast implants which affected tens of thousands of women in Europe and around the world,” said John Dalli, the European Union’s Health and Consumer Policy Commissioner in September 2012. “As policymakers, we must do our best never to let this happen again. This damaged the confidence of patients, consumers, and health-care professionals in the safety of the devices on which they rely every day.”

To improve the safety profile of the industry, the European Commission put together a package on innovation in health, the European Medical Device Directive, consisting of proposals to revise the European Union’s regulatory framework for medical devices. The package included a wider and clearer scope for EU legislation, extending it to include, for example, implants for aesthetic purposes. It also sought to grant national regulatory authorities more power to supervise and assess medical device manufacturers and collect better data on the medical devices available in Europe to support better traceability of devices throughout the supply chain and enable a swift and effective response to safety concerns when they arise. Though not a ground-shaking departure from existing EU guidance, the new regulations do propose stron-
ger controls on medical devices in Europe, while stopping short of implementing the sort of pre-marketing authorization system governing new therapeutics.

Under Commission guidance, three directives—one on active implantable medical devices, a second on other medical devices, and a third on in vitro diagnostic medical devices—will be replaced by two regulations to be implemented in national laws throughout Europe: one on medical devices and one on in vitro diagnostics.

"Importantly, the Commission will be directly or indirectly involved in all stages of the marketing of new devices," said Covington & Burling’s European food and drug practice group. For new applications for high-risk devices in particular, national regulators will have to notify the medical devices coordination group of any new applications for high-risk medical devices. The group, formed of representatives of European member states that can advise and assist the Commission, could then request national regulators’ preliminary reviews before issuing its own certificate of approval.

European medical device sales generated an estimated 81.5% of $21.5 billion (€95 billion) in 2009, the most current data available, according to Eucomed, a pan-European industry trade group. But while Eucomed welcomed most of the recommended measures in the European Medical Device Directive, it said that the proposed "scrutiny procedure" would fundamentally change the current system. "The measure would address some political calls to move the European food and drug administration’s approach to reviewing biosimilars will take the form of a two-step process. "Companies first will submit analytic data showing how similar their compounds are to an FDA-approved innovator version. The agency then will determine, on a case-by-case basis, how much animal and clinical data are required for approval," Rachel Behrman, Associate Director for Medical Policy in the Center for Drug Evaluation and Research said during an interview on BioCentury This Week.

Behrman’s comments lend insight into the agency’s thinking about the new pathway. Starting with an assumption that approved biologics are already safe and effective, Behrman said that the agency will be looking for data establishing that biosimilars submitted for approval have the same effect in patients without illustrating clinically meaningful differences.

Once biosimilarity is established, companies could then pursue a second step of review to establish interchangeability, a designation that would allow for the automatic substitution of a biosimilar in place of an already approved biologic. Representatives of biopharmaceutical companies, during hearings in May 2012 intended at helping fine tune the agency’s recently issued draft guidance on biosimilars, urged the FDA to tread cautiously. "Though industry representatives expressed concern about safety related issues, underlining their warnings to the agency were worries about the extent to which biosimilar regulations will open the door to new competition for their products after patents on them have expired," Sandoz, the generics division of Novartis, used the occasion to urge the agency to establish "a single science-based regulatory standard that FDA should apply across all biologics, irrespective of the business model of the sponsor."

Mark McCamish, head of the company’s global biopharmaceutical development spoke in support of abbreviated clinical trials and scaled-back testing for biologics proven to be "highly similar" to the original biologic they mimic.

Companies seeking the approval of biosimilars will have to pay fees to support the reviews.

**Figure 5.7** Authorized Biosimilars in Europe

<table>
<thead>
<tr>
<th>COMPANY</th>
<th>PROPRIETARY NAME</th>
<th>ESTABLISHED NAME</th>
<th>THERAPEUTIC AREA</th>
<th>DATE APPROVED</th>
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</thead>
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<td>filgrastim</td>
<td>Cancer</td>
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<td>Zarzio</td>
<td>filgrastim</td>
<td>Cancer</td>
<td>2/6/2009</td>
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<td>filgrastim</td>
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<td>9/15/2008</td>
</tr>
<tr>
<td>Ratiopharm</td>
<td>Ratiograstim</td>
<td>filgrastim</td>
<td>Cancer</td>
<td>9/15/2008</td>
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<tr>
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<td>Tevagranst</td>
<td>filgrastim</td>
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<td>9/15/2008</td>
</tr>
<tr>
<td>Hospira UK</td>
<td>Retacrit</td>
<td>epoetin zeta</td>
<td>Anemia</td>
<td>12/18/2007</td>
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<tr>
<td>Stada Arzneimittel</td>
<td>Silapo</td>
<td>epoetin zeta</td>
<td>Anemia</td>
<td>12/18/2007</td>
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<tr>
<td>Medice Arzneimittel Pütter</td>
<td>Abzeamed</td>
<td>epoetin alfa</td>
<td>Anemia</td>
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</table>

Source: European Medicines Agency
Naming conventions, a hot topic because of its potential sales impact, were also addressed. Amgen’s Joseph Miklich, the company’s senior vice president of R&D, argued for the idea of using unique names for biosimilars rather than calling them by the same established names used by innovator products. Using identical names would make it easy for pharmacists and payers to substitute biosimilars for prescribed reference biologics, but could also make competition tougher for innovators by making it harder to distinguish between a reference biologic and its biosimilar competitor. “Distinctive product names,” he said during his testimony, “facilitate manufacturer accountability and avoid incorrectly implying that the molecules are identical.”

The Alliance for Safe Biologic Medicines, a biosimilars-focused umbrella group representing members including the American Academy of Dermatology and Genentech, also addressed the naming issue, arguing for “traceability measures,” including unique nonproprietary names for all biologic therapies. The Alliance’s chair, Richard Dolinar, also argued for “recognition that the similarity between the reference product and its interchangeable biologic product(s) may change over time as a result of manufacturing or environmental labeling a biosimilar as ‘interchangeable.’” Interchangeability—a status that would allow biosimilars to be substituted for innovator therapeutics, just as generics are often provided in place of branded small molecule drugs—was a hot topic at the hearing. The underlying message by most presenters was that biologics are complex and that the FDA should set a high bar when it eventually designates certain biosimilars as interchangeable with their reference products [See Figure 5-2].

Sara Radcliffe, executive vice president of health at BIO, addressed one more issue important to innovator companies: keeping an innovator company’s confidential commercial and trade secret information protected from intentional or inadvertent use or disclosure in the review and approval of biosimilars. The FDA is likely to continue to adapt its approach to biosimilars as it moves ahead to review applications that employ the new biosimilars pathway. But how eager companies will be to use that new pathway remains to be seen. In August 2012, Teva’s U.S. unit Sicor Biotech sought and got approval from the FDA for Tho-filgrastim, a drug that is marketed as a biosimilar in Europe. In the United States, Tho-filgrastim was approved in an original biologics license application, not as a biosimilar to Neupogen (filgrastim), a product that contains “a related drug substance,” said the FDA.

China readies for biosimilars

China moved to develop its regulatory framework for the development of biosimilars too, part of its plan to meet a demand for biologics that will only grow as the country implements its national healthcare reform and insurance programs. The guidelines, which will draw from U.S. and European rules on biosimilars, are expected to further improve regulations on technical requirements and the quality control of biologics to streamline the approval process. The effort is part of China’s State Food and Drug Administration’s attempt to speed up drug registration and harmonize the nation’s drug standards with global rules. The SFDA, according to BioPharm Insight, planned to release a new Drug Registration Regulation after the 18th National Congress of the Communist Party in November 2012. While domestic biosimilars have been on the market in China for 20 years, according to the SFDA’s Southern Medicine Economic Research Institute, growing demand for specialty drugs will create new opportunities for biosimilars, the institute’s vice president, Jian-houng Tao, told BioPharm. Already, biologics and biosimilars account for 10 percent of the

Obama Administration Sets Bioeconomy as Priority

Plan is welcomed by industry, but short on details

At the end of April 2012, the Obama administration released its National Bioeconomy Blueprint, a 43-page policy statement from the White House that sought to spell out the important role it sees biotechnology playing in building the future economy and generating desirable jobs. While welcomed by the industry, the plan delivered few details about what steps the administration will actually take to realize the future it envisions.

“The bioeconomy has emerged as an Obama Administration priority because of its tremendous potential for growth, as well as the many other societal benefits it offers,” the blueprint said. “It can allow Americans to live longer, healthier lives, reduce our dependence on oil, address key environmental challenges, transform manufacturing processes, and increase the productivity and scope of the agricultural sector while growing new jobs and industries.”

In broad terms, the blueprint outlined five strategic imperatives it said are necessary to drive the bioeconomy. This includes supporting R&D investments, improving commercialization of bioinventions, reducing regulatory barriers, updating training to meet new workforce needs, and forging public-private partnerships that build the bioeconomy.

But rather than provide a true blueprint of specific initiatives or funding that can be used to construct a bioeconomy, the document gathered disparate initiatives already underway through various departments and programs to make the case that the administration was already working toward a grander vision of the economy’s future. The efforts highlighted range from the U.S. Department of Agriculture and the U.S. Department of Energy’s biomass program, which committed up to $30 million over several years to support R&D in advanced biofuels to the National Institutes of Health’s National Center for Advancing Translational Sciences, which launched in December 2011.

The document lacked the clear commitment of China’s 12th Five Year Plan, ratified in March 2011, which called for $300 billion to be invested in the biomedical sector between 2011 and 2015. It also lacked the coherence and specificity of the European Commission’s February release of its Bioeconomy Action Plan for Europe, a document accompanied by a detailed action plan that spells out specific steps to be taken to invest in, build, and enhance the European bioeconomy.

The Biotechnology Industry Organization welcomed the blueprint and called it “a testament to the Administration’s commitment to spurring 21st century innovation and ingenuity.” But when laid alongside the trade group’s June 2011 five-year policy agenda for growing the bioeconomy, Unleashing the Promise of Biotechnology, it reveals a significant disconnect between how government and industry view what’s needed to bring it about.

BIO’s five-year agenda called for a very specific set of policies to minimize the high level of risk faced by investors in the sector. Because of the expense, risk, and long-term commitment it takes to commercialize bioinventions, it argued that incentives are needed to unleash needed private capital necessary to realize the promise of biotechnology in health, agriculture, and industrial applications.

The BIO agenda also focused a great deal of attention on specific tax policy changes needed to incentivize private investment in the sector such as angel investor tax credits, new R&D partnership structures that provide investors an opportunity to offset income with partnership losses on a tax basis, matching grants for private funding, special capital gains treatments for investments in small biotech companies, and providing a tax holiday for repatriated investments in small biotech companies.

“The White House made a good start, but what we find is that the administration, as reflected in this blueprint, tends to focus on government programs,” said Jim Greenwood, CEO of BIO, pointing to initiatives underway at the FDA and NIH, and the administration’s focus on science, technology, education, and math education initiatives. “What we are focused on, of course, is the private sector side, and we are constantly trying to encourage the administration to recognize that we need policies that are going to drive investors toward our sector. That’s about FDA policy, but that’s about tax policy as well.”
total pharmaceuticals market in China, but their recent annual growth rate has reached 32.2 percent, according to Deloitte. Domestic enterprises welcome the introduction of biosimilars guidelines, which can reduce the cost and duration of clinical studies, said Guozhong Rui, director, China Pharmaceutical Technology Transfer Center. Current regulations state that companies are required to conduct phase 3 trials for all biosimilars, he noted.

Dulling the competitive edge

Although the United States has led the world in biomedical research and innovation for the past century, its leadership continued to be under pressure in 2012, as countries around the world embraced biomedical innovation as a source of economic growth and U.S. government policy became less consistent and predictable, according to two new reports. Two studies, commissioned by advocacy groups worried that the government’s increasing austerity measures will have a lasting impact on biomedical innovation, show that America’s competitive advantage in biomedicine is narrowing with respect to countries around the world that increasingly view investing in the sector as an important way to boost their economies for the long term.

The first report from Battelle Technology Partnership Practice, commissioned by PhRMA, examined 18 countries that are focused on boosting biomedical research and development through pro-innovation policies and programs as a major component of their economic growth strategy. Countries selected include a mix of developed countries with existing biopharmaceutical presence (Australia, Canada, France, Germany, Ireland, Israel, Italy, Japan, Sweden, and the United Kingdom) and emerging countries that are targeting the sector for new growth (Brazil, Chile, China, Russia, Saudi Arabia, Singapore, South Africa, and South Korea).

These countries are increasingly seeking to make substantial public investments in R&D infrastructure, fostering R&D investment via tax and other research incentives, focusing on attracting and growing talent in related employment fields, ensuring access to capital, and fostering public-private partnerships. At the same time, many of them are cutting public expenditures, even as they continue to expand government policy steps to counter these efforts, such as progressing the Trans-Pacific Partnership, implementing intellectual property incentives like the 12 years of data protection for innovator biologics, and establishing a permanent R&D tax credit could place the United States’ global leadership in medical innovation at risk, said PhRMA CEO Castellani.

A U.S. policy framework to help counter these efforts would provide regulatory certainty, ensure patient choice and access to medicines, and incentivize future research and development, he said. “Without a national biomedical innovation agenda, we’re not pitting America up against other countries—we’re pitting our states up against like-minded foreign governments,” said Castellani. “So states with vibrant biopharmaceutical research clusters, like North Carolina and Massachusetts, aren’t just competing with each other. They’re competing with countries like Singapore.” According to Battelle, the U.S. biopharmaceutical sector is a large contributor to the economy, with more than 650,000 direct jobs (supporting a total of nearly 4 million jobs) and an economic output that totals more than $900 billion. The sector also accounts for nearly 20 percent of all research and development investment by businesses in America. Beyond jobs, the sector has brought more than 300 new medicines to the patients who need them.

A separate report by The Information Technology and Innovation Foundation, a Washington, D.C.-based think tank, examined the role publicly supported innovation through the National Institutes of Health has played in the United States’ leadership in biomedical innovation, and it makes the case that this support needs to be increased if the country is to remain competitive globally. The study was commissioned by United for Medical Research, a group that advocates for NIH funding. The report argues that the United States’ leadership position is under threat from intensifying global competition from countries such as China, Germany, Singapore, Sweden, and the United Kingdom, all of which have been expanding their financial support for biomedical research and enacting policies to bolster the sector.

Despite increases to the NIH budget, the report notes that NIH has seen its annual budget decrease every year since 2003 in terms of inflation-adjusted dollars and as a share of GDP. As a consequence, there has been a sharp decline in the success rate of applications for investigator-initiated basic research grants at the NIH. In addition, the increasing pool of more senior investigators has pushed average age of grantees at the time they receive their first award to 42 in 2005 from 34 in 1970, “Maintaining our competitive edge in a globalized, 21st century economy will require us to make a renewed and strengthened commitment to public investment in biomedical research,” said Carrie Wolinetz, president of United for Medical Research. “We cannot afford to fall behind our international competitors as they attempt to emulate our past success.”

The budgetary challenge ahead

Budgetary pressures in Washington are putting pressure on the U.S. Food and Drug Administration’s budget just as Congress has asked the agency to expand its role. In passing FDASIA into law, Congress has given the FDA more FDA inspectors closer to drug manufacturing hotspots, such as India and China.

But government budget projections of FDA revenue plunged to 15 percent of GDP in 2009 and remained at 15 percent through 2011, the lowest levels in decades. While spending to support Medicare and Medicaid is required, the FDA’s budget falls under the category of discretionary spending, which is set by Congress through

Figure 5.8

U.S. SHARE OF NEW ACTIVE SUBSTANCES FIRST LAUNCHED ON THE WORLD MARKET

U.S. share of new active substances (NAS) first launched on the world market

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### Figure 5.9 New Molecular Entities and Biologics Approved in 2012*

#### Drug Designation Summary
- **First in Class:** New and unique mechanism of treatment
- **Orphan Drug:** For small populations of patients with rare diseases
- **Fast Track:** Treating unmet medical conditions
- **Priority Review:** Target review of six months instead of ten
- **Accelerated Approval:** Early approval based on markets that predict benefit
- **Met PDUFA Target Date:** Meets Prescription Drug User Fee Act dates for review
- **First Cycle:** Approved without request for additional information
- **First Approved in U.S.:** First in the U.S. before any other country

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<td>taluprost</td>
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*Includes New Molecular Entities and Biologics approved by the FDA’s Center for Drug Evaluation and Research

**elvitegravir, cobicistat, emtricitabine, tenofovir

Source: Burrill & Company, FDA
Pharma 2020 Plan Boosts Industry in Russia

Legal and regulatory frameworks are evolving to keep pace

As Russia moved to develop an economy that was less dependent on the production of oil, gas, and other natural resources, it struggled with an unregulated healthcare system, unhealthy lifestyles, and low domestic and foreign investment. In order to enhance long-term investments and technological progress, the government developed roadmaps to advance a broad array of high tech pursuits, medical technology and pharmaceuticals development among them.

One of the roadmaps that emerged from then Prime Minister Vladimir Putin’s push, the Pharma 2020 strategic plan, is driving rapid development of the pharmaceutical sector. At the same time, legal and regulatory frameworks are evolving rapidly to keep pace especially as its ascension to the World Trade Organization in August 2012 opened up economic opportunities for multinational companies.

On the legal front, as the newly-elected Russian president, Putin signed into law in July 2012 legislation bringing Russia’s trading laws into compliance with the international standards set under the World Trade Organization. As part of Russia’s ascension to the WTO, the country’s trade and intellectual property laws are being brought into compliance with international standards set forth in the Trade-Related Aspects of Intellectual Property Rights agreement, more commonly known as TRIPS. The agreement covers a wide range of subjects, from copyright and trademarks, including patents for pharmaceuticals.

The intellectual property protections afforded by TRIPS are made all the more important because as part of Pharma 2020, international pharmaceutical companies entering the market will have some obligation to conduct some or all of their manufacturing for the domestic market in Russia. Already, Bayer and Novartis have invested in upgrading existing manufacturing facilities and building new manufacturing plants in Russia to comply the plan.

In implementing the first stage of the Pharma 2020 strategy, the government has focused on construction of new production sites and ensuring harmonization with global good manufacturing practices, improvements in quality control, educational and professional training programs, and adoption of necessary legislation, such as implementation of an anti-corruption measure.

The government has also sought to address areas of competitive concern. Igor Artemiev, head of the Federal Antimonopoly Service, discussed in November 2012 the modernization of Russian competition legislation that had just been completed and that included a reform to its goals, later that month the FAS called out frequent findings of “outrageous” differences in prices for similar drugs in the same presentation and dosage, that it said is the result of the absence of competition.

The FAS identified the problems preventing competition in the domestic pharmaceutical sector as stemming from unregulated drug substitutability and non-transparent, controversial procedures for drug registration. Taken together, the factors create what FAS said was an “environment conducive to anticompetitive cooperation of unfair market participants at all stages of drug circulation, aimed primarily against consumers and the state budget, resulting in high drug prices.”

It noted that global experience had shown that Russia’s traditional administrative command methods of problem solving and supporting drug affordability by increasing budget allocations was inefficient. “Even rich countries cannot make drugs affordable for most of the population without developing competition and establishing strong surveillance supporting the basic conditions and requirements for bona fide drug production and conduct of all market participants,” FAS said.

“We all live in an increasingly globalized world. We (should) make sure we’re adequately positioned for the challenges of today, tomorrow, and the future. Science must be the critical tool in our decision-making.”

Margaret Hamburg, FDA Commissioner

Russian president

Advancing Technology

Because global healthcare systems struggle to meet the challenges of aging populations, rising costs, and the growing threat posed by chronic diseases, they are struggling with the uncertainties created by an ever more costly and complex medical landscape. These forces are driving demand for greater transparency, accountability, and flexibility in regulation. Medical regulatory authorities that have in the past focused primarily on safety and efficacy are finding that solutions to today’s cost crunch increasingly demand their expertise. Whether they are called upon to streamline the bureau-
drugs to submit fewer drugs to regulatory approval earlier and more deeply into product development.

The rise of comparative effectiveness efforts, such as NICE’s make-or-break assessments and the hint of the potential for similar efforts to emerge in the United States, is concerning to drugmakers. The establishment of the Patient-Centered Outcomes Research Institute in the United States has worried industry. “If you took a time machine and went back 15 or 20 years, you would be in a world in which if you produced a better technology for treating a disease, a better drug, or a better device, your path to market was a time machine and went back 15 or 20 years, you would be in a world in which if you produced a better technology for treating a disease, a better drug, or a better device, your path to market was very clear,” said California Healthcare Institute president and CEO David Gollaher. “Today that’s not true. You need to not only establish superiority, but market superiority, and show how you fit into the cost mosaic of medicine.

In both Europe and the United States, Gollaher said, policymakers are putting drugs and devices through a tight screen to see whether they’ll be covered and what the levels of payment will be. That’s only going to worsen as the debt crisis both in the European Union and United States puts more and more pressure on public payers to figure out how to contain their budgets.

The interplay between regulatory and pricing policies has never been so dynamic. Post-approval determinations, such as those made by NICE and Germany’s Institute for Quality and Efficiency in Health Care, are all altering pharmaceutical development strategies. “The devil is in the details,” said Steve Arlington, global pharmaceutical and life sciences advisory leader at PriceWaterhouseCoopers. “Our view is that one needs to be able to prove health economic benefit of a new biologic or a new drug when you bring it out onto the marketplace. And, in order to do that, one needs to have data generated during the development cycle of the drug.” He said that drugmakers will need to ensure they collect data that demonstrates health economic benefits which is linked to a positive patient outcome. That will lead drugmakers to not only change the way they conduct R&D, and collect data, but also the ways in which they work with payers, providers, patients, and regulators.

As a result, companies are working more closely than ever with payers and policymakers to define which trials will be necessary to obtain not only approval, but also reimbursement and good pricing. “It is not good enough for healthcare systems, for organizations like NICE to say, ‘Well, wouldn’t it be nice if you’d have done it this way?’” said NICE’s founding chief executive, Andrew Dillon, during a briefing organized by the Alliance for Healthcare Reform in November 2011. Rather, said Dillon, it’s more desirable for pricing bodies like NICE and regulators to talk to companies early to help them identify and design trials to generate the data necessary to make judgements in the review process.

“To prove health economic benefit of a new biologic or a new drug when you bring it out onto the marketplace… one needs to have data generated during the development cycle of the drug.”

Steve Arlington
Global pharmaceutical and life sciences advisory leader, PriceWaterhouseCoopers
Global Markets

As the world moves toward becoming an interconnected, borderless marketplace, opportunities are growing for companies to leverage specific geographical markets, national economic growth incentives, diverse local customs, and regulatory regimes as a means to successfully achieve their goals. Governments around the world see the importance of investing in the life sciences to build innovation-based economies that can provide high quality jobs and transform their societies for the better, especially amid the austere economic times and global problems facing the world today.

The challenge for innovative companies is to understand and be able to take advantage of opportunities when and where they arise. Those that succeed are poised to reap huge rewards for their efforts, both in monetary terms, and in terms of improved human health and welfare.
CHAPTER 6:
The Geography of Value
Leveraging global opportunities

Governments around the world are stepping in to advance life sciences in their countries to boost their economies and address the growing healthcare needs of their citizenry. In some emerging countries, such as Russia and China, the government is actively participating in funding startups and investing in new technologies that can be brought into their country, developed locally, and adapted to address unmet needs, and add new fuel to their growing economies [See Figure 6.1]. In other places, such as in Europe and the United Kingdom, regional organizations have formed investment funds to attract startups and strengthen their economies. While the developed world continues to be an important source of innovation and business opportunity, life sciences companies in more advanced economies, China, for example, has set ambitious targets to ramp up its innovation capability, and has targeted biotechnology as a strategic pillar for growth under its 12th Five-Year Plan. The plan aims to double biomedical R&D innovation funding from the previous Five-Year Plan’s $300 billion and seeks to provide basic healthcare services to at least 90 percent of its 1.3 billion citizens by 2020.

In July 2012, CompanyX, a U.K. diagnostics startup, raised $8.1 million (59.6 million RMB) from the Chinese government and private investors to develop and commercialize its products in China. The investment is non-dilutive. Instead of taking an equity stake in the startup, investors will be eligible for a percentage of any revenue from commercialized products sold in China.

Based in the biotech incubator BioCity Not-
tingham, the 2009 spinout from Nottingham Trent University applies proprietary bioinformatics technology to advance personalized medicine. Originally offering support services for research on a fee-for-service basis, CompanDX in 2012 refocused its business beyond oncology to wider applications in personalized medicine for all major indications.

The company said the Chinese investment would speed up its product development due to the regulatory climate in China and the willingness of major regional science parks there to provide funding for accelerated development of products relevant to the Chinese marketplace. CompanDX planned to establish an office in China shortly after receiving the funding and expects to generate revenue from approved products in less than three years.

"The recent paucity of early-stage funding in our sector has stifled expansion and potential growth for companies at a critical stage of their development, but CompanDX has shown great initiative in sourcing finance this way," said Glenn Crocker, CEO of BioCity Nottingham. "Several of our other fast-growing companies could learn from this model, so we will watch the CompanDX development with interest."

Life sciences companies, such as CompanDX, are finding that the value of their technology can vary by geography, and what may have marginal value in a developed market where healthcare providers have many competing choices, may have much greater value in emerging markets with unmet needs that are hungry for new technologies.

**Value determined by clinical practice**

Sometimes a company can create value depending on the market it chooses to enter. **Taiwan Liposome Company** developed a technology that can create what it calls "super generics," reformulations of existing drugs with better pharmacological properties. The startup, based in Taiwan and San Francisco, first approached potential investors with plans to commercialize its technology in the United States. But the U.S. market for its lead product was small, given a choice, doctors in the country could prescribe a wider range of products for the indication, even if they carried a greater risk of side effects. In Asia, where there are fewer prescription drug choices, doctors transitioning from traditional medicines to Western drugs are more likely to prescribe the one with the least side effects. This difference in clinical practice created a huge potential market for the young biotech.

Taiwan Liposome Company has grown, and currently has several products in clinical trials. The company is now working on reformulations aimed at Western markets, and has set up an office in The Netherlands ahead of seeking marketing approval there. It has also attracted the attention of several large pharmaceutical companies, signing collaborative agreements with companies including Hidong Pharmaceutical of South Korea and Teva Pharmaceuticals of Israel. Taiwan Liposome listed on the Taiwan Stock Exchange in 2011 and completed a successful IPO in December 2012 with shares almost doubling in value in the first month of trading [See Figure 6.4]. Burrill & Company, publisher of this report, is an investor in the company.

**Partnerships of convenience**

In some cases, early-stage biotechs are able to get partners in emerging markets to fund clinical development and still retain rights to those products outside of those markets. In other cases, partners can help companies leverage an asset that they may be ill-prepared to commercialize in an emerging market, or help them use market demands in those countries to accelerate the development and cut the cost and risk of bringing those products to market in developed countries.

**Cleveland BioLabs** strategy is to create separate, independently funded entities to develop a broad pipeline of drug candidates and allow the company to move multiple drug candidates forward, with separate management teams focused on smaller sets of goals. While its treatment for radiation syndrome has shown positive results and is currently in pivotal trials, the company had many other compounds in its pipeline for...
which it wanted to accelerate the development process. So it looked outside the United States to Eastern Europe and Asia, where it felt it could get its drugs to market sooner.

In 2010, Cleveland BioLabs found funding and partners in Russia for its anticancer therapies based on drug candidates of the curaxin family, forming the joint venture Incuron with Bioprocess Capital Ventures, a Russian government-backed venture fund that contributed $18 million. Cleveland BioLabs contributed two curaxins for oncology and orphan indications, taking a 75.8 percent stake in the Russia-backed startup.

“This investment will enable us to support curaxin development through advanced human trials,” said Cleveland BioLabs president and CEO Michael Fonstein, when the joint venture was launched. In April 2012, Incuron was given permission by Russian regulatory authorities to conduct early stage human trials in Russia in an oral formulation of one of the compounds in projects that are being initiated at the center, one to identify previously unknown cancer pathogens that will lead to the development and patenting of commercial vaccines and the other to establish a catalogue of genetic variations in Danish people that can be used for new studies into the hereditary causes for a number of common diseases, as well as their treatment and prevention.

In February, BGI also teamed up with the Asia Cancer Research Group to conduct genomic research on lung cancer and liver cancer, two of the most common cancers in Asia, in order to speed the discovery and development of new treatments. The Asia Cancer Research Group was established in 2010 as an independent, not-for-profit, company by Lilly, Merck, and Pfizer in order to accelerate research and ultimately improve treatment for patients affected by the most commonly diagnosed cancers in Asia by freely sharing data with the scientific community.

BGI’s purchase of U.S. sequencing company Complete Genomics for $118 million would be the first acquisition of a publicly traded U.S. company by a Chinese firm.

**Figure 6.5**  **Innovation Performance in Emerging Economies**

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<th>Innovation Indicators</th>
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<th>Columbia</th>
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Source: Charles River Associates, Policies that Encourage Innovation in Middle Income Countries, 2012

**GLOBAL EXPANSION PLANS**

**BGI Partners to Advance Genomics Research**

Rise of sequencing powerhouse mirrors China’s innovation ambitions

China’s BGI continued its partnering activity in 2012 as it aims to be a major force in genomics and bioinformatics, opening a new research center in Europe, researching cancers prevalent in Asia, and collaborating to sequence genomes of children with rare diseases.

BGI is emblematic of China’s growing status in biomedical innovation. The world’s largest genetic sequencing company got its start as Beijing Genomics Institute in 1999 to help on the Human Genome Project. At the time, it was the only research organization in a developing nation to contribute to the project. Subsequent to this, BGI gained worldwide attention for its work in sequencing the rice genome. It also got funding from China’s government and other governments and private foundations, giving Russia access to not only product candidates, but also global pharmaceutical expertise. Both ventures reflect ongoing efforts by the Russian government to strengthen its pharmaceutical industry, which it sees as an important driver of economic growth. [See Figure 6.5]

In February, BGI also teamed up with the Asia Cancer Research Group in order to accelerate research and development of new treatments. The Asia Cancer Research Group was established in 2010 as an independent, not-for-profit, company by Lilly, Merck, and Pfizer in order to accelerate research and ultimately improve treatment for patients affected by the most commonly diagnosed cancers in Asia by freely sharing data with the scientific community.

In February 2012, BGI officially opened its first European Genome Research Center in Copenhagen, Denmark. The center’s primary mission is to provide BGI’s expertise and infrastructure to European researchers in genomics, proteomics, bioinformatics and other related areas, said Ning Li, director of BGI Europe. The center also will strive to cultivate joint collaborations between China and Europe, he said.

Denmark’s National Advanced Technology Foundation is supporting two integrated

 projects that are being initiated at the center, one to identify previously unknown cancer pathogens that will lead to the development and patenting of commercial vaccines and the other to establish a catalogue of genetic variations in Danish people that can be used for new studies into the hereditary causes for a number of common diseases, as well as their treatment and prevention.

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BGI also teamed up with the Children’s Hospital of Philadelphia in June to sequence 1,000 rare diseases with the aim of accelerating the discovery of their genetic variants. The 1,000 Rare Diseases Project will cover diseases that affect both children and adults, employing next-generation sequencing technologies and analysis to lay a solid genetic foundation for future clinical diagnosis and treatment.

Under the collaboration agreement, BGI and CHOP will use next generation sequencing technologies and bioinformatics to analyze well-characterized DNA samples from patients and families with single-gene inheritance patterns. “The BGI/CHOP collaboration is an ideal partnership,” said Hakon Hakonarson, director of the Center for Applied Genomics at CHOP and co-director of the new BGI@CHOP Joint Genome Center. “This will undoubtedly facilitate rapid and accurate diagnosis of rare diseases and lead to new therapeutic interventions.”
Russia Builds High-Tech Parks
Effort brings together industry, academia, and investors

Russia has invested energy and capital into building its technological capacity, specifically by backing the creation of several high-tech science parks that bring together universities, companies, and investors to foster science innovation.

The Skolkovo Institute of Technology, research centers of top level corporations, and high-tech startups and venture investors are part of the Biomedical Cluster, one of the center’s five priority areas, which also include cleantech—energy conservation and renewable energy technology, telecommunication systems and navigation systems, and nuclear technology and new materials. The goal is to develop and commercialize new technologies by tapping into global expertise to advance domestic innovation and competence. Companies that choose to participate can receive significant tax benefits because Skolkovo operates as a tax-free economic zone.

The Biomedical Cluster has established partnerships with leading academic institutions including Harvard Medical School, the Weizmann Institute of Science, and the European Molecular Biology Laboratories among others. Johnson & Johnson and Janssen Pharmaceutica are among more than 100 companies that have already joined the center. Incubating startups is an important part of Skolkovo, which has set aside significant amounts of non-dilutive funding for these companies.

Grants of up to $150,000 support seed stage capital, after which Skolkovo expects co-investment by venture and private investors. By December 2012 more than 700 companies had become Skolkovo residents and the Foundation had approved 170 non-dilutive grants totaling $260 million with third party co-financing of more than $190 million. The average grant amount was $1.7 million.

A second regional center, ChemRar, came into existence in 1990 essentially as a contract organization providing services to the pharmaceutical industry. The company moved into performing more and more R&D work, culminating in 2007 when in collaboration with the Federal Science and Innovation Agency, it began a three-year, jointly financed project to develop new clinical candidates for the treatment of infectious diseases, called Intellectual Dialog, which was set up at the Yaroslavl State Pedagogic University. One year later it created ChemRar Ventures to incubate early-stage pharmaceutical innovation. Two startups formed by ChemRar have in-licensed compounds for development in Russia: SatRx licensed a Pfizer molecule to treat type 2 diabetes while NewVac licensed a novel drug from Janssen to treat solid tumors.

While Skolkovo and ChemRar are the most well known, regional centers are being set up in other places such as Kaluga and Yaroslavl to create the conditions that will train skilled workers and entice pharmaceutical companies to set up operations in the area. For example, Yaroslavl officials encouraged generic pharmaceutical Nycomed (now Takeda) to build a manufacturing facility in Yaroslavl in 2009 and partnered with it to start a pilot education program in 2010 to train workers for GMP production. In 2011, Indian pharmaceutical Ranbaxy partnered with the Yaroslavl State Medical Academy to advance biomedical education with a focus on clinical trial expertise, and also signed a letter of intent to build a facility in the region.

In November 2012 the Kaluga Pharmaceutical Cluster signed a memorandum of cooperation with Chemical Cluster Bavaria to speed up the commercialization of research into systemic pharmaceutical technologies, the use of nanotechnologies in healthcare, and the recycling and disposal of pharmaceutical production wastes. The Kaluga Cluster also signed a memorandum of intent with Rosttechnologies-Biotechprom, a public-private holding company established in 2009 to enable all pharmaceutical companies to set up operations in the area. For example, Yaroslavl officials encouraged generic pharmaceutical Nycomed (now Takeda) to build a manufacturing facility in Yaroslavl in 2009 and partnered with it to start a pilot education program in 2010 to train workers for GMP production. In 2011, Indian pharmaceutical Ranbaxy partnered with the Yaroslavl State Medical Academy to advance biomedical education with a focus on clinical trial expertise, and also signed a letter of intent to build a facility in the region.

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ChemRar Hi-Tech Center, a group of biotech startups, R&D service companies, and venture investment firms dedicated to commercializing innovative medicines in Russia and abroad. The license agreement, signed during the St. Petersburg Economic Forum on June 23, 2012, builds on a March 2011 agreement between Pfizer and ChemRar to mutually explore collaborations focused on research, development, and commercialization of new medicines and vaccines to treat cardio-metabolic, infectious, and oncologic diseases in Russia and other countries.

SatRx, which ChemRar formed in 2010 specifically to address cardio-metabolic diseases, was granted exclusive worldwide rights, excluding China, to develop and commercialize Pfizer’s experimental diabetes drug PF-00734200 as a stand-alone therapy, or in combination with other drugs for the Russian market. Although financial terms were not disclosed, Pfizer will receive royalties and milestone payments based on commercialization activities.

The deal struck between Pfizer and SatRx follows a similar deal between Merck and the Russian biotech R-Pharm in infectious diseases announced during the BIO International Convention in June 2012 for narlaprevir, an investigational hepatitis C once-daily protease inhibitor ready for late-stage trials. Under their agreement, Merck Sharp & Dohme, the international division of Merck, has granted R-Pharm development and commercialization rights to narlaprevir in Russia and the Commonwealth of Independent States. The agreement provides an opportunity for R-Pharm to conduct late-stage clinical trials in Russia, an activity that is among the goals of the Russian government’s Pharma 2020 initiative.

“Today the Russian state policy is aimed at fostering the local pharmaceutical industry and providing the Russian population with the most effective, safe, and qualitative medicines. Using foreign partners’ experience is compulsory for reaching these goals,” said Sergey Tsyb, head of the department of the chemical technological complex and bio-engineering technologies of the Russian Ministry of the Industry and Trade. “Definitely, transfer of unique technologies and joint R&D projects as a part of partnership between international and Russian companies will contribute to introduction of the international manufacturing standards of medicines and, ultimately, to improvement of the quality of life of the Russian patients, which is fully in-line with the tasks and goals of the Pharma 2020 strategy.”

Under their agreement, R-Pharm will pay Merck an undisclosed upfront payment and undisclosed royalties on sales of narlaprevir. Narlaprevir is a second generation NS3 serine protease inhibitor developed by Merck. In a mid-stage clinical study, narlaprevir administration resulted in a robust decline in the level of hepatitis C virus detected in the blood and high sustained viral response rates when followed by standard of care in both treatment-experienced and treatment-naive HCV genotype 1-infected patients. The hepatitis C virus drug market in Russia is expected to grow 9 percent annually, reaching $327 million by 2013.

“This unique technology transfer deal is consistent with the Russian government’s desire to create a stronger local innovative pharma industry to drive economic growth in the sector,” said Kevin Ali, president for MSD’s emerging markets division. "Developing narlaprevir will enable R-Pharm to gain deep experience in late stage clinical trials—the crucial phase of drug development.”

A marketplace without boundaries

As the world moves toward becoming an interconnected, borderless marketplace, opportunities are growing for companies to leverage specific geographic markets, national economic growth incentives, diverse local customs, and regulatory regimes as a means to successfully achieve their goals. These trends have been going on for some time, as developing countries shift to technology-based economies, improve their education systems, and increase their scientific output. They are moving the global economic focal point, dominated historically by the developed markets of the United States, Europe, and Japan, toward increased reliance on emerging nations with their exploding middle classes [See Figure 6.7] as new centers of opportunity and growth [See Figure 6.8]. The influence of the United States and, to a lesser extent the European Union, remains preeminent, but it is continually counterbalanced by what happens in China and India [See Figure 6.8]. China now has the second largest economy

Figure 6.6  Russia’s Pharmaceutical Market in 2011

Figure 6.7  The Middle Class is Expanding

Figure 6.8  Global Growth of Pharmaceuticals from 2007 to 2016
in the world, having surpassed Japan in 2011, and is projected to overtake the United States by 2020, India’s economy is expected to overtake Japan in 2013 to become the world’s third largest economy. And the gross domestic products of Brazil and Russia are higher than any European country except Germany. More and more, cross-border deals are being made that don’t involve a Western entity. While capital has long flowed to the United States and Europe in search of innovation, it is increasingly going in other directions, where the West is neither the source nor the destination. For example, an early 2013 Brazilian transaction for sugarcane and ethanol production involved a division of the Indonesian conglomerate Salim Group. In another deal in 2012, Indian biopharma Biocon invested in building a $160 million insulin manufacturing facility in Malaysia because its government provided favorable tax incentives.

**Economic growth slows**

The Eurozone debt crisis, a sluggish recovery in the United States, and slowing growth in China and other BRIC nations contributed to a challenging economic environment in 2012. Austerity measures, elections, and leadership changes in several influential countries, including the United States, Russia, China, Japan, and France, contributed to uncertainty throughout the year. Business and government leaders gathered at the World Economic Forum summit in Davos, Switzerland in January 2013 were cautiously optimistic, however, that the worst of the prolonged financial crisis

**Figure 6.11  Global Growth Moves South**

But Latin America will grow less than other emerging areas of the world

**Figure 6.9  Top Ten Economies by GDP in 2050**

Comparison of three year average in selected countries; 2003-2006 versus 2007-2010

**Figure 6.10  Drug and Pharmaceutical Foreign Direct Investment Growth**

Circle size shows relative amount of investment; circle position on horizontal scale shows percent change. Alignment and color indicate region. Totals in USD B.

-100% 0 200% 300% 400% 500% 600% 700% 800% 900% 100%

Percent change from 2003-06 to 2007-10

Source: Goldman Sachs

Source: FDI Intelligence from Financial Times Ltd, Jones Lang LaSalle analysis, Burrill & Company

Source: Economist Intelligence Unit
Driving innovation and opportunities

As governments around the world strive to grow their knowledge-based industries to provide higher paying jobs and meet the challenge of providing healthcare for their aging populations, they have instituted national innovation strategies to grow their economies, often with a strong focus on building domestic pharmaceutical and biotechnology sectors.

Strategic initiatives in these countries often include making substantial public investments in R&D infrastructure, fostering R&D investment via tax and other research incentives, focusing on attracting and growing talent in related employment fields, ensuring access to capital, and fostering private-public partnerships [See Figure 6.12].

European countries and Canada have turned to a host of new initiatives focused on funding translational research and early-stage companies, particularly with the goal of building life sciences centers in specific locations. The efforts reflect broad attempts to forge creative new models for funding translational research and spur the development of important new therapies. They also demonstrate that governments across the globe, despite facing fiscal pressure, see the importance of investing in the life sciences to build innovation-based economies that can provide high-quality jobs [See Figure 6.13].

In one instance, the Welsh government made an $80 million commitment to what is expected to eventually be a $375 million fund. In another instance, Merck Canada, Lumira Capital, and other venture capital firms formed a $100 million R&D fund to attract pharmaceutical companies to Quebec. U.K.’s largest charity, the Wellcome Trust launched a $336 million investment arm to back early-stage life sciences companies and technologies in Europe with significant potential to grow. Called Syncona Partners, it will support new companies in the therapeutics, diagnostics, medical devices, and information technology sectors as well as long-term investments of about $1.5 million to $30 million each.

One of the largest funding mechanisms for early-stage research is Europe’s Innovative Medicines Initiative, the world’s largest public-private partnership in health. It is a coordinated program of the European Union and the European Federation of Pharmaceutical Industries and Associations, each of which has contributed and that private sector investment and decision-making is central to their long-term success.

The biggest portion of the new capital, $250 million, will be used to establish two large private-sector led national funds managed by an experienced general partner who has a substantial presence in Canada. These funds will be big enough to be credible lead investors in venture capital funds that have committed to invest one-third of their total capital in Canada-based companies. Investments will be targeted at companies developing marketable products in the information and communications technologies, life sciences, and cleantech sectors, high-growth sectors where Canadian firms have existing strengths.

Up to $100 million will go to recapitalizing existing large private sector-led funds, in partnership with provinces. Finally, up to $50 million will be invested in three to five existing venture capital funds in Canada. The plan also includes actions to help establish networks that link investors with innovative companies.

The government is calling on experts in the private sector for advice on the selection of the management of the large-scale, national fund of funds, and venture capital funds into which the money will be invested.

In March 2012, Merck invested $25 million to launch the $50 million Merck Luminra Biosciences Fund in collaboration with Lumira Capital, Teralys Capital, and other partners to provide investment capital to support early-stage life science innovation in Quebec. Designed to provide capital to fuel innovation as well as attract life science entrepreneurs to the province, the fund is a novel collaboration between a drugmaker, a specialized venture capital firm, and a Canadian technology fund of funds, as well as other limited partners.
National Innovation Strategies

Governments around the world have developed strategies to advance life sciences in their countries as a way to grow their economies, diversify into knowledge-based industries, provide jobs, and address the growing healthcare needs of their citizenry. They often see the development of a domestic biotechnology and pharmaceutical industry as key to sustainable growth. Initiatives vary from country to country, but for most, they are looking for ways to boost scientific knowledge, promote foreign investment, and increase the translation of domestic innovation into useful products that can meet the healthcare needs of their populations. Besides a strong focus on encouraging scientific output and improving educational capabilities, many initiatives include provisions aimed at supporting private research and development activities. These can take the form of outright grants, tax incentives, low-interest loans, and other policies on the national and regional level.

Select Government Initiatives to Boost Life Sciences

**AUSTRALIA**

2011 R&D Tax Incentive

Encourages R&D activities by providing a 45 percent refundable tax offset (equivalent to a 150 percent deduction) in the form of a cash refund to eligible companies with less than $20 million in annual revenue

**BRAZIL**

2004 Profarmá

Ongoing program aims to develop innovation in the pharmaceutical sector through low-interest, long-term loans to help national companies increase R&D activities and production.

2007-2010 Action Plan on Science, Technology and Innovation for National Development

Builds Brazil’s innovation economy in 12 sectors, including pharmaceuticals and biotechnology, with a focus on strengthening education and public institutions and building manufacturing capacity

**CANADA**

2007 Mobilizing Science and Technology to Canada’s Advantage

Designed to strengthen private sector investment in R&D and encourage academic pursuit of science and engineering programs, with a focus on four areas: natural resources, environment, health, and information technology

2012 Venture Capital Action Plan

Supports commercialization of Canada’s R&D by helping startups access capital to grow and create jobs

**CHINA**

2011-2015 12th Five-Year Plan

Biotechnology is targeted as a key sector for development as part of overall economic goals; the plan allocates $1.9 billion toward R&D for innovative drug development, mandates pharmaceutical companies to invest more than 5 percent of their annual revenue in R&D

**INDIA**

2008 Biotechnology Industry Partnership Programme

Support for all levels of high-risk innovative R&D through cost-sharing with industry

Continued on page 174
An Economic Priority
Russia looks to biotech for energy and biomedical solutions

The State Coordination Program for the Development of Biotechnology in the Russian Federation until 2020, or Bio 2020, defines biotechnology as a priority for economic development of Russia as a whole and delineates programs and program goals at both the national and state levels. The plan is to spend an estimated $39 billion to modernize the industry over eight years and was accepted in April 2012 as one of the last things Vladimir Putin did as prime minister before taking over as President of the Russian Federation.

By 2020, Russia plans to have in place the infrastructure and institutions required for modernization of all sectors impacted by the program, which include environmental protection, forestry, fishery, biopharmaceutical, biomedicine, agriculture and food, industrial, and bioenergetics. Together, the industrial biotech and bioenergetics sectors will receive nearly 50 percent of allocated funding. The goal is to increase production of all biotechnology-related products to 1 percent of GDP by 2020, and to at least 3 percent by 2030.

With this and other government-sponsored programs, Russia aims to improve its economic situation, clean up its environment, develop new sources of energy, elevate food safety, and accelerate medical and healthcare improvements, while at the same time reducing adverse impacts of current industrial practices on the environment.

To do so, the government has interim goals to advance scientific potential at home, and to integrate the scientific and technical sectors of Russia into the international community. By 2015, Russia hopes to create domestic and international demand for its biotechnology products. This will mean creating an infrastructure to foster development of the biotech industry from all angles, including policies that support innovation and investment projects, education and workforce training, and natural resource management. Between 2016 and 2020, the goal is to establish the necessary expertise for a biofuels industry, and to develop both the production and the technical skills bases for moving from reliance on chemically synthesized products to reliance on biologically synthesized products.

The effort involves seven out of fifteen government ministries under the direction of Prime Minister Dmitry Medvedev. The first stage of the program, through 2015, will be funded by federal and state budgets, state corporations and companies with a state share, and businesses. Russia will also look to investments from international corporations with interest in locating production facilities in Russia, as well as Russian and international capital markets. The second stage of the program, 2016 through 2020, will be a challenge: little if any federal or state money will go to the program.

By then Russia hopes to have enough funds available to advance the program from their own as well as international corporations, small and medium businesses, state development institutions, and market investments. Both Putin and Medvedev, together with Russian scientists and biotech leaders, understand that a focused effort is needed in order to leverage biotechnology solutions for the social, economic, biomedical, environmental, and energy problems that currently face Russia.

Promoting technology transfer
Emerging countries shifting their economies to high-value industries from a dependence on low-value commodities and manufacturing see biotechnology and other medical technologies as important drivers of economic growth. They are investing heavily in education, infrastructure, and healthcare to develop homegrown industries to serve the needs of their people and fuel further growth of their economies. This provides an opportunity for companies to leverage an asset they may not be prepared to commercialize in an emerging market, and use the needs in those countries to accelerate the development and cut the cost and risk of bringing those products to market in developed countries.

Many nations are also leveraging their financial strengths to gain industry expertise. Russia is a leader in this trend. In order to diversify its economy from a dependence on natural resources toward more high-technology sectors, the Russian government in 2010 launched Pharma 2020 as a national roadmap to develop the country’s biomedical sector to meet the growing healthcare needs of its citizens. Then Prime Minister Vladimir Putin pledged about $12 billion over ten years toward increasing the country’s capacity to produce drugs and medical equipment, including the establishment of more than a dozen centers of innovation and the training of people to staff them. The goal is to increase domestic market share to 50 percent by 2020, from 20 percent in 2011. Eventually, the country hopes to become a major exporter of medicines—an ambitious goal at the time considering that few of the country’s manufacturing facilities met international standards.

Russia is also seeking to build its biotechnology industry, which had been neglected for many years after the fall of the Soviet Union. “Twenty years ago we were one of the three or four biggest countries for biotech and now it is very little, which is awful,” says Professor Konstantin Skryabin, head of the Department of Biotechnology at Lomonosov Moscow State Uni-
versity and venture partner with Burrill Russia. “So there was a definite need to push biotech as a priority in the country.” Having biotech be a government priority will open up opportunities for other countries to participate, says Skryabin. “This is the motive of the initiative.” As one of his last acts as Prime Minister, Putin formally signed the Russia Bio2020 initiative in April 2012 to advance all areas of biotechnology in Russia. The plan includes an estimated $33 billion to be spent by 2020 in biomedical, bioagricultural, bioindustrial, aquaculture, forest biotech, environmental, and bioenergy projects.

Innovating is capital intensive, and governments realize that public funding is often not enough alone. Because of that, they are taking steps to not only fund innovation directly, but also to encourage private investment. Russia sees technology transfer as a major component of its Pharma2020 plan, and several government-backed investment funds have been making significant bets in innovative Western life sciences companies that are willing to set up drug development and manufacturing facilities in Russia. Rusnano, for example, has made several investments in Western companies that include agreements to develop their compounds and commercialize them first in Russia.

Backed by $10 billion in government money, Rusnano entered into a $760 million equal-partner deal with U.S. venture capital firm Domain Associates in February 2012 to back up to 20 companies willing to develop their compounds in Russia. Most of the opportunities will be for late-stage products. By the end of 2012 it had invested $113 million in four Domain portfolio companies, three of which have transferred intellectual property rights to NovaMedica, a Moscow-based pharmaceutical company formed specifically to manufacture and distribute products from the partnership in Russia. On the Russian side, NovaMedica will be eligible for special grants from the government provided to companies that engage in technology transfer of innovative products.

**Bringing talent back**

China’s current economic plan calls for doubling biomedical R&D innovation funding from the previous plan to $300 billion and moving to provide basic healthcare services to at least 90 percent of its 1.3 billion citizens. China’s policies have focused on boosting the country’s R&D capabilities, racing toward the United States and Europe in the output of scientific publications and patent applications [See Figure 6.15 and 6.17]. One of China’s first initiatives as it began to transform itself to a high-tech knowledge economy was the Thousand Talents program in 2003 to encourage 1,000 talented Chinese to return to their homeland with offers of well-paid prestigious positions and research funding. Returning Chinese expatriates often go back with extensive managerial skills to start companies that can take advantage of Western expertise and affordable talent in China. The program proved very successful with more than 150,000 expatriates, often fluent in English and experienced in business, returning to work in China and contributing to the surge in biopharmaceutical patents and scientific publications [See Figure 6.15].

Jinji Wu, CEO of Ascletis and an expatriate who had been vice president of global HIV drug discovery at GlaxoSmithKline, launched his company in 2011 as a joint venture between U.S. and Chinese entrepreneurs with $100 million in backing to discover and develop new treatments for cancer and infectious diseases. The com-

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**Figure 6.13** **Ease of Doing Business Index in 2011 and 2012**

Countries ranked according to World Bank standards, with rank of 1 indicating the most business-friendly regulations.

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<tr>
<th>COUNTRY</th>
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<td>India</td>
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Source: World Bank

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**Figure 6.14** **Partnering Deals in China in 2012**

- **By therapeutic sector**
  - Pharma 54%
  - Vaccines 6%
  - TCM* 5%
  - Diagnostics 7%
  - Devices 9%
  - Service 10%

*Traditional Chinese Medicine

- **By indication**
  - Oncology 28%
  - Cardiovascular 15%
  - Infectious disease 12%
  - All other 27%

- **By deal type**
  - Licensing 41%
  - Marketing & distribution 17%
  - Co-development 23%
  - Broad collaboration 13%

- **By stage of development**
  - Phase I 42%
  - Preclinical 9%
  - Phase II 10%
  - Phase III 8%
  - Marketed 30%
company’s management team, made up of seasoned pharmaceutical industry veterans like himself, is based in the United States, while most of the staff is based in China. After breaking ground on its Chinese headquarters in Hangzhou, the company received a research development grant of about $1.6 million from Hangzhou National Hi-Tech Industrial Development Zone as part of its plan to help technology-based startups within the technology cluster. “This grant recognizes the outstanding opportunity offered by Ascletis to create a world-class pharmaceutical company in Hangzhou that will develop innovative products both for China and for the rest of the world,” said Sheng Kong-Liang, director of the industrial park when he presented the award.

Ascletis has wasted no time in getting up and running. In February 2012, it announced a strategic partnership with Minsheng Pharma, which has a U.S. Food and Drug Administration-certified GMP manufacturing facility and sales and marketing strength in China in oncology and cardiovascular diseases. Then in July, Ascletis formed a strategic collaboration with U.S. biotech Alnylam Pharmaceuticals for the development of ALN-VSP, a first-in-class, systemically delivered RNAi therapeutic for the treatment of liver cancers including hepatocellular carcinoma, a significant area of unmet need in China. China has the highest incidence of liver cancers in the world and currently there are no effective treatments for the disease. Encouraging data from an early-stage study of ALN-VSP prompted Ascletis to license the compound for development in China (See Figure 6.14).

The deal gives Ascletis exclusive rights to develop and commercialize ALN-VSP in China, Hong Kong, Macau, and Taiwan. Alnylam retains all rights in the rest of the world, and is eligible to receive milestones and royalties based on product sales. “With this collaboration, we are able to develop ALN-VSP globally through the product’s advancement in a region where HCC is a particular challenge,” said Lawrence Reid, SVP and Chief Business Officer of Alnylam. “As we retain all rights in the rest of the world, this partnering strategy provides multiple future opportunities for Alnylam to advance this novel therapeutic in other markets.”

**Aiming for leadership in biosimilars**

South Korea is among the top countries in terms of its public expenditure on science and technology research and development. In 2012, South Korea poured about $55.8 billion, or 3.48 percent of its GDP, into boosting innovation in the country. With a goal to be a leader in biotechnology, it pledged increased funding for stem cell research in April 2012, describing it as a “new growth engine.” Its drug agency approved the first therapeutic using allogeneic stem cells in January 2012, developed by Seoul-based Medipost, to regenerate knee cartilage.
Neighbors Seek Healthcare in Malaysia

Country is a growing destination for medical tourism

With its central location and growing range of healthcare services, Malaysia has become a destination for medical tourists from neighboring countries seeking treatment. The value of goods and services has grown to almost $140 million in 2011 from about $40 million in 2005, according to data from Frost & Sullivan as nearly 450,000 people come to Malaysia annually for medical treatment. One big draw is the national network of hospitals and clinics, nine of which have received international accreditation. Revenues for the private hospital services market in 2011 were $140 million and growing at a compound annual growth rate of 16.5 percent a year. Frost & Sullivan expects revenues to reach $4.5 billion in 2015.

The July 2012 IPO in Singapore of IHH Healthcare, Malaysia’s largest hospital operator, was at the time the third largest IPO of the year. IHH priced at the high end of its range to raise $2 billion. The offering was 100 times oversubscribed, Bloomberg reported. IHH operates hospitals in Asia and Turkey, and has more than 4,900 beds with another 3,330 beds planned over the next five years, according to the company. It said it was prepared to benefit from increased medical tourism with the rise in wealth and an aging population in Southeast Asia.

Figure 6.A Malasya Sees a Rise in Medical Tourism

Sales of biosimilars are expected to reach between $4 billion and $6 billion by 2016, up from $693 million in 2011, according to IMS Health, representing 2 percent of biologic spending. With a new abbreviated approval pathway for biologics expected in the United States, and increasing adoption of biosimilars globally, both partners have made ramping up their presence in the biosimilars market a priority.

In February 2011, Samsung partnered first with Quintiles to set up Samsung Biologics, and in December 2011 with U.S. biotech Biogen Idec in a $300 million joint venture to advance the development of biosimilars. Three months later, the joint venture had appointed its first chief executive and had begun construction of a Korean facility to house its work, named Samsung Bioepis.

Malaysia

| Population (2012 estimate) | 29.2 million |
| Population growth rate (2012 estimate) | 1.54 percent |
| GDP (2012) | $492 billion |
| Total health expenditure as share of GDP (2010) | 4.4 percent |
| Public health expenditure as share of total (2010) | 35.5 percent |
| Size of pharmaceutical market (2011) | $1.6 billion |
| Pharmaceutical market growth rate (2011-2016) | 10 to 12 percent |

Sources: CIA World Factbook; World Bank; IMS Healthcare Institute; Business Monitor International; GDP at purchasing power parity prices

India

| Population (2012 estimate) | 1.21 billion |
| Population growth rate (2012 estimate) | 1.31 percent |
| GDP (2012) | $4.74 trillion |
| Total Health Expenditure as share of GDP (2010) | 4.1 percent |
| Public Health Expenditure as share of total (2010) | 29.2 percent |
| Size of pharmaceutical market (2011) | $14.3 billion |
| Pharmaceutical market growth rate (2011-2016) | 14 to 17 percent |

Government life sciences initiatives:
- National Biotechnology Policy
- Biotechnology Commercialization Fund

Sources: CIA World Factbook; World Bank; IMS Healthcare Institute; Business Monitor International; GDP at purchasing power parity prices
Although the Indian government has an innovation strategy, it has yet to implement it. But India is far ahead of most developing countries as far as its biomedical sector is concerned. The country has a vibrant generic pharmaceutical industry, supplying much of the developing world with affordable drugs [See Figure 6.18]. It also has a robust biotechnology sector that has been growing at a compounded annual growth rate of 20 to 24 percent over the past ten years, reaching $4 billion in revenue in 2011. Leading Indian biotech Biocon received Indian regulatory approval to sell ilotizumab, a biologic drug to treat psoriasis, in January 2013, and many Indian companies are developing biosimilars for the rapidly growing global market [See Figure 6.19].

As Indian drugmakers have become experts at making cheaper copies of small molecule pharmaceuticals, so to are they striving to develop their skills at making cheaper versions of biologic drugs. India’s Dr. Reddy’s Laboratories, which had already launched four biosimilars, teamed up with Geneva-based Merck Serono in a global partnership to develop, manufacture, and sell biosimilar cancer therapies. Dr. Reddy’s hopes to expand its presence in the biosimilar space in select emerging markets by combining its expertise with Merck Serono’s.

Dr. Reddy’s will lead early product development and initial clinical trials of compounds covered by the agreement. Once early-stage trials are complete, Merck Serono will take over manufacturing of the compounds and lead late-stage development and global commercialization outside the United States, except select emerging markets, where Dr. Reddy’s maintains exclusive rights, or the companies will share commercialization responsibilities. Within the United States, the companies will co-commercialize products and share profits, they say.

Addressing local needs

Because India’s government is concerned about providing its 1.2 billion citizens access to healthcare, three quarters of which are poor and still live in rural areas, the country is fertile ground for companies developing what is often referred to as “frugal innovation.” Companies such as GE Healthcare and Siemens are working to develop medical devices that are affordable, convenient, and accessible to a large swath of the population. GE Healthcare spends about $50 million annually on product innovation in India focused primarily on infant and maternal care. The company said it chose to work in India because it was a consumer driven market, it has a large pool of patients for conducting research, and the path to regulatory approval could be as much as 18 months shorter than in the United States.

Abbott, which became one of India’s largest generic drugmakers after acquiring Piramal Healthcare Solutions in 2010 for $3.7 billion, said in May 2012 it would collaborate with India’s Syngene, the contract research services subsidiary of Biocon, to open its first nutrition research and development center in the country. Abbott’s strategy, like GE’s, is to focus on the women and children. The R&D center will develop products to enhance nutrition and address diabetes, an increasingly common chronic condition in India, where an estimated 51 million people live with the disease.

At a time when its European sales have slowed, GlaxoSmithKline has also sought opportunities in India’s nutrition sector, targeting the country’s growing urban middle class consumer. In November 2012, the U.K. pharmaceutical offered to increase its stake in its publicly listed subsidiary, GlaxoSmithKline Consumer Healthcare in India, to 75 percent from its current 43.2 percent ownership. The offer represented a 28 percent premium to its closing price the day before the announcement and, if consummated, would be valued at $940 million. Under Indian securities regulations, an Indian company must maintain at least 25 percent public ownership to remain publicly listed. David Redfern, chief strategy officer for GSK, said that the transaction represented a further step in GSK’s strategy to invest in the world’s fastest growing markets.
Growing market opportunities

Aging global populations and the rising incidence of chronic diseases worldwide coupled with changing global business models are driving new market opportunities for life sciences companies and offering new economic opportunities for emerging nations. Within Brazil, Russia, India, and China, the middle class is expanding rapidly—growing 21 percent a year to reach 1.8 billion people by 2014. The increased affluence is creating greater demand for healthcare, in part because with changing lifestyles, have come a growing incidence of chronic disease. India and China will make up nearly one third of the world’s total patients with type 2 diabetes by 2030, with more than 150 million people afflicted with the disease by then. At the same time, evolving pharmaceutical business models have increased the outsourcing of many parts of the drug development process providing emerging markets with R&D and clinical trial opportunities that can help develop their local industry and technical expertise.

Emerging markets have targeted emerging markets as a primary source of sales growth in the coming years with many products facing patent expirations and slowing sales growth in developed countries. Big Pharma sees emerging markets providing an opportunity to extend product life after loss of exclusivity in established markets. Emerging markets have a high regard for brands, giving product originators a leg up over generic competitors. Five years ago, emerging markets accounted for just 5 percent of global pharmaceutical companies’ profits; today they make up 20 to 30 percent of profits, according to global consultancy Cegedim.

Every multinational pharmaceutical company has established a presence in China. Global consultancy McKinsey notes that China has overtaken the United States in terms of the number of sales representatives, which has grown more than fourfold to 25,000 between 2005 and 2011. In August 2012, Roche CEO Severin Schwan told a Swiss weekly that the company planned to create 1,000 new jobs in China by the end of the year, while at the same time cutting 1,000 jobs in New Jersey as it shuttered its U.S. research and development headquarters there.

Abbott is positioning itself to take advantage of the trends driving market growth. At the annual JP Morgan Healthcare Conference in January 2013, Abbott CFO Tom Freyman told his audience that approximately 40 percent of the company’s sales are in emerging markets, a number he expects will increase to 50 percent of sales by 2015. These sales came mainly from its established pharmaceuticals division, which he described as “more like our consumer-driven nutrition business than a typical pharmaceutical business” [See FIGURE 6.21].

At the same conference, Elias Zerhouni, Sanofi’s global head of R&D, stressed the company’s strategy of growth without reliance on R&D. “We threw away what we call the NIH syndrome—NIH meaning ‘not invented here’ syndrome,” he told his audience. While the company still prides itself on its innovative drugs and continuing R&D programs, it has moved to what Zerhouni calls “investing in growth platforms that are more reliable emerging markets in diabetes and vaccines.” That has led to an increase in its non-patented business. These platforms now make up about 71 percent of total sales, Zerhouni said. Since 2009, Sanofi has pushed aggressively into emerging markets, spending more than $2 billion to acquire Medley in Brazil, Shantha Biotechnics in India, BMP Sunstone in China, and Nepente in Poland.

As they get access to healthcare, consumers in emerging markets are also hungry for prescription drugs, often paying out-of-pocket for branded drugs perceived to be of higher quality than local generics. Global prescription drug sales are expected to reach $1.2 trillion in 2016 from $958 billion in 2011, according to projections from the IMS Institute for Healthcare Informatics, a unit of the health information company IMS Health [See FIGURE 6.20]. Although the patent cliff is peaking in 2012, 2013, developed markets will account for just
The Fulcrum to Leverage Asia

Australia’s Queensland—on the doorstep to connectivity with Asia

As the global center of gravity shifts to Asia, the tyranny of distance is being replaced by the prospect of proximity. Given Australia’s geographic location in the Asia Pacific region, and close strategic and economic ties with the economies of Asia, Australia is a vital proponent of any strategy to engage Asia—the world’s fastest growth region.

Asia’s growth is changing the world and will have profound global implications defining the 21st century—the “Asian Century.” Within the next few years, Asia will not only be the largest producer of goods and services in the world, but also the largest consumer. Already the world’s most populous region, it will be home to the majority of the world’s middle class.

This extraordinary ascent has already impacted Australia’s economy, society, and strategic relevance, and at a time when other economies have faltered has been key in maintaining the upward trajectory of Australia’s economy—an engine with 21 years of uninterrupted growth. Australia is well positioned as a gateway to Asia, with world-leading institutions; a multicultural and highly skilled workforce; and a productive, open, and resilient economy.

Australia is the leading location for life sciences companies in the Asia Pacific with a significant component of the country’s life sciences industry being based in Queensland. It has the third largest economy in the country, growing at an average annual rate of 4 percent over the past decade. Queensland, as Australia’s doorpost to Asia, is a driving force behind the country’s export growth, accounting for more than 20 percent of the nation’s total exports.

The 2012 state election swept a new state government into office. The new government is committed to economic diversification—including maintaining the driver health and medical research—to leverage the multi-billion dollar investments by the previous government. It said it will work to leverage the state’s significant knowledge-based competencies to assist stakeholders in the agricultural sector in order to help them become the food bowl for Australia and Asia. Of course, a by-product of increased agricultural activity will be the resultant increase in biomass—a resource that Queensland already has in abundance, particularly from the bagasse derived from sugarcane, Queensland’s largest crop—and a growing opportunity for the life sciences sector.

The government is reducing regulation, improving approval processes, and inviting a bigger role for private sector innovation in public policy and services. Now is an opportune time for life sciences organizations to harness ideas into successful commercial ventures. Both programs are designed to help stimulate and support research, development, and commercialization activities. Other federal initiatives include the Clean Energy Investment Program, and the Clean Energy Finance Corporation. At the state level, opportunities also exist with the Queensland Government’s investment in a venture fund.

This will be a milestone year for Queensland with the opening of the world-class Translational Research Institute and the commissioning of the DSM Biologics manufacturing facility in 2013. These world-class facilities will follow on from the recent opening of the extension to the Queensland Institute of Medical Research.

Life Sciences in Queensland

There continues to be significant momentum in the Queensland marketplace across many and varied stakeholders and subsectors, including:

- Some 66 institutes and approximately 18,000 research-related roles
- The Nanopatch technology being developed by Vaxxas University of Queensland’s Australian Institute for Bioengineering and Nanotechnology spin-out, partnered with Merck to painlessly deliver vaccines
- The Australian Institute of Tropical Health and Medicine at James Cook University in Cairns and Townsville, in the state’s far north, to help the effort against tropical diseases
- Therapeutic Innovation Australia—Queensland Node—leveraging the facilities and capabilities of five world-class Queensland research centers to collaboratively undertake preclinical and clinical translational research
- Nature Bank at Griffith University’s Es-Kits Institute—a collection of over 200,000 optimized natural product fractions from samples of plants and marine invertebrates linked to a robotic compound management facility
- Pancreatic cancer research facilities at the Institute of Molecular Biosciences for International Cancer Genome Consortium
- Tissue Therapies (Queensland University of Technology spin-out) is developing a product called Vitro-Gro, which is aiming for approval and sales in Europe later this year
- Bill and Melinda Gates Foundation’s continued interest in the bio-fortification of bananas for Sub-Saharan Africa
- Indian Government Department of Biotechnology—funding research to develop iron-rich bananas
- University of Queensland, collaborating with U.S.-based Clemson University to advance biofuel research, commercialization and large-scale production projects, with numerous stakeholders involved, including the U.S. Department of Defense
- A pilot biofuels facility in Mackay—leveraging Queensland’s sugarcane industry
- Queensland University of Technology’s Centre for Tropical Crops and Biocommodities pulse crops research in Queensland.
- International companies that have made Queensland their home including Cook Medical, Sanofi Consumer Healthcare, LEO-Pharma, and DSM-Biologics.
- Companies with a Queensland genesis including QXR Pharma, Alchemia, Protagonist, Codon, ImpediMed, Implicit Bioscience, Immunexpress, Bioproton, Leaf Energy, Magnetica, Spinifex, Protagonist, and many more, all key stakeholders in the diversification of Queensland’s economy.
57 percent of total spending in 2016, down from 73 percent in 2008. IMS Healthcare Informatics projects emerging market spending will grow at a compounded annual growth rate of 12 to 15 percent, compared to just 1 percent to 4 percent spending growth in the United States and an overall 3 percent to 6 percent growth in global spending.

**Emerging markets drive global M&A**

Indeed, emerging markets drove global M&A activity in 2012, as life sciences companies jockeyed to gain a strong foothold in these markets [See Figure 6.28]. In the largest deal, the Swiss health and wellness company Nestlé acquired Pfizer’s nutrition business for $11.9 billion in an effort to capture the global infant nutrition market. Nestlé’s largest acquisition ever expands its presence in emerging markets, the source of 85 percent of Pfizer Nutrition’s sales. The combined businesses will command a 10 percent share in China and a 38 percent share in the Middle East and Africa, according to Euromonitor International.

In a separate bid for emerging market share, Watson Pharmaceuticals agreed to pay $5.6 billion for privately-held Swiss generics powerhouse Actavis Group, making Watson the third largest global generics company and significantly increasing its market presence outside the United States. Actavis has a commercial presence in more than 40 countries. The deal more than doubled Watson’s international market access and strengthened the company’s commercial position in key established European markets, emerging growth markets such as Central and Eastern Europe, and Russia, said Paul Bisaro, president and CEO of Watson. Bisaro estimated that once the transaction was completed, approximately 40 percent of Watson’s generic revenues would come from markets outside of the United States.

The U.S. biotech Amgen made a play in Turkey, agreeing to pay $700 million to acquire 95.6 percent of privately-held Mustafa Nevzat Pharmaceuticals. The deal significantly expanded Amgen’s presence in Turkey and the surrounding region, which are large, fast-growing, priority markets for the company. Amgen established an affiliate in Turkey in 2010 and currently markets two products there, with plans to develop its robust pipeline of clinical candidates for the benefit of patients in Turkey, as well as other markets around the world. The deal is part of a broad international expansion strategy that includes its 2011 acquisition of the Brazilian pharmaceutical Ber

**Figure 6.23**  
**LIFE SCIENCES M&A IN CHINA BY SECTOR FROM 2008 TO 2012**

<table>
<thead>
<tr>
<th>Year</th>
<th>Drugs</th>
<th>Services</th>
<th>Medical Devices</th>
<th>Diagnostics</th>
</tr>
</thead>
<tbody>
<tr>
<td>2008</td>
<td>43%</td>
<td>20%</td>
<td>20%</td>
<td>17%</td>
</tr>
<tr>
<td>2009</td>
<td>25%</td>
<td>30%</td>
<td>35%</td>
<td>16%</td>
</tr>
<tr>
<td>2010</td>
<td>18%</td>
<td>5%</td>
<td>1%</td>
<td>34%</td>
</tr>
<tr>
<td>2011</td>
<td>8%</td>
<td>4%</td>
<td>22%</td>
<td>1%</td>
</tr>
<tr>
<td>2012</td>
<td>2%</td>
<td>1%</td>
<td>5%</td>
<td>39%</td>
</tr>
</tbody>
</table>

**Figure 6.24**  
**LIFE SCIENCES M&A IN CHINA**

While China continues to grab the lion’s share of global research and development dollars, Big Pharma has been upping its R&D and manufacturing capabilities around the world. Singapore is a central hub for companies seeking to do business in the Asia-Pacific region and a global hot spot for biomedical R&D. A*STAR, Singapore’s government research organization, is ranked among the top government research institutions based on the quality and quantity of its research activities. Many of the top biopharmaceutical companies have a presence in the city-state. In October 2011, Merck’s international division MSD said it would invest $1 billion over ten years to build up its operations in Singapore. That followed an announcement by Novartis that it was preparing to spend $500 million to build a new biologics facility there, construction of which commenced in October 2012.

Japanese biotech Chugai Pharmaceuticals, a subsidiary of Swiss drugmaker Roche, said at the opening of Chugai Pharmabody Research that it would invest more than $150 million on antibody research in Singapore over five years. The new facility opened in July 2012 and will work on developing new antibody drugs for cancer and other diseases. Amgen, too, is planning to build a new facility in Singapore to expand its production capability for monoclonal antibodies. Amgen plans to invest about $200 million to set it up.

In a different kind of R&D investment, AstraZeneca and Pfizer teamed up with the government of Québec in November 2012 in an effort to translate promising research into useful products. Together they committed $100 million over five years to establish Neomed Institute, a new non-profit life sciences research center. The institute is intended to create a bridge between academic researchers and life sciences companies and create synergies. The plan is to bring researchers, universities, venture capital funds, and biotechnology and pharmaceutical companies under one roof, working together in an open, collaborative environment that will employ more than a hundred contributors when it reaches full capacity. The Québec government is contributing $28 million toward Neomed, while AstraZeneca Canada is donating assets it values at $35 million including land, a neuroscience basic research facility, laboratory equipment, the intellectual property of three AstraZeneca pain molecules, and $5 million to support the institute’s activities. Pfizer Canada is providing $3.5 million.

By providing expertise and funding for academic labs and early biotechs, assisting them in bringing emerging therapeutic approaches to human proof of concept, the institute hopes to produce and showcase de-risked projects that present significant value for international investors.

French biopharma Sanofi is establishing a beachhead in the Middle East, laying the foundation for an industrial facility in King Abdullah Economic City, almost three years after it said it would do so. The agreement will make Sanofi the first multinational pharmaceutical company to establish its industrial facility with a 100 percent foreign direct investment in Saudi Arabia.

The facility will initially host research focused on developing oral anti-diabetic and cardiovascular products, in line with the growing prevalence of diabetes and hypertension in Saudi Arabia over the last two decades. Cardiovascular disease is the leading cause of death in Arab countries, at nearly 45 percent, according to M B Bdier, the director of cardiac clinics at King Abdullah Cardiac Centre. Sanofi credited an “encouraging investment environment” as a main reason for deciding to locate the project in Saudi Arabia.

**Sanofi will establish an industrial facility with a 100 percent foreign direct investment in Saudi Arabia.**
Aging populations need medical devices

Medical device makers have also pursued growing opportunities to sell their products in China and other countries with large populations of seniors. U.S. medical device maker Medtronic established a Chinese headquarters in Shanghai in March of 2011 in order to take advantage of the country’s fast growing healthcare sector, saying at the time that it would hire and train about 1,000 skilled workers over the next five years. At the end of August 2012, it opened its first R&D center in the Shanghai Innovation Center as a first step toward local development and manufacturing activities. One month later, it said it was buying orthopedic device maker China Kanghui Holdings for approximately $816 million, its largest overseas acquisition to date [See FIGURE 6.23 AND 6.24]. “This agreement is directly aligned with our corporate strategies of globalization and economic value,” said Omar Ishrak, chairman and CEO of Medtronic when the deal was announced. “Kanghui represents a significant investment in China, accelerating Medtronic’s overall globalization strategy with an established value segment distribution network and

Figure 6.25 DISTRIBUTION OF GLOBAL CLINICAL TRIALS BY REGION AND PHASE

Source: Charles River Associates, Policies that Encourage Innovation in Middle Income Countries, 2012; clinicaltrials.gov.

gamo. Amgen’s emerging market sales were $250 million in 2011, a number the company wants to raise to $1 billion by 2015 [See FIGURE 6.22].

Drugmakers invest in overseas innovation

Big Pharma is also investing in research and development around the world to take advantage of low cost talent, local expertise, and proximity to new markets. Some governments also require a local presence in order to make and sell products in their country as a way to develop their biopharmaceutical industry. In China, for example, it is preferred that the local presence be majority domestically owned. Russia has warned companies that drugs sold in Russia will soon have to be manufactured there. In any case, outsourcing research and clinical trials to these countries has been increasing as governments invest in developing their indigenous research capabilities. While India and China have been the top destinations for outsourcing services, other countries are fast catching the eye of drugmakers [See FIGURE 6.25]. For example, Singapore and South Korea are growing rapidly as centers for R&D and clinical trials. Singapore’s government has invested more than $1 billion in translational and biomarker research and its A*Star program is one of the top R&D programs in Asia. South Korea, too, has invested heavily in its healthcare infrastructure to become a top location for clinical trials. The government has established a collaboration with global contract research organization Quintiles through its KoNECT initiative to provide clinical research resources, training and support to Korean life sciences groups. The number of new clinical trials being conducted there grew 150 percent in the three years between 2006 and 2009. Eastern Europe is also becoming a preferred destination for smaller companies due to its large pool of treatment-naïve patients and well-established hospital systems.

China requires the local manufacture of medicines that have not been approved in other markets in order to develop and commercialize a drug in the country. So MedImmune, AstraZeneca’s biologics division, teamed up in a joint venture with the Chinese contract research and development outsourcing company WuXi AppTec in order to conduct clinical trials of its experimental biologic for autoimmune and strong R&D and operational capabilities.”

Figure 6.26 LIFE SCIENCES VENTURE CAPITAL IN CHINA

Source: ChnnalBio Consulting

Figure 6.27 CHINESE CROSS-BORDER PARTNERING

Source: ChnnalBio Consulting

Notes: Singapore was the top country in World Bank’s Ease of Doing Business Index three years in a row.

Singapore

Population (2012 estimate): 5.4 million
Population growth rate (2012 estimate): 1.99 percent
GDP (2012): $327 million
Total Health Expenditure as share of GDP (2010): 4 percent
Public Health Expenditure as share of total (2010): 36.3 percent
Size of pharmaceutical market (2011): $716 million
Pharmaceutical market growth rate (2011): 2 percent
Government Life Sciences Initiative: Biomedical Sciences Initiative

Source: OIA World Factbook, World Bank, MIE Healthcare Institute, Business Monitor International, GDP at purchasing power parity prices

6.26

Source: ChnnalBio Consulting

Source: ChnnalBio Consulting

6.27
inflammatory diseases in China. The company's experimental drug MEDI5117 is a fully human antibody designed to have a long-lasting effect and was being evaluated in early-stage clinical trials in the United States and Europe in autoimmune and inflammatory diseases, such as rheumatoid arthritis.

As part of their joint venture, MedImmune is providing technical and development expertise, while WuXi is taking care of local regulatory, manufacturing, pre-clinical, and clinical trial support. "This strategic partnership will enable us to establish a leadership presence in developing novel biologics in China, complementing AstraZeneca’s investment in this important emerging market," said Bahija Jallal, executive vice president of research and development at MedImmune.

The joint venture will control the development of MEDI5117 for autoimmune and inflammatory diseases in China. MedImmune is retaining the option to acquire full rights to commercialize MEDI5117, and if it does not exercise its option, the joint venture will have the right to commercialize the product. WuXi will earn revenue based on services provided to the joint venture, while MedImmune will receive various milestone payments as the program progresses. "WuXi is working to build long-term drug development partnerships with leading biopharmaceutical companies like MedImmune to help accelerate the development of novel medicines for the large and rapidly growing Chinese pharmaceutical market," said Ge Li, chairman and CEO of WuXi.

Like most emerging market research service providers, WuXi had been primarily engaged in the development of pharmaceuticals. But with higher aspirations to become a leading provider of biologics R&D and having recently entered into three deals focused on biologics, including the deal with MedImmune, WuXi opened its first cGMP biologics manufacturing facility in October in WuXi, the first in China to meet its first cGMP biologics manufacturing facility requirements.

In a sign of a potential trend in the making, AstraZeneca has also begun to outsource early-
Drug Developers Embrace Global Clinical Trials

EGeen says the cost advantage is in the speed of recruitment

Pharmaceutical and biotech companies are increasingly conducting clinical trials across the globe, especially in emerging markets, where they can reduce the cost of drug development and access a larger pool of patients. Nearly half of the 29,000 studies recruiting patients listed in the ClinicalTrials.gov database in September 2012 were done so outside the United States. The database lists more than 134,400 studies in 180 countries sponsored by the National Institutes of Health, government agencies, non-profit organizations, and private industry. Patient recruitment is one of the biggest bottlenecks to trial advancement and is driving rising clinical trial costs for many companies. It has become increasingly difficult to find treatment-naïve patients in the United States where many new drugs are first approved and become available. On the other hand, emerging markets provide opportunities for faster recruitment and high per-site enrollment.

“In the United States, for a number of indications such as oncology, most of the patients are literally booked by Genentech, already in clinical trials, or taking many of the existing therapies on the market,” says Kalev Kask, CEO of EGeen, a contract research organization that specializes in clinical studies in Eastern Europe. “That’s the opening for Eastern Europe, India, China—all these new markets.”

Tapping into the right pool of patients quickly is a primary reason for conducting a clinical trial in emerging markets, according to a research survey of biopharmaceutical companies conducted in 2011 by the research firm UBM TechWeb and Wipro, a leading global provider of information technology services. They found that more than half of the companies had already begun conducting clinical trials in emerging markets and the rest were planning to do so within the next two years. Their reasons were two-fold: the potential to lower costs of R&D, and the opportunity to serve patients’ healthcare needs in those countries, eventually marketing their products there.

EGeen has been providing outsourced clinical development services to companies for more than ten years. Its area of expertise is running clinical trials in oncology, urology, and CNS indications in Eastern Europe. Most of EGeen’s clients are small biotechs and specialty pharma companies.

Kask says his company focuses mainly on mid- and late-stage clinical trials, where it can provide a definite cost advantage in terms of speedy recruitment of qualified patients and quality control. Eastern Europe has an advantage, he says, in that it has a well developed system of large hospitals and a population used to going to large centers for specialty treatments.

“We run trials in large hospitals that have significant patient flow,” says Kask. Of course quality is important and the data generated from the trial must meet U.S. Food and Drug Administration standards. Kask says all of the sites where his company has conducted trials have been audited by the FDA and his company makes sure that all FDA protocols are followed by the clinical investigators. “Everything we do is according to FDA documentation,” says Kask. “Doctors are very comfortable with the brand product already on the market.”

Governments in emerging markets are also receptive to clinical trials being conducted in their country as it can mean their populations will gain access to experimental treatments and diagnostics they could not otherwise get.

The Russian government requires a local clinical trial of a novel product in order to gain marketing approval and its investment arm, Rusnano, has invested in several promising U.S. and European technologies with the condition that they conduct clinical trials in Russia and set up manufacturing facilities there. While there are a lot of challenges to conducting trials outside the United States and Europe, such as supply chain issues, variations in regulatory processes, data gathering, and maintenance of strict quality control, the potential to streamline clinical development through access to a larger patient pool is attractive.

EGeen says it doesn’t get paid unless it recruits the patients promised and Kask says the company has never failed to deliver. As a CRO, you have to be honest about what is doable, says Kask. “You have to know the idiosyncrasies of the countries.”
Pfizer Teams Up with Hisun in China

Joint venture targets branded generics opportunities

Pfizer and Zhejiang Hisun Pharmaceutical launched a joint venture in September 2012 to develop, manufacture, and commercialize off-patent pharmaceutical products throughout China and global markets, where such medicines account for a growing slice of the market. The launch brought to fruition an agreement the companies entered into in June 2011.

Hisun Pfizer Pharmaceutical, with $295 in committed working capital, is 51 percent owned by Hisun and 49 percent owned by Pfizer. Both companies are contributing selected existing products in areas covering cardiovascular and infectious diseases, chronic, mental health, and other therapeutic areas, plus manufacturing sites, cash, and other relevant assets. The joint venture aims to build a robust sales network that covers most areas and hospitals in China and to enter the international market by leveraging Pfizer’s global business networks. Pfizer plans to use the joint venture as a base on which to extend its branded generic business to India and other Asia-Pacific markets.

The move is a growing necessity as competitors to both companies jockey for position in the branded generics market, which is expected to account for at least half the value of new revenue opportunities in emerging markets. Drug sales in China, the world’s second largest pharmaceutical market, reached $66.7 billion in 2011, according to IMS Health, and are expected to grow to $161 billion in 2016 with most of the growth coming from off-patent drugs and generics.

A branded generic version of Lipitor is a possible offering for the new joint venture. Other products with expiring patents such as Viagra, Celebrex, and Detrol could also be on the list.

For Hisun Pharmaceuticals, the deal provides a way to transition from a manufacturer of active pharmaceutical ingredients to an established branded generics company.

“The joint venture will provide our patients with high-quality and low-cost branded generic medicines through our internationally compatible management systems and R&D and production technology. This will help us better contribute to the development of the Chinese pharmaceutical industry, advance the drug innovation and manufacturing capabilities of Zhejiang province and China, and lay a solid foundation for Chinese pharmaceutical companies to enter the international market,” said Bai Hua, chairman and president of Hisun.

Pfizer plans to use the joint venture as a base on which to extend its branded generic business to Asia-Pacific markets.

Pfizer has already made significant commitments to develop branded generic medicines in Brazil, where it spent $240 million to take a 40 percent stake in Indian pharmaceutical market by leveraging Pfizer’s global business networks. Pfizer plans to use the joint network that covers most areas and hospitals in China and to enter the international sites, cash, and other relevant assets. The joint venture aims to build a robust sales network that covers most areas and hospitals in China and to enter the international market by leveraging Pfizer’s global business networks. Pfizer plans to use the joint venture as a base on which to extend its branded generic business to India and other Asia-Pacific markets.

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and general business environment conducive to innovation vary from country to country. Keen to grow their domestic resources, many countries favor local businesses over foreign companies and will offer better incentives if the operation is majority domestically owned.

After 18 years of negotiations, the Russian Federation became a member of the World Trade Organization in August 2012, agreeing to abide by international trade rules. Still, in early 2013, Pharma Times reported Russian President Putin said that he expected 90 percent of the medicines deemed “strategically important” to be produced domestically by 2020. He planned to do this by forbidding state drug buyers from buying drugs from foreign suppliers if there are two or more approved alternatives available from domestic manufacturers. Russia had already warned multinational pharmaceutical companies that soon they would have to establish local manufacturing facilities if they wanted to sell their products in Russia [See Figure 6.29].

Increasing access to healthcare and aging populations in emerging markets are both a boon and a challenge for life sciences companies looking to enter these markets, offering large untapped demand for products while at the same time, dealing with governments burdened with...
escalating healthcare costs and driven toward price controls. Big pharmaceutical companies, most of which rushed into China, India, and other emerging markets in the hopes of offsetting sales lost to patent expirations with sales in fast growing markets, have experienced growing pains. Most, however, have dampened their expectations, though they remain optimistic about their prospects. Pfizer has scaled back its growth in the Asian arena, with its $545 million joint venture with Zhejiang Hisun Pharmaceutical. The companies officially launched Hisun-Pfizer in September 2012 to develop, manufacture, and commercialize off-patent pharmaceutical products in China and global markets. The joint venture combines the strengths of both companies to reach more

tionals to keep up with that growth because we don’t have the products there,” he said.

Pfizer hopes to remedy the situation in China, which is poised to become the second largest pharmaceutical market, and throughout the Asian arena, with its $545 million joint venture with Zhejiang Hisun Pharmaceutical. The companies officially launched Hisun-Pfizer Pharmaceuticals in September 2012 to develop, manufacture, and commercialize off-patent pharmaceutical products in China and global markets. The joint venture combines the strengths of both companies to reach more

patients with high-quality and low-cost medicines in the branded generics arena.

With Pfizer’s blockbuster Lipitor now off-patent and several others due to go off-patent in the next few years, establishing the groundwork to transition from brand name drugs to branded generics was a strategic necessity as competitors to both companies jockey for position in a sector that is expected to account for half of the value of new revenue opportunities in emerging markets. Off-patent medicines, including branded generics, represent one of the fastest-growing segments in the global pharmaceutical market [see Figure 6.30 and 6.31], especially in emerging markets, where cost and access are the primary drivers of growth. Branded generics account for 70 percent of the domestic pharmaceutical market in China, according to Hisun-Pfizer.

Roche has responded to pricing pressures in India by offering to cut the price of its cancer drugs Herceptin and Mabthera. The offer was propelled by India ordering Bayer to grant a compulsory license of its cancer drug Nexavar because the price was too high for most of its population. In China, Roche teamed up with health-care insurer Swiss Re to offer private insurance to cover the cost of its drugs in that market.

**Think globally, grow locally**

While drug sales in emerging markets are expected to grow by $157 billion over the next five years, reaching at least $345 billion by 2016, according to IMS Health, competition from local players will carve out a growing portion of that growth. Emerging markets differ in their demographics, governments, regulatory policies, economic structures, per capita income, and cultures—all things that must be taken into account when devising an emerging markets strategy.

As in developed countries, emerging markets governments face increased pressure to rein in healthcare costs. In most of these countries government regulations and policy are designed to benefit local companies, and demand that for-
Innovative companies are using the tools of biotechnology and engineering to improve crop productivity and develop low-carbon, renewable, bio-based fuels, chemicals, and products as alternatives to those made with fossil fuels. In 2012 they made headway toward creating a viable biorenewables industry in a challenging economic climate, and demonstrating their technologies at scale. While their success is not yet assured, the drivers of the industry are there with energy and food prices only going up, land becoming scarcer, and demand on natural resources intensifying. In a finite world, biotechnologies that can move us to a low-carbon future will eventually gain in value, and deliver it to the benefit of mankind.
CHAPTER 7:  

The Value of Sustainability  
Biogreentech companies move toward profitability  

In the New York borough of Staten Island, heavy winds ripped two young boys from their mother's grip as she tried to escape rising floodwaters after her SUV stalled. They were found dead two days later. In nearby Breezy Point, Queens, fire whipped up by 79 miles an hour wind gusts destroyed more than 100 homes. By the time firefighters arrived, the streets were awash, chest-high with water. Most of the rest of the area’s more than 2,800 homes were left filled with water, missing walls, or tipped due to sunken foundations. Down the coast, New Jersey’s Seaside Heights, the 3,000-person town made famous by MTV’s Jersey Shore, was declared uninhabitable.

More than 1,100 miles across, Hurricane Sandy cut a deadly swath through the most populous part of the country, a 15-state region that is home to about 30 percent of the U.S. population. It destroyed coastal areas, flooded buildings, and claimed 110 lives. It brought New York City home to about 30 percent of the U.S. population. Ecological damage from the storm was estimated to top $50 billion, adding a significant financial burden to the region. Sandy was so large partly because it added moisture from warm ocean water as it came up the East coast and hit the cold jet stream from Canada, adding to the pressure to seek ways to address these challenges in an environmentally sustainable way. Working toward that end, many innovative companies, especially in the United States and Europe, are using the tools of biotechnology and engineering to improve crop productivity and develop low-carbon, renewable, bio-based fuels, chemicals, and products as alternatives to those made with fossil fuels.

In 2012 industrial biotech companies made headway toward creating a viable biorenewables industry in a challenging economic climate, and moved to demonstrate their technologies at scale. The industry opened a handful of commercial facilities and moved to demonstrate their technologies at scale. The industry opened a handful of commercial facilities and moved to demonstrate their technologies at scale.

Critical to the success of the nascent industry were sourcing capital and integrating the supply chain from feedstock aggregate to broad supply contracts downstream. Investments moved from being majority venture capital-based to corporate venture-based and included strategic partnerships and joint ventures with big companies in the oil, chemicals, agribusiness, and consumer goods industries looking for sustainable growth by diversifying their own supply chains away from total dependence on fossil fuels.

Companies engaged in improving crops took advantage of a growing toolbox of biologic and genomic technologies to tolerate drought and other stressors, improve yield, add nutritional value or to engineer crops for specific purposes such as biorenewables feedstocks.

Precision agriculture, a convergence of synthetic biology, big data, and algorithms, is taking root in new plant breeding technologies that may avoid the regulatory pitfalls of traditional GM technology. And robots are being developed that can distinguish the crop from the weed in the field, potentially enabling farmers to use less herbicides and pesticides.

Severe weather and global warming

A hurricane such as Sandy could occur with or without global warming, say scientists, but they also agree that global warming could contribute to the severity of the storm. Sandy was so large partly because it added moisture from warm ocean water as it came up the East coast and hit the cold jet stream from Canada, adding energy to the storm. The atmospheric effects of Arctic sea ice melt in the summer—due to global warming—contributed to the jet stream sweeping down from Canada.

Climate change has also been blamed for excessive heat and drought such as that which spread across the United States in the summer of 2012, the hottest summer on record in the country. In August, at the height of the drought, the United Nations called on the United States government to suspend mandated federal ethanol targets, fearful that too much of a withering corn harvest was going toward biofuel rather than food production.

Scientists aren’t the only group of people that see a causal link between climate change and severe weather events. Just weeks before Sandy began gathering strength in the North Atlantic, Munich Re, one of the world’s largest reinsurers, issued a study titled “Severe Weather in North America.” It estimated that the United States has suffered more than $1 trillion in losses from weather related events in the period from 1980 to 2011. Weather related losses quintupled during that period.

"Nowhere in the world is the rising number of natural catastrophes more evident than in North America," wrote the study’s authors. "Global climate change is a major cause of the...
trend, they said. “Climate change particularly affects formation of heat-waves, droughts, intense precipitation events, and in the long run most probably also tropical cyclone intensity.”

Along with the increased levels of carbon dioxide in the atmosphere attributed to global warming, scientists have tied extreme weather events to the variability of crop yields, which could lead to reduced productivity as global warming continues. Although corn yields have increased over the years due to improved crop technologies, unusual climate events have caused significant yield reductions in some years [See Figures 7.1 A and 7.1 B].

Carbon dioxide emissions are at record highs, fueled by increasing economic activity in developing countries such as China and India that spurs energy demand, according to the annual outlook from the International Energy Agency, an autonomous organization that provides research and analysis to its 28 member countries [See Figure 7.2]. While China’s emissions are growing at the fastest rate, at about 2.9 percent a year, the United States is still the world’s largest polluter and expected to remain so. The agency warns that without immediate action to reduce emissions, global temperatures could increase 3.6 degrees Celsius, well above the 2 degrees Celsius rise already expected.

Recent analysis by the Organisation for Economic Cooperation and Development suggests that greenhouse gas emissions are likely to increase 70 percent by 2050 without policy action to reverse the trend.

For investors and companies in alternative energy and biorenewables, clear policy action on climate change is imperative to spur the growth of the industry.

Climate change on the backburner

Specific policy discussion about ways to mitigate global warming was relegated to the back burner during most of 2012 in Europe and the United States as economic worries and debt crises trumped all other concerns. The U.S. government avoided focusing on environmental concerns.

Instead, any reference to developing green or clean energy technology was made in the same breath as the sector’s job-creation potential. The National Bioeconomy Blueprint, released by President Barack Obama’s Administration in April 2012, outlined a general strategy to drive economic growth through research and advances in the biosciences. But energy security and independence, two of the main forces driving development of clean energy to date, no longer command the attention they received ten years ago.

In the United States, advances in technology, specifically horizontal drilling and hydraulic fracting, have made it possible to tap what is called unconventional fossil fuel and natural gas reserves, extracting oil and gas that until recently was too difficult and costly to get. This has created economic momentum in states such as North Dakota, Texas, Oklahoma, Colorado, and Ohio, among others, and opened up previously untapped reservoirs of oil and natural gas in shale rock, sending the price of natural gas plummeting and making it an attractive alternative to coal for power production. Whereas in 2001 the United States imported more than 60 percent of the petroleum it consumed, by the end of 2012 the U.S. Energy Information Administration projected oil imports to drop to 41 percent, with only 16 percent of those imports coming from the Middle East.

U.S. oil

North America is leading a transformative shift in the global energy balance, says Maria van der Hoeven, executive director of the International Energy Agency. The United States is projected to become the largest global oil producer by 2020, according to the International Energy Agency’s 2012 World Energy Outlook, surpassing Saudi Arabia until the mid-2020s. The agency says that increased fossil oil production coupled with fuel efficiency measures in transport will result in North America becoming a net oil exporter around 2030 [See Figure 7.3]. However, this will not lead to a drop in oil prices, which are expected to continue to rise, reaching an average of $125 a barrel in real terms by 2020.

As the United States’ dependency on Middle Eastern oil diminishes, international oil trade will shift its focus to Asia [See Figure 7.4], where rising living standards in emerging economies are fueling demand, estimated to increase by more than a third between now and 2035 [See Figure 7.5]. China, India, and the Middle East are expected to account for 60 percent of the increase. Energy consumption by Organisation for Economic Cooperation and Development member countries will remain relatively flat due to higher fuel economy standards in the United States, the European Union’s commitment to cut its energy demand 20 percent by 2020, and Japan’s goal to reduce its electricity consumption 10 percent by 2030.

The biofuels industry is also growing to address global environmental and energy challenges. A 2012 report commissioned by the Global Renewable Fuels Alliance found that the global biofuels industry contributed $277 million in 2010.
billion to the global economy and supported more than a million jobs in 2010. But fossil fuels will continue to remain dominant in the global energy mix, according to the International Energy Agency’s report, supported by subsidies that in 2011 jumped by almost 30 percent to $523 billion globally, mainly due to increases in the Middle East and North Africa. That compares to $88 billion in global subsidies for renewables, including biofuels. The agency expects renewables to become the second largest source of power generation by 2015 and almost equal to coal by 2035, but only if subsidies are continued [See Figure 7.6].

Opportunity for biorenewables
Renewables made up about 16.7 percent of total global energy consumption in 2011 [See Figure 7.7]. Although biofuels make up only 0.7 percent of total global energy consumption, their adoption increased at an annual growth rate of about 17 percent between 2007 and the beginning of 2012. Global ethanol production, currently corn or sugarcane-based, has flattened in the past two years, but is expected to pick up as cellulosic and other advanced biofuels become commercially available. Biodiesel production, on the other hand, has had an annual growth rate of 27 percent during the five-year period between the end of 2006 and the beginning of 2012, driven by increased interest from the airline industry.

Biofuels could represent 27 percent of all transportation fuels by 2050, compared to just less than 3 percent today, and could provide one-fifth of emissions reductions in transportation, according to the IEA’s Biofuels Roadmap issued in 2011. Countries will have to spend between $11 trillion and $13 trillion on biofuels over the next 40 years to make that happen, but even in the worst case scenario, it will only increase the total costs of transportation fuels by around 1 percent over that time, asserts the agency. However, this can only happen with a stable long-term government policy framework that allows for sustained investment in their development.

With the advent of biorefineries in the United States, Brazil, and elsewhere, biofuels producers can take advantage of opportunities not only for producing biofuels, but also biochemicals that are the building blocks of products such as plastics, lubricants, waxes, and cosmetics [See Figure 7.8]. The consumer goods, packaging, automotive, medical device, electronics, and construction industries are all adopting sustainability strategies and looking to source bio-based renewable chemicals.

For example, the automotive parts industry has been especially interested in using bio-based plastics to replace conventional plastic in vehicle interiors. In November, biorenewables company BioAmber said that it was chosen to supply bio-based succinic acid to a Faurecia-Mitsubishi Chemical partnership set up to develop 100 percent bioplastics designed for mass production for use in automotive interiors. Based in Europe, Faurecia is one of the world’s biggest automotive equipment suppliers. Environmental constraints associated with vehicle weight reduction and European regulations intended to increase the recyclability of materials used in the automotive industry are driving the need to use renewable materials.
Figure 7.8  BIOCHEMICALS CAN REPLACE PETROCHEMICALS IN MANY PRODUCTS

<table>
<thead>
<tr>
<th>BIOCHEMICAL</th>
<th>PRODUCT</th>
<th>OVERALL MARKET SIZE</th>
<th>CUSTOMERS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Propylene</td>
<td>Drop-in Gasoline/ Alkylate</td>
<td>$485 billion</td>
<td>Refiners</td>
</tr>
<tr>
<td></td>
<td>Automotive, Packaging</td>
<td>$110 billion</td>
<td>Consumer products, chemical companies</td>
</tr>
<tr>
<td></td>
<td>Super-absorbers</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cellulosic acetate</td>
<td>Rayon, filters</td>
<td>$180 billion</td>
<td>Consumer products, Paint companies</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Chemical companies</td>
</tr>
<tr>
<td>EVA</td>
<td>Paint, adhesives</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Polyethylene</td>
<td>Packaging</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ethylene glycol</td>
<td>PET</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Linear a-olefins</td>
<td>Jet fuel, Diesel</td>
<td>$245 billion</td>
<td>Airlines, refiners</td>
</tr>
<tr>
<td>Ethanol, butanol</td>
<td>Gasoline blending</td>
<td>$60 billion</td>
<td>Refiners</td>
</tr>
<tr>
<td></td>
<td>Drop-in gasoline</td>
<td>$1 billion</td>
<td>Consumer products</td>
</tr>
<tr>
<td></td>
<td>Rubber, plastics</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Source: ZeaChem, Silicon Valley Bank

Currently the bio-based share of the global fuels and chemicals market is about 3 percent, or $148 billion of a $5 trillion global market. By 2025, the bio-based share of the global fuels and chemicals market is expected to reach 17 percent, or about $1.4 trillion of an $8 trillion total market [See Figure 7.9]. Several forces worldwide are driving this opportunity including a push for energy independence, diversification of energy sources, efforts to hedge against oil price volatility, and policies to reduce carbon emissions [See Figure 7.10].

Figure 7.9  BIO-BASED MARKET OPPORTUNITY

Biofuels hits a blend wall

Biofuels production in the United States has grown rapidly and is expected to account for more than 9 percent of the transportation fuel supply in 2012, or almost 13 billion gallons. This has been largely due to the Renewable Fuel Standard, instituted through the Energy Independence and Security Act of 2007, mandating that transportation fuels be blended with increasing amounts of biofuels.

Starting with conventional biofuel, namely corn-based ethanol, the mandate requires increasing amounts of cellulosic ethanol and advanced biofuels to be blended into the fuel supply reaching 36 billion gallons by 2022. Advanced biofuels range from cellulosic ethanol derived from non-food crops, such as agricultural and forest residues, and other sources of waste to drop-in fuels, renewable fuels that can

Post-Election, Biofuels Industry Moves Ahead

For the biorenewables industry, the re-election of President Barack Obama for a second term in office represents a continuation of support for industry growth and investment in advancing technology development in the space.

Obama is likely to put renewed focus on climate change during his second administration. Reducing carbon emissions, a chief cause of global warming, is one of the major drivers for the adoption of low-carbon bio-based technologies.

Tom Buis, CEO of industry trade group Growth Energy, hopes to be able to work with Congress in a bipartisan manner to expand market access for biofuels. There will likely be a fight over the Renewable Fuel Standard, established in 2007, that mandates increasing amounts of biofuels be blended into the national transportation fuel supply. Buis calls it “the most successful energy policy this nation has enacted in the last half century.”

The Renewable Fuel Standard came under attack in the summer of 2012 as a severe drought damaged corn and soybean crops, leading to soaring grain prices. Food and livestock producers claimed they were being hurt by the diversion of food crops to ethanol production and the governors of eight states asked the Environmental Protection Agency to waive the mandate, at least temporarily. The EPA, on November 15, declined to waive the standards, saying that it did not find evidence of severe economic harm.

With Obama in the White House and a Democrat-controlled Congress, it is unlikely that the Renewable Fuel Standard will be waived or repealed. The EPA has enforced stricter standards on air pollution and worked to close the oldest coal-burning power plants. Obama has also used an executive order to institute stricter fuel efficiency standards for cars and light trucks.

While ethanol production has boomed during Obama’s first term, so has oil and gas production. This is not likely to change during the second term as energy independence and job creation continue to be major themes supported by his administration. The military’s continued investment to accelerate the development of advanced biofuels for military purposes under the Defense Production Act has also been left intact in the final defense budget.

Although current tax credits and loan guarantees for commercial projects are more likely to stay in place with Obama in the White House, they may be used as a bargaining chip as Obama tries to end tax credits enjoyed by oil companies. As both the White House and Congress come to terms with ways to cut the budget deficit, it is more likely that any subsidies the industry receives will be on the chopping block. However, ending the tax benefits oil companies have enjoyed may provide a bigger boost to renewable fuel companies than extension of the paltry tax credits they currently get.

The $1.01 per gallon tax credit for cellulosic biofuel was extended at the beginning of the year with extension of the fiscal cliff negotiations until March. Robert Dinneen, CEO of the Renewable Fuels Association, says that the end of the cellulosic tax credit would hurt companies that are commercializing their technology.

Most biofuel and biochemical developers don’t expect things to change significantly; however, their main concerns, raising enough capital, successfully completing and powering up their first commercial projects, and delivering a return on investment are constant, whatever happens on Capitol Hill.
California Begins Carbon Cap and Trade Program

California held its first auction of carbon emissions permits in November 2012, inaugurating the country’s largest cap-and-trade program designed to reduce greenhouse gas emissions. The program is a central part of the state’s landmark legislation enacted in 2006 by then Governor Arnold Schwarzenegger with the aim of cutting California’s greenhouse gas emissions back to 1990 levels by 2020, a 30 percent reduction.

The legislation did not specify how the emissions were to be reduced, but directed the California Air Resources Board to devise a plan to reduce emissions. The board’s final plan of action was a collection of policies to move the state to a cleaner economy and included standards, regulations, and incentives for the adoption of cleaner fuels, energy efficiency, and renewable energy.

A market for carbon allowances was created, with the largest auction occurring November 14, 2012, in which 96.2 million pollution allowances for 2013 emissions were auctioned by the state, with a floor price of $10 a permit. The state also sold 5.6 million of 39.5 million allowances that cover 2015 emissions. The final price of the allowances settled at $10.09, what the market felt was the price of one ton of carbon dioxide.

Cap and trade, the state sets a limit, or cap, on emissions from individual businesses, which decreases over time to meet the 2020 reduction goals. In order to keep up with the lowering emissions cap, businesses have three options: reduce emissions, buy permits to cover emissions above the cap, called allowances, or offset their emissions through financial support of projects that reduce emissions of greenhouse gases in the short-term or long-term.

Each allowance permits a company to emit one ton of carbon dioxide, and companies can buy or sell allowances on a carbon market depending on how much greenhouse gases they emit. California’s carbon futures will trade on the U.S. Exchange. Approximately 600 industrial concerns ranging from utilities to the University of California system were eligible to participate in trading, according to the board. These entities emit more than 25,000 metric tons of carbon into the air. For the first two years of the program, large industrial emitters receive 90 percent of their allowances for free with the remaining 10 percent up for auction.

On November 14, 2012, during a three-hour period, 23 million pollution allowances for 2013 emissions were auctioned by the state, with a floor price of $10 a permit. The state also sold 5.6 million of 39.5 million allowances that cover 2015 emissions. The final price of the allowances settled at $10.09, what the market felt was the price of one ton of carbon emitted into the atmosphere. While some people were disappointed that the price wasn’t higher, others considered it a milestone toward action to mitigate climate change.

“The fact that the prices are clearing a little above the reserve is a good sign that people’s fears about out of control costs for cleanup are not justified by the way the market actually worked,” Mary Nichols, head of CARB told the Associated Press.

California raised $289 million from the first auction and plans to hold four auctions each year. The money raised will be used both for clean energy projects and returned to California residential utilities users as a “climate dividend.”

The California Chamber of Commerce has filed a lawsuit challenging the air resource board’s authority to sell the allowances to generate revenue for the state, claiming it an illegal tax, a fight which is being watched closely by experts and lawmakers in Washington. Some experts feel that cap and trade is not a solution to reducing greenhouse gas emissions. In a speech at San Francisco’s Commonwealth Club in early December, climatologist James Hansen, head of NASA’s Goddard Institute for Space Studies, called cap and trade a “half-baked system” especially since it allows for offsets. “Offsets allow industry to comply with the regulation partially by funding carbon-reduction projects elsewhere, rather than cleaning up their own operations, he told the audience and pointed to the small effect it has had on Europe’s emissions. He called for a simple solution such as a direct tax on carbon.

be directly substituted for gasoline or diesel. By 2022, the Renewable Fuel Standard requires a total of 21 billion gallons of advanced biofuels to be blended into the transport fuel supply.

But U.S. biofuels production has hit a blend wall, currently at 10 percent for all car and light truck fuels. Although the EPA has approved a 15 percent blend for model years 2001 and newer, infrastructure costs and the slow adoption of flex-fuel vehicles, among other concerns, have limited its acceptance in the market.

U.S. gasoline consumption was 134 billion gallons in 2011, according to the Energy Information Administration, and with new fuel efficiency standards is not expected to increase significantly. At an ethanol blend rate of E10, the amount of ethanol that can be used for transportation is capped at 13.4 billion gallons. And exporting the excess is problematic if Brazil’s sugarcane harvest is good.

The predicament for biofuels producers has been compounded by severe drought in the United States, which pushed corn prices to new highs and squeezed producer margins. The result was reduced estimates for biofuels production for 2012 to 13 billion gallons, 5.6 percent below the 13.8 billion gallon target required by the Renewable Fuel Standard. Valero, Bunge, and several other companies slowed production and idled refineries until margins improve [See Figure 7.11] or the technology to shift corn ethanol production to biobutanol runs more smoothly, where the blend rate can go to 16 percent.

Cellulosic biofuels have yet to materialize in significant commercial quantities as companies struggle to lower the cost of breaking down cellulose into usable sugars. The 30.45 million gallon cellulosic ethanol mandate for 2012, already downgraded by the EPA from 500 million gallons, was still not met. The U.S. Energy Information Administration’s 2013 outlook is less optimistic than it was in previous years about the ability of advanced biofuels to capture a rapidly growing share of the liquid fuels market in the United States. With new commercial facilities coming online, the agency projects cellulosic ethanol production at 9.6 million gallons in 2013, an almost 20 percent increase from less than 500,000 gallons in 2012.

To meet Renewable Fuel Standard goals for advanced biofuels, the United States will need to build between 300 and 600 biorefineries over the next ten years. While there were about 200 commercial advanced biorefineries in the planning or development stage at the end of November 2012, according to Biofuels Digest, and a handful becoming operational or in the commissioning stage, it remains to be seen whether the industry will be able to raise the capital needed to reach the Renewable Fuel Standard goals.

Indeed, as far as producing billions of gal-
lons of any type of biofuels, some experts believe that it will not be economically possible without a price on carbon. And adoption of biofuels, to hedge against oil price volatility, will be increasingly predicated on demand from emerging markets rather than developed countries.

**Policy needed for parity**

Although the production of ethanol is an age-old process, the increasing use of biofuels for transport is an attempt to address growing environmental concerns about man-made greenhouse gas emissions. Many believe that in order for bioenergy to compete with fossil fuels, the cost of greenhouse gas emissions must be factored into the price of the energy source.

However, carbon pricing has been slow to take hold. Australia introduced a carbon tax in July 2012 at $24 per ton of greenhouse gas emissions. The European Union’s Emissions Trading Scheme is a cap and trade market vehicle that puts a price on carbon emissions for most industries; originally it was to include airlines in 2012, but the program was deferred at least until 2015. Many believe that in order for bioenergy to compete with fossil fuels, the cost of greenhouse gas emissions must be factored into the price of the energy source.

Figure 7.11 shows the U.S. ethanol inputs and production from 2009 to 2012.

**Government policy is necessary and the most efficient policy is pricing those emissions.**

**New threats in Europe**

Europe has been at the forefront of environmental policy. The European Union launched its cap and trade scheme in 2005 to combat climate change that was expected to lead to a 21 percent reduction in greenhouse gas emissions by 2020. The EU’s Renewable Energy Directive mandates that by 2020, 10 percent of member states’ transportation fuel come from renewable sources, chiefly biofuels. Currently, biofuels account for about 4.5 percent of transportation fuel, mostly as biodiesel, and a $22 billion industry has emerged to meet the growing demand. European biofuels are made mostly from rape-seed, palm oil, wheat, corn, and sugarcane feedstocks. Direct land use analyses that take into account land conversion from food to fuel claim that the use of food-crop derived biofuels does not result in reduced greenhouse gas emissions. Based on recent studies that support these claims, in October, the European Commission proposed limiting the share of food crop-based biofuels to no more than 5 percent of the total renewable transport fuel mandate. While the proposal supports the growing use of advanced biofuels from non-food feedstocks, the industry fears it will severely limit growth opportunities.

The proposal must still be approved by EU ministers and the European Parliament and is not expected to be completed until 2015, but it adds to regulatory certainty. Even so, it did not keep two large-scale biorefinery projects from receiving European Commission-backed funding in December through the New Entrants Reserve 300 program, funded from the sale of emissions permits to European companies. The Woodspirit partnership, a consortium that includes BioMCN, Siemens, Linde, and Venter, received a $262 million grant to build a biorefinery in the Netherlands that will use residues from forestry and milling operations to produce bio-based chemicals and biofuels. The program also awarded a grant to UPM Biofuels for construction of a wood-based biorefinery in Strasbourg, France that will produce renewable diesel.

**EPA protects standard**

Recent droughts and rising food prices have heightened the food-versus-fuel controversy. In the summer of 2012, livestock and poultry producers petitioned the EPA to suspend, and even do away with the Renewable Fuel Standard’s requirement to blend ethanol in the transportation fuel supply because they said it was driving up the cost of their main feedstock and causing severe harm to the industry. Analysts at Morgan Stanley pointed out that blenders would continue to use ethanol, with or without the Renewable Fuel Standard’s mandate, as it was cheaper than oil. Iowa State University researchers found that blending ethanol into the fuel supply in 2011 reduced the price at the pump by an average of $1.09 a gallon.

The EPA decided in November not to waive the standard, which is important because it provides regulatory certainty, and is a strong driver for the development of advanced biofu-

**“Government policy is necessary and the most efficient policy is pricing those emissions.”**

**J. Craig Venter**

Co-founder and CEO, Synthetic Genomics
Select government mandates and subsidies

**EUROPEAN UNION**
- 5.75 percent blending target by 2010 and 10 percent by 2020
- Proposal for 5 percent of biofuels from non-food feedstocks
- Airlines in CO2 emission cap in 2012, non-EU airlines exempt until September 2013

**UNITED STATES**
- RFS: Mandate of 36 billion gallons of biofuels annually by 2022
- 2012: 15.2 billion gallons of biofuels of which 2 billion gallons are advanced biofuels and up to 12.9 million gallons are cellulosic biofuels
- 2013: 13 billion gallons of biomass-based diesel
- Tax credit of $1.01/gallon for cellulosic biofuels

**ARGENTINA**
- Biodiesel mandate of 7 percent; target 10 percent
- Ethanol mandate is 5 percent
- B10: 18 to 20 percent ethanol blend, reduced from 25 percent in 2011
- Lower taxes for E100 than gasoline and FFV sales tax of 14 percent compared to 16 percent for gasoline-only vehicles
- Biodiesel: 5 percent blend policy expected to rise to 10 percent by 2014 but 60 percent of capacity idled due to lack of investment

**CHINA**
- Moving toward 10 percent biofuels mandate by 2020; nine provinces already require a 10 percent ethanol blend
- Investments in second-generation technologies by COFCO, PetroChina, and Sinopec

**INDIA**
- Blending targets of 5 percent in 2012, and 20 percent by 2020 for all transport

**SOUTH KOREA**
- Biodiesel mandate of 2.5 percent, mostly from Malaysian palm oil

**INDONESIA**
- Ethanol mandate of 3 percent and a biodiesel mandate of 2.5 percent

**MEXICO**
- Biodiesel mandate of 5 percent

**THAILAND**
- Biodiesel mandate of 5 percent

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**Figure 7.12 GLOBAL BIOFUELS POLICIES ENHANCE LONG-TERM DEMAND**

Select government mandates and subsidies

**MILITARY LEADS THE WAY**

The U.S. Department of Defense has been one of the biggest boosters of the development of advanced biofuels. The military, especially the U.S. Navy, has been at the forefront of supporting the development of advanced biofuels and could provide a market of approximately 450 million gallons a year by 2016, rising to 650 million gallons a year by 2020.

The Navy wants to get 30 percent of its energy from low-carbon emitting alternative source by 2020, and has invested heavily to help develop bio-based diesel and aviation fuels. The military is also concerned about its ability to supply the energy needs of its troops on the ground, which can cost upwards of $400 per gallon and carries mortal risks for its troops. Although the U.S. has reduced its dependency on foreign oil, for the military, using renewable fuels for transport and power is a matter of national security. Former NATO Commander Wesley Clark has called the failure to develop alternatives to fossil fuels as “the single greatest U.S. policy failure of the past 40 years.”

Altogether on U.S. military transport, those components account for approximately one-third of the Navy’s total fuel consumption and a very substantial portion of the energy consumed by the armed forces. The military has been at the forefront of supporting the development of advanced biofuels and could provide a market of approximately 450 million gallons a year by 2016, rising to 650 million gallons a year by 2020.

The report noted that the advanced biofuel industry is already leveraging $3.4 billion in private capital invested since 2007 to build new commercial facilities to meet the military’s cost and volume targets. Military demand is helping to shape the early market and scale the advanced biofuel industry, which could benefit the commercial airline industry and other industries hoping to expand its use of biofuels.

In late November, Sens. Mark Udall and Susan Collins sent a letter that was signed by 38 senators to Senate Majority Leader Harry Reid and Senate Minority Leader Mitch McConnell voicing their strong opposition to two provisions in the National Defense Authorization Act for fiscal year 2013 that they felt could harm “national security and military readiness while
Figure 7.13 Fuel Is Largest Cost for Airlines

Airlines seek stability

With fuel costs comprising more than a third of its average operating costs, the commercial airline industry wants sustainable renewable fuels in its mix both as a hedge against the rising price of fossil fuels and to reduce its carbon emissions [see Figure 7.13]. "If you build it, we will buy it," said Julie Felgar, director of Environment & Aviation Policy at Boeing. She said biofuel demand is huge in the airline industry. Aviation fuel prices have been rising an average 12 percent per year since 2000, so the aviation industry has formed consortia to advance development of sustainable low-carbon drop-in aviation fuel. The Sustainable Aviation Fuel Users Group counts 29 airlines among its members, representing almost a third of commercial aviation fuel demand. They have pledged to advance the development, certification, and commercial use of drop-in sustainable aviation biofuels. Formed in 2008, the group believes that sustainable aviation fuels are an important driver to achieving a carbon neutral aviation industry. European airlines have also banded together with biofuel producers and the European Commission to accelerate the development of aviation biofuels in Europe. The European Advanced Biofuels Flightpath initiative, launched in 2011, provides a roadmap for developing a supply chain capable of producing 2 million tons of sustainably hindering national efforts to develop viable domestic alternative fuels."

They managed to get both provisions struck from the Senate bill, a major victory for moving the biofuels industry forward. Although they do not expect alternative fuels to totally replace fossil fuels, they argued that even replacing a small portion of the Defense Department’s fuel consumption with alternative fuels “has the potential to advance U.S. national security, improve strategic flexibility, and insulate the defense budget against future spikes in the cost of fossil fuels.” In late December, the House also dropped its effort to prevent the military’s efforts to develop or buy biofuels.

"Amid the budget wrangling, in October 2012, the Defense Department, announced plans to award up to $30 million in grants under the Defense Production Act to help bring several commercial scale integrated biorefineries online. But besides increasing production capacity, some experts have suggested that the Defense Department help finance an increase in feedstock capacity without which increased production capacity is useless. Jim Lane, editor of Biofuels Digest, suggests creating a “Naval Agricultural Reserve,” for example, modeled after U.S. Strategic Petroleum Reserve. Production from such a resource, which could be privately run, would be reserved for military and aviation use, says Lane.

Airbus will use its experience in the European Union and the United States to support Sinopec in establishing a Chinese certification standard for alternative aviation fuels and in the selection of sustainable locally grown feedstocks. Sinopec will then produce the certified fuel, known as “1# biojetfuel,” at a newly built commercial scale refinery in Hangzhou, near Shanghai.

As one of the world’s fastest-growing aviation markets, the importance of these initiatives are apparent not only to China, but also to Boeing and Airbus, who aim to supply many of the new airplanes that the country will need in the years ahead.

The Civil Aviation Administration of China has forecast that passenger traffic in China will surpass 300 million in 2012 and will reach 1.5 billion passengers in 2030. Boeing has estimated that Chinese airlines will need to buy 5,000 new airplanes by 2030 to meet this extraordinary demand.

China’s energy consumption has grown by 136 percent over the past decade, as strong economic growth and a growing middle class have increased demand, along with a steep rise in air pollution. While coal, one of the dirtiest forms of energy, will continue to supply more than half of the country’s energy needs for the next decade, China has taken “all of the above” energy approach with an aim to develop all sectors of its renewables industry while working on ways to develop cleaner and more energy efficient industrial processes. The country’s renewable energy law mandates that 15 percent of energy consumption come from non-fossil fuel sources by 2020.

China Focuses on Aviation Biofuels

Airbus has been partnered with the Chinese aviation industry for 40 years and is the largest domestic partner. As one of the world’s fastest-growing aviation markets, the importance of these initiatives are apparent not only to China, but also to Boeing and Airbus, who aim to supplier many of the new airplanes that the country will need in the years ahead.

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"Bio-jet fuel is becoming increasingly important in aviation and the energy market," says Dai Houliang, senior vice president of Sinopec. "Sinopec has developed its own technology for producing aviation fuel from biomass and waste oil and has already produced aviation fuel meeting international standards."

Besides establishing an aviation fuel certification standard, the partners also hope to accelerate commercialization by establishing a sustainable alternative aviation fuel value chain in China that will use only domestic resources and refining capabilities. Airbus currently supports alternative fuel value chains in Australia, Latin America, Europe and the Middle East.

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produced biofuel for aviation by 2020.

In May 2012, United Airlines, Boeing, Honeywell’s UOP, the Chicago Department of Aviation, and the Clean Energy Trust formed the Midwest Aviation Sustainable Biofuels Initiative, designed to advance aviation biofuel development in a 12-state region and evaluate its biofuel potential. The consortium will focus on the whole value chain, including the biomass feedstock, technology development, job creation and sustainable commercialization.

“In just a few short years, aviation biofuels have developed from a hopeful vision of the future to an exciting reality of more than 1,500 passenger flights flown with advanced biofuels,” said Jimmy Samartzis, head of environment and sustainability for United. Airlines operating in the Midwest transport more than 234 million passengers and consume nearly three billion gallons of jet fuel annually.

The Midwest initiative could lead to “biofuels in the backyard” whereby the feedstock source and production facility would be located next to the airport, eliminating shipping costs, which are a major portion of feedstock costs, and stabilizing fuel prices. The consortium will evaluate the region’s feedstock options, commercialization, logistics and infrastructure needs, and regional policy measures in order to draw up an actionable roadmap, said James Rekoske, head of Renewable Energy and Chemicals at UOP. The goal, he said, is for consortium participants across the biofuel value chain to act on recommendations intended to enable the development and commercialization of aviation biofuels.

Consortium members say their efforts in promoting sustainable fuel supplies ultimately will spur economic growth, create jobs, and promote energy security. “When you consider the U.S. aviation industry uses more than 20 billion gallons of fuel each year, the environmental and economic potential of commercializing biofuels technology becomes truly game-changing,” said Amy Francetic, executive director of Clean Energy Trust.

Readying for take-off

Researchers at the Energy Biosciences Institute at the University of California, Berkeley, reported in Nature in November, that they had developed a two-step conversion technology using a modified bacterium that first breaks and then ferments cellulosic sugars into acetone and ethanol. The ethanol then undergoes a chemical catalysis step to increase its energy potential, necessary for the development of an alcohol based jet fuel on par with diesel and conventional jet fuels. Their next step is to scale their process to make it commercially viable.

Globally, companies such as Dynamic Fuels, LanzaTech, Solazyme, Algae.Tec, Amyris, and Neste, to name a few, are actively working to develop feedstocks and conversion technologies for the production of aviation biofuels. LanzaTech is partnered with Virgin Airlines. Solazyme has a supply agreement with Australia’s Qantas Airlines, and Gevo has agreement with United (Burrill & Company, publisher of this report, is an investor in Gevo and LanzaTech).

British Airways, in December 2012, said they had committed to buying $500 million in aviation biofuel from GreenSky London over the next ten years. GreenSky, a joint venture between the airline and the U.S. industrial bio-tech Solena, will begin construction of a facility in London in 2013, with plans to begin supplying British Airways with aviation biofuel by 2015.

While most of the early aviation biofuels have been derived from oil-based feedstocks such as animal and cooking grease, algae, palm oil and jatropha, in March 2012, biofuels
Waste is everywhere: garbage and trash from human consumption, used cooking grease and rendered animal fats, crops left on fields after the harvest, wood waste from milling and forestry operations, or steam from exhaust pipes at industrial plants and power stations. But for some industrial biotechs, this abundance of waste can be a valuable, cheap, and sustainable source of feedstock to be converted into useful renewable fuels and chemicals. And companies attempting to commercialize their technologies have not been welcoming to biorenewables companies seeking to better understand the environmental impact of biofuels.

Applied Research Associates and Chevron Lumus Global produced the biofuel used by the flying using non-food oilseed crops commercialized by Agrisoma Bioscience to specifically maximize their energy potential. The project was funded by Canada’s Clean Transportation Initiatives and the Green Aviation Research and Development Network.

**A drop in investment**

Global investment in all renewable clean energy technologies declined 11 percent in 2012 to $240 billion, according to Bloomberg New Energy Finance, the first year of decline in the past eight years. Besides general economic challenges in the United States and Europe, the industry was faced with regulatory uncertainty in the United States and several European countries, and the poor performance of clean energy stocks in the public markets. Although the United States continues to lead in venture and R&D investment, it has lagged in asset financing for biorenewables, investments that build commercial capacity [See Figure 7.14 and 7.15].

Capital markets, with their short-term view, have also made it difficult to jumpstart the new industry [See Figure 7.16].

**Source:** Burrill & Company

Figure 7.16 **Burrill Biogreentech Index 2008 through 2012**

<table>
<thead>
<tr>
<th>Year</th>
<th>Burrill Biogreentech Index</th>
<th>Dow</th>
<th>NASDAQ</th>
</tr>
</thead>
<tbody>
<tr>
<td>2008</td>
<td>-22%</td>
<td>0%</td>
<td>20%</td>
</tr>
<tr>
<td>2009</td>
<td>-26%</td>
<td>-6%</td>
<td>20%</td>
</tr>
<tr>
<td>2010</td>
<td>-20%</td>
<td>-10%</td>
<td>10%</td>
</tr>
<tr>
<td>2011</td>
<td>-14%</td>
<td>-14%</td>
<td>-4%</td>
</tr>
<tr>
<td>2012</td>
<td>-8%</td>
<td>-8%</td>
<td>-8%</td>
</tr>
</tbody>
</table>

Tamar will develop a network of more than 40 anaerobic digestion plants in the United Kingdom. Another U.K. industrial biotech, Gazasia, received a $150 million strategic investment in June from Aboitiz Equity Ventures, a major Philippine energy company, and entered into a joint venture agreement to develop facilities in the Philippines to create liquid biomethane from organic waste for use as a transportation fuel. Gazasia will provide the technical expertise, equipment, and project management, while Aboitiz will provide the core funding over the next five years.

U.S.-based Harvest Power, which is also engaged in converting organic waste materials in municipal solid waste into renewable energy and fertilizers, closed a $125 million series C investment in July that included financing from American Refining and Biochemical, an affiliate of oil refiner ARG that is planning to build small facilities in Pennsylvania to turn organic waste into a source of renewable power and fertilizers.

Waste streams from industrial operations present another opportunity to capitalize on a feedstock source and at the same time help the industrial partner reduce its carbon footprint. Such is the case with LanzaTech’s partnership with Shanghai-based Baosteel. Through a joint venture, established in March 2011, LanzaTech will channel the carbon monoxide off gases from Baosteel’s steel mill into a proprietary bioreactor to produce ethanol.

Another potential opportunity lies in the growing amount of natural gas that is being burned off from new shale oil field production rather than being collected and piped because it is so cheap and difficult to transport. Several companies are emerging that can take the natural gas—basically methane—and with biotechnology turn it into a much more valuable chemical. Siluria is one such company that says it has resolved problems in the technology that can convert methane into ethylene, a widely used chemical that is worth six times more than methane.

Calysta Energy, a new company headed by Alan Shaw, formerly the CEO of Codexis, also says it has developed a biotechnology that can economically convert methane into liquid hydrocarbons, the building blocks of higher-value, easily transportable fuels and chemicals. Calysta is a spinout of DNA 2.0, which claims to be the largest U.S.-based provider of synthetic genes for industrial and academic use.
After cutting the path for others on building a biorenewables company, attracting partners, and setting up operations in Brazil to access the cheap sugar feedstocks available there, Amyris told its shareholders in February 2012 it had been unable to produce the commercial volumes it had promised. In a conference call with investors at that time, president and CEO John Melo reported that although the company had proven its technology works at scale, it had learned that “it takes time to translate from peak yield levels in the lab to maintaining those yields over longer operational periods in the field.”

Amyris, which had seen its shares more than double in the space of four months after its initial public offering in the lab to maintaining those yields over longer operational periods in the field. It was good that those companies that got out did so,” said Biofuels Digest’s Lane. “When you read the analysts’ reports, you see that they are highly undervalued because the markets are placing such a huge discount premium on the risk. As they de-risk the company by hitting their milestones, you’ll see that stock price return.”

But value varies from company to company, and it is difficult to look at the entire sector as unified. Companies are using a variety of feedstocks and processing technologies, and making many different end products. Those companies that are feedstock flexible, have technologies that can be adapted to different environments, and that produce a variety of chemicals for different markets, are the ones more likely to achieve success.

Despite the poor public performance of companies that have gone public, private money has helped shore up the sector in the hopes that companies will soon begin selling their products, earning revenue, and potentially being acquired by their strategic investors. Companies raised about $2.1 billion in equity and debt capital in the public markets during 2012, while strategic and venture investors invested approxi-
Public Markets Need a Success Story

Challenges and opportunities for biorenewables companies

By Roger E. Wyse

The biorenewables industry is not only racing to scale, but also racing to profitability in order to maintain its sustainability. To reach good margins early, two things are necessary: access to competitively priced feedstocks and access to capital.

There's lots of capital on the sidelines, but investors are waiting to see that the technology will work at a commercial scale. Until that happens, it's going to be difficult to raise money right at the time when first commercial projects need it the most.

It takes a long time to build a new industry. New relationships need to be established, new value chains created, and markets penetrated. That takes time. Venture capitalists want to invest their money, grow it, and then exit. To date, investors have yet to see attractive returns in this industry. Expected timeframes are only growing longer, the path to commercialization is costing more, and exit opportunities, so far, are not clear. From a venture capitalist point of view, this is a challenging, early industry to bet on.

But there are opportunities globally. Although most of the innovation occurring in biorenewables is happening in the United States and Europe, the application of the technology is global. Right now, the industry is experiencing growing pains of scaling up and commercializing. But commercialization depends on access to competitively priced feedstocks and capital. To find that, companies need to think globally.

Understanding the complex biorenewables value chain and how to optimize the elements is one of the great challenges of this industry. Can you get your feedstock aggregated at the right price? Can you sell your product to an offtake partner at the right price?

A company will have to find the money at whatever price, because unless it can survive to commercialization, it has lost the game. There have been significant financings. Good companies are able to raise money, but it takes them longer and they must work harder to do so. The amount of money needed to fund operations alone is significant. Conservatively, there’s a $1 billion gap between the capital that’s been raised and what’s needed to fund ongoing operation in the industry. It’s not just the capital expenditures. Gevo, which had to go out and raise additional funding, found it to be expensive.

The public markets have not treated the biorenewables industry well and that affects not only the ability of these companies to raise additional money, but also the valuation of the companies that are still private. It has had a very dampening effect on the industry. At a time when investors have stepped in to diversify their portfolios by helping fund the commercialization of technologies, and forming partnerships and joint ventures [See Figure 7.21].

Creating value

Although some biorenewables companies’ first projects were up and running during 2012, this is still on the horizon for most first commercial scale plants, set to open over the next few years. To finance these projects, which can cost between $100 million and $300 million to build, companies have had to raise the necessary capital during economically constrained times and regulatory uncertainty, and attract investors that can stand to wait for a return on their investment.

In the production of biorenewables, value creation lies in the integration of the supply chain rather than just the feedstock, the conversion technology, or the end product pursued. Each step along a complex supply chain must be taken into account in order for the end product to be able to compete on a cost basis with products derived from fossil fuels. The feedstock, the first step in the supply chain, is often the biggest obstacle to bringing down costs of production, accounting for more than half of overall production costs in many cases.

In order to control feedstock costs, a biore-
Figure 7.20 **Top Venture/Private Investments in 2012**

<table>
<thead>
<tr>
<th>COMPANY</th>
<th>RAISED (US$M)</th>
<th>FOCUS</th>
<th>ROUND</th>
<th>STRATEGIC INVESTOR</th>
<th>PRIVATE EQUITY</th>
<th>INVESTORS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gazasia (United Kingdom)</td>
<td>150</td>
<td>Waste-to-biofuels</td>
<td>Strategic Investment</td>
<td>Y</td>
<td>N</td>
<td>Abolitz Equity Ventures (Philippines)</td>
</tr>
<tr>
<td>Sapphire Energy</td>
<td>144</td>
<td>Algae-based biofuels</td>
<td>Series C</td>
<td>Y</td>
<td>Y</td>
<td>Arrowpoint Partners; Monsanto; undisclosed investors</td>
</tr>
<tr>
<td>Harvest Power</td>
<td>126</td>
<td>Waste-to-energy</td>
<td>Series C</td>
<td>Y</td>
<td>N</td>
<td>True North Venture Partners; American Refining and Biochemical; Kleiner Perkins Caufield &amp; Byers; DAG Ventures; Generation Investment Management</td>
</tr>
<tr>
<td>Tamar Energy (United Kingdom)</td>
<td>113</td>
<td>Waste-to-power</td>
<td>Launch funding</td>
<td>N</td>
<td>Y</td>
<td>BT Capital Partners; Fay Capital; Duchy of Cornwall; Lord Rothschild’s Family Interests; Sustainable Technology Investments; Low Carbon Limited; private investors</td>
</tr>
<tr>
<td>Elevance Renewable Sciences</td>
<td>104</td>
<td>Renewable chemicals</td>
<td>Series E</td>
<td>Y</td>
<td>N</td>
<td>Genting Berhad; Total Energy Ventures International</td>
</tr>
<tr>
<td>LanzaTech (New Zealand/US)</td>
<td>71</td>
<td>Biorenewables</td>
<td>Series C</td>
<td>Y</td>
<td>N</td>
<td>Malaysian Life Sciences Capital Fund; Petronas Technology Ventures; Kholsa Ventures; Qiming Venture Partners; KWI; Dialog Group Berhad</td>
</tr>
<tr>
<td>Joule Unlimited</td>
<td>70</td>
<td>Renewable fuels/ chemicals</td>
<td>Series C</td>
<td>Flagship Ventures; undisclosed institutional and private investors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Syra Innovations</td>
<td>50</td>
<td>Biorenewables</td>
<td>Series C</td>
<td>N</td>
<td>N</td>
<td>Kleiner Perkins Caufield &amp; Byers</td>
</tr>
<tr>
<td>Renmatix</td>
<td>50</td>
<td>Renewable chemicals</td>
<td>Series B</td>
<td>Y</td>
<td>N</td>
<td>BASF Biorenewable Beteiligungen; new and existing investors</td>
</tr>
</tbody>
</table>

newables producer must lock down the cost of the feedstock, whether it is sugarcane, a grain or oil-seed, agricultural or wood residues, municipal solid waste, or industrial waste gases such as carbon monoxide and carbon dioxide. While most of the non-food feedstocks are basically free, aggregating and shipping them is not. In the case of biomass, currently only the pulp and paper industry can aggregate and deliver it cheaply.

The choice of biomass, therefore, has to take into account the amount of land needed to harvest the amount of carbon dioxide that was used to produce the feedstock, whether it is sugarcane, a grain or oil-seed, agricultural or wood residues, municipal solid waste, or industrial waste gases such as carbon monoxide and carbon dioxide. While most of the non-food feedstocks are basically free, aggregating and shipping them is not. In the case of biomass, currently only the pulp and paper industry can aggregate and deliver it cheaply.

In the current environment, biorenewables companies, which are pursuing a diversified array of technologies and end products that can be defined as leading to renewable chemicals and bio-based fuels, need to secure a long-term supply of feedstock at stable prices and have offtake agreements in place—a ready market for their products once they are produced—in order to attract investors. Companies that can integrate the supply chain will be the most likely to succeed. Industries operating at either end of this complex chain, the feedstock suppliers and offtake buyers, often become the industrial biotechs’ strategic investors and partners.

There is no one-size-fits-all solution and companies are evaluating their particular situations in order to create value, often ahead of realizing revenues. But despite its difficulties, the sector has continued to attract investment from both the private and public markets due in part to its huge, potentially $1 trillion market opportunity.

**Strategies guide development**

While companies are taking a variety of strategies to realize the value of their technologies, a strategic investor often guides them. These investors are often oil and gas companies, chemicals companies, and consumer goods companies. Analogous to biotechs’ symbiotic relationships with Big Pharma to bring their innovations to the market, biorenewables companies need strategic investors to fund and expertise to advance their technologies into the industrial fuels, chemicals, and consumer goods market-place [See Figures 7.22 A and 7.22 B].

Danish industrial enzyme producer Novozymes took a 10 percent stake in Beta Renewables for $17 million at the end of October 2012. Beta Renewables is a $350 million joint venture formed by Chemtex, the engineering division of Italian chemical company Gruppo Mossi & Ghisolfi, and the private investment firm TPG. As part of Novozymes’ investment, the companies entered into a strategic partnership making Novozymes the preferred enzyme supplier for all of Beta Renewables’ cellulosic ethanol projects. Beta Renewables’ technology combines an enzymatic pretreatment process with fermentation to turn biomass into sugars that can then be processed into a variety of biochemicals.

The company had already teamed up with Gevo in July 2012 to integrate its technologies to produce isobutanol from various biomass feedstocks. If successful, that would enable renewable sourced, competitively priced jet fuel, as well as other chemicals and fuels made from isobutanol.

Biofuels producer POET teamed up with ingredients and materials company Royal DSM in a 50/50 joint venture called POET-DSM Advanced Biofuels that will produce cellulosic ethanol and license the technology to other plants in the United States and globally. It will be headquartered in South Dakota and the initial capital expenditure by the joint venture in Project Liberty, the venture’s first commercial cellulose ethanol biorefinery, will be about $250 million [See Figure 7.23].

But relying on strategic investors can have drawbacks, as was the case for advanced biofuels developers Qteros in 2011 and Terrabon in 2012. Both companies lost the backing of their strategic investor at a crucial time in their development cycle and had to declare bankruptcy and close their operations. In the case of Qteros, its strategic partner, the gasoline refiner Valero, declined to continue investing in the company. Instead, it increased its investment in Mascoma’s initial commercialization project and gave the go-ahead to finance Diamond Green Diesel’s renewable diesel project.

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**Pursuing lower-cost fuels requires a facility that can process bigger volumes, while pursuing higher value chemicals can justify aggregating less biomass, having higher capital costs, but lower operating costs.**
<table>
<thead>
<tr>
<th>DEAL TYPE</th>
<th>COMPANY/LICENSEE</th>
<th>DEAL VALUE (USD M)</th>
<th>PRINCIPAL FOCUS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Collaboration</td>
<td>NexSteppe DuPont’s Pioneer Hi-Bred</td>
<td>N/A</td>
<td>Feedstock breeding for sorghum and switchgrass for use as bioenergy feedstocks.</td>
</tr>
<tr>
<td>Joint venture</td>
<td>AlgaeTec (Australia) Shandong Keniu (China)</td>
<td>N/A</td>
<td>50/50 joint venture to produce biofuels from algae in China.</td>
</tr>
<tr>
<td>Joint venture</td>
<td>POET Royal DSM (Netherlands)</td>
<td>250.0</td>
<td>50/50 joint venture called Poet-DSM Advanced Biofuels to produce cellulosic ethanol and license the technology to other plants globally.</td>
</tr>
<tr>
<td>Collaboration</td>
<td>Seab Energy (India) Novozymes (Denmark)</td>
<td>N/A</td>
<td>Exploratory research agreement to jointly develop a process for the production of biofuels from seaweed. Novozymes will contribute enzymes while Seab contributes its offshore seaweed cultivation technology.</td>
</tr>
<tr>
<td>Alliance</td>
<td>GeoSynFuels Sermatec Zanini (Brazil)</td>
<td>N/A</td>
<td>Development and commercialization of cellulosic ethanol in Brazil, with an option for Sermatec to take an equity position in GeoSynFuels in exchange for engineering services. The initial project will be the construction and operation of a demonstration plant adjacent to a Brazilian sugar cane mill to treat sugarcane bagasse.</td>
</tr>
<tr>
<td>Joint venture</td>
<td>BioAmber NatureWorks</td>
<td>N/A</td>
<td>Joint venture AmberWorks formed to advance the commercialization of bio-succinic acid, bringing new performance bio-based polymer compositions to market.</td>
</tr>
<tr>
<td>Partnership</td>
<td>BlueFire Renewables GS Calltex (South Korea)</td>
<td>N/A</td>
<td>SureSource, a subsidiary of BlueFire, will build a cellulosic sugar plant in Korea to process two tons of construction and demolition debris per day into cellulosic sugar, which will be converted into high value chemicals by GS Calltex’s technology. GS Calltex, jointly owned by GS Group and Chevron, provides more than half of South Korea’s oil needs.</td>
</tr>
<tr>
<td>Partnership</td>
<td>Avantium (Netherlands) Danone Research (France)</td>
<td>N/A</td>
<td>Joint development agreement to develop bio-plastic bottles for Danone, the number two worldwide in bottled water business.</td>
</tr>
<tr>
<td>Partnership</td>
<td>Solazyme; Amyris Volkswagen of America</td>
<td>N/A</td>
<td>Evaluation and demonstration of performance of VW’s TDI clean diesel technology when powered by advanced biodiesel and renewable diesel fuel over a one-year period.</td>
</tr>
<tr>
<td>Joint venture</td>
<td>Solazyme Bunge</td>
<td>N/A</td>
<td>Joint venture to build, own, and operate a commercial-scale renewable tailored oils production facility adjacent to Bunge’s Moema sugarcane mill in Brazil. Startup is expected the second half of 2013.</td>
</tr>
<tr>
<td>Collaboration</td>
<td>Gevo VP Racing Fuels</td>
<td>N/A</td>
<td>VP Racing Fuels and Gevo will jointly evaluate the commercial potential for isobutanol in a wide array of markets with a goal of developing a product line of renewable, high-performance, isobutanol-based fuel blends for the small engine market, and other applications.</td>
</tr>
<tr>
<td>Agreement</td>
<td>Solazyme Dow Chemical</td>
<td>N/A</td>
<td>Extension of current joint development agreement accelerating the commercialization of Solazyme’s tailored renewable oils and an offtake agreement where Dow will purchase from Solazyme all of its requirements of non-vegetable microbe-based oils for use in dielectric fluid applications through 2015, contingent upon Solazyme’s ability to supply such oils within agreed specifications and terms and conditions of sale.</td>
</tr>
<tr>
<td>Partnership</td>
<td>Novozymes (Denmark) Shengquan Group (China)</td>
<td>100.0</td>
<td>Cellulosic ethanol production from a waste product in Shengquan’s current production of furfural from corncob xyllose for resin production, used in the foundry industry.</td>
</tr>
<tr>
<td>Acquisition</td>
<td>Cilion Aemetis</td>
<td>37.3</td>
<td>Aemetis acquires Cilion to advance its bolt-on technology to create next-generation biofinery producing advanced biofuels and renewable chemicals in addition to ethanol and animal feed products.</td>
</tr>
<tr>
<td>Joint development agreement</td>
<td>Gevo Beta Renewables (M&amp;G-Italy)</td>
<td>N/A</td>
<td>Development of an integrated process to produce bio-based isobutanol from cellulosic biomass and commercialization of the technology upon project success, with the aim of making renewable jet fuel and other biochemicals and fuels from isobutanol.</td>
</tr>
<tr>
<td>Collaboration</td>
<td>Amyris Total (France)</td>
<td>82.0</td>
<td>Total renews commitment for the development of Amyris’ Biofene, a renewable farnesene, for the production of renewable diesel and jet fuel. The partners will form a joint venture after completion of the research and development program.</td>
</tr>
<tr>
<td>Collaboration</td>
<td>Cargill Novozymes BASF (Germany)</td>
<td>N/A</td>
<td>BASF, Cargill and Novozymes will develop technologies to produce acrylic acid from renewable raw materials. BASF is the world’s largest producer of acrylic acid, while Cargill and Novozymes have been collaborating on producing bio-based acrylic acid. Acrylic acid is used in a broad range of products with an annual global market volume around 4.5 million tons, valued at the end of 2011 at $11 billion.</td>
</tr>
<tr>
<td>Collaboration</td>
<td>Agrivida POET</td>
<td>N/A</td>
<td>Four-year agreement to develop engineered corn stover feedstock and feedstock processing technology for integration with POET’s existing commercial cellulosic technology. The goal is to significantly reduce the capital and operating costs of commercial cellulosic ethanol production facilities.</td>
</tr>
<tr>
<td>Agreement</td>
<td>Renmatix Waste Management</td>
<td>N/A</td>
<td>Strategic investment and joint development agreement to explore the feasibility of converting post-consumer waste, such as that managed by Waste Management, into affordable, sufficient-quality sugars for manufacturing bio-based materials.</td>
</tr>
<tr>
<td>Partnership</td>
<td>Joule Audi (Volkswagen-Germany)</td>
<td>N/A</td>
<td>Strategic partnership to accelerate the commercialization of Joule’s renewable fuels for the global ethanol and diesel markets.</td>
</tr>
</tbody>
</table>

Continued on next page
Terrabon’s strategic partner Waste Management, a major strategic investor in a number of advanced biofuels developers, went through a corporate reorganization after a drop in earnings in the summer of 2012 that resulted in its decision to stop backing the developer of “green” gasoline. “A very small change in direction at a very large company can have a deep effect on the smaller player,” says Biofuels Digest’s Lane. “What is a ripple to Waste Management can be a tsunami for the earlier stage companies in which it invests.”

A long running partnership between enzyme maker Codexis and oil major Royal Dutch Shell also ended at the end of the summer, possibly over the fact that Codexis’ enzymes are less cost efficient than its competitors, although Codexis is confident a recent partnership with Raizen, a major strategic investor in Codexis.

“Biorenewables companies are using a variety of strategies to achieve profitability. Some companies, such as the renewable oils producer Solazyme, have chosen to sell smaller volumes of their products into the cosmetics and food additives markets as they develop their biofuels technology. Solazyme makes its renewable oils with genetically engineered algae grown in closed containers. The company can tailor the oil to fit a specific need, much like a seed developer engineering an oil seed crop with specific characteristics, but

**Figure 7.21  SELECT BIORENEWABLES DEALS IN 2012  continued from previous page**

<table>
<thead>
<tr>
<th>DEAL TYPE</th>
<th>COMPANY/LICENSEE</th>
<th>COMPANY/LICENSEE</th>
<th>DEAL VALUE (USD M)</th>
<th>PRINCIPAL FOCUS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alliance</td>
<td>Ensyn (Canada)</td>
<td>Fibria Celulose (Brazil)</td>
<td>N/A</td>
<td>Strategic alliance that includes establishing a 50/50 joint venture for the production of cellulosic liquid fuels and chemicals in Brazil, as well as a $ 20 million equity investment in Ensyn by Fibria. Fibria is one of the world’s leading pulp producers.</td>
</tr>
<tr>
<td>Partnership</td>
<td>logen Energy (Canada)</td>
<td>Raizen Group (Brazil)</td>
<td>N/A</td>
<td>Raizen will develop a commercial cellulosic ethanol project in Brazil with logen to be co-located with Raizen’s Costa Pinto facility in Piracicaba, Sao Paulo.</td>
</tr>
<tr>
<td>Partnership</td>
<td>LanzaTech</td>
<td>Petronas (Malaysia)</td>
<td>N/A</td>
<td>LanzaTech and the Malaysian national oil company, Petronas, will work together to accelerate the development and commercialization of technologies to produce sustainable chemicals from carbon dioxide and natural gas.</td>
</tr>
<tr>
<td>Equity stake</td>
<td>Beta Renewables</td>
<td>Novozymes (Denmark)</td>
<td>116.2</td>
<td>Industrial enzyme producer Novozymes takes a 10 percent stake in Beta Renewables, part of Italian chemical company Gruppo Mossi &amp; Ghisolfi, and the two companies will jointly market, demonstrate and guarantee cellulosic biofuel solutions.</td>
</tr>
<tr>
<td>Collaboration</td>
<td>Biosynthetic Technologies</td>
<td>Monsanto</td>
<td>N/A</td>
<td>Monsanto takes an equity stake in Biosynthetic Technologies and the two companies will collaborate to use Monsanto’s VisiPon soybean oil in the production of biosynthetic lubricant oils.</td>
</tr>
<tr>
<td>Partnership</td>
<td>Bio Architecture Lab</td>
<td>Xunshan Group (China)</td>
<td>N/A</td>
<td>Collaboration to develop an integrated seaweed bio-refinery to produce a low cost carbohydrate for the production of renewable chemicals, fuels, animal feed and a variety of other high-value products using Xunshan’s seaweed and BAIL’s conversion technologies.</td>
</tr>
<tr>
<td>Supply agreement</td>
<td>BioAmber</td>
<td>Faurecia-Mitsubishi</td>
<td>N/A</td>
<td>BioAmber will be the supplier of biobased succinic acid to a Faurecia-Mitsubishi Chemical partnership for the production of automotive plastics.</td>
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<tr>
<td>Marketing</td>
<td>Ceres</td>
<td>Syngenta (Syngenta)</td>
<td>N/A</td>
<td>The companies will work together to support the introduction of sweet sorghum as a source of fermentable sugars at Brazil’s 400 or more ethanol mills, collaborating on small-scale trials as well as larger demonstration-scale field evaluations with mills, and using Syngenta’s crop protection products with Cerex hybrids.</td>
</tr>
<tr>
<td>Joint venture</td>
<td>Biomax Fuels (India)</td>
<td>Middle East Environment Protection (Saudi Arabia)</td>
<td>N/A</td>
<td>50/50 joint venture to build the first biofuel plant in Saudi Arabia, which will use cooking oil as a feedstock and is expected to be commissioned by the end of 2013 with the ability to produce 2.5 million tons of biodiesel per year.</td>
</tr>
</tbody>
</table>

Source: Burrill & Company

**TERRABON**

Terrabon’s strategic partner Waste Management, a major strategic investor in a number of advanced biofuels developers, went through a corporate reorganization after a drop in earnings in the summer of 2012 that resulted in its decision to stop backing the developer of “green” gasoline. “A very small change in direction at a very large company can have a deep effect on the smaller player,” says Biofuels Digest’s Lane. “What is a ripple to Waste Management can be a tsunami for the earlier stage companies in which it invests.”

A long running partnership between enzyme maker Codexis and oil major Royal Dutch Shell also ended at the end of the summer, possibly over the fact that Codexis’ enzymes are less cost efficient than its competitors, although Codexis is confident a recent partnership with Raizen, a major strategic investor in Codexis.

“Biorenewables companies are using a variety of strategies to achieve profitability. Some companies, such as the renewable oils producer Solazyme, have chosen to sell smaller volumes of their products into the cosmetics and food additives markets as they develop their biofuels technology. Solazyme makes its renewable oils with genetically engineered algae grown in closed containers. The company can tailor the oil to fit a specific need, much like a seed developer engineering an oil seed crop with specific characteristics, but

**Jim Lane**

Editor, Biofuels Digest

its biofuels efforts on sugarcane bagasse in Brazil. Following Shell’s decision to discontinue the partners’ $60 million enzyme development program, Codexis moved to layoff about a third of its employees, or 116 people. Shell, through its Raizen joint venture with Brazilian biofuels producer Cosan, remains Codexis’ largest shareholder and Codexis remains partnered with Raizen. (Burrill & Company, publisher of this report, is an investor in Codexis.)

The breakup with Shell, though painful, frees Codexis to pursue other partnerships. Shell and Codexis entered into a new agreement expanding Codexis’ ability to commercialize their jointly developed enzymes that break down cellulose. Shell granted Codexis a royalty-bearing, non-exclusive license to develop, manufacture, use, and sell cellulase enzymes developed under the companies’ original 2006 agreement. The license is worldwide, except Brazil, for enzymes used in the biofuels field. Codexis already had exclusive rights to commercialize its cellulase enzymes in other fields. Shell is entitled to a small royalty on sales of the enzymes to customers other than Shell or its affiliates, such as Raizen, and on its own use of the enzymes in the biofuels field. Shell will also continue to pay Codexis royalties for use of technology developed under their original agreement that remains exclusively licensed to Shell. Meanwhile Codexis, which has a strong business selling its enzymes to pharmaceuti-
without the long timeframe. It has joint ventures with Bunge to build a commercial facility in Brazil for producing renewable oils and one in France with food processor Roquette to produce nutritional ingredients.

Solazyme has also secured contracts with the military and aviation industry to supply test amounts of aviation biofuels. Solazyme’s engineered algae were also used in a biofuel blend, amounts of aviation biofuels. Solazyme’s engineering of synthetic biology to engineer microorganisms to excrete oils and chemicals that can be blended directly with diesel fuels or gasoline, such as Amyris found out in early 2009.

Some companies have capital efficient strategies. Gevo has developed technology that can be bolted on to existing facilities, providing a lower-cost path to commercialization. Gevo’s first commercial facility in Luverne, Minnesota became operational at the end of May, producing bio-based isobutanol, a renewable chemical that can go into the fuels or chemicals market. When a lawsuit by Butamax, a bio-renewable joint venture between DuPont and BP, charged Gevo with patent infringement, Gevo was able to temporarily stop producing the isobutanol and revert the bio-refinery back to producing ethanol, thus continuing to produce a revenue stream.

Gevo has negotiated a place for its technology into a LanzaTech bioreactor to produce ethanoll. In December 2012, the company reported as a feedstock for producing renewable products. Some, such as LanzaTech, have turned to industrial waste gases as a feedstock. By locating a biorefinery adjacent to a steel mill in China, the industrial plant reduces its carbon footprint by turning waste carbon from a problem into an opportunity.

LanzaTech had established its joint venture in 2011 with Shanghai-based Baosteel, the second largest steel producer in China and the fourth largest in the world, to channel the carbon monoxide waste gas from steel production into a LanzaTech bioreactor to produce ethanol. In December 2012, the company reported successfully meeting all pre-commercial milestones at its first 100,000 gallon demonstration facility, allowing the joint venture to proceed...
<table>
<thead>
<tr>
<th>COMPANY</th>
<th>PRINCIPAL ACTIVITY</th>
<th>STRATEGIC INVESTORS</th>
<th>PRIMARY INDUSTRY OF STRATEGIC INVESTOR</th>
<th>TOTAL RAISED (USD M)</th>
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<td>Internet Software &amp; Service</td>
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<td>Saudi Basic Industries; DSM</td>
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<td>Itochu</td>
<td>Industrials, textiles</td>
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</table>

Source: Burrill & Company
well as China's new energy development,” said Baosteel Chairman Jia Yanlin, commenting on the successful demonstration.

**Natural gas changes the equation**

The advent of cheap natural gas has clear implications for the growing bioenergy industry in the United States, providing challenges and opportunities. On the one hand, the abundance of cheap natural gas challenges biofuels’ importance to securing the nation’s energy independence and competes with renewable energy sources for power generation. On the other hand, some companies, such as Coskata, Sundrop Biofuels, and Primus Green Energy, are switching to natural gas as a primary feedstock for conversion into higher value biofuels, including ethanol and biochemicals, both because of its low cost and also because of strategic backers in the gas industry. With technologies that first convert the feedstock into syngas, these companies can use either biomass or natural gas to produce ethanol.

**Chesapeake Energy**, the second largest producer of natural gas, invested $155 million to acquire a 50 percent stake in Sundrop Biofuels in mid-2011. Sundrop, which uses an ultra-high temperature gasification process to convert any biomass into what it calls “green gasoline,” moved from the use of all cellulosic biomass to a mixture of natural gas and biomass as its primary feedstock. Coskata, in July, said it was switching to using all natural gas as a feedstock. Previously it had used a combination of natural gas and wood chips to produce biofuels. The biofuels developer went on to launch a $100 million financing round aimed at strategic investors with interests in natural gas.

Natural gas is not without its challenges, which include the high capital costs of the conversion technologies. Also it is only suited to geographic areas with abundant supplies, for now the United States and Canada, and eventually Russia.

**Commercialization begins**

Industrial biotechs are at the tipping point as they begin to put their technology to the test at commercial scale. More than 200 advanced biorefineries are in the works, and the first commercialization projects began to come on line in the second half of the year. Besides Gevo, which started up production at the end of May, KiOR, and Ineos Bio announced the completion of construction. These plants are relatively small compared to oil refineries and must first go through a commissioning phase that could take up to nine months before they can be operated at full scale.

Gevo, which uses engineered yeast to turn corn sugars into isobutanol, began commissioning its new plant in June 2012 with a plan to produce one million gallons of isobutanol a month. It expects to reach full capacity by the end of 2013. KiOR’s technology turns wood waste into a so-called “renewable crude” that can be further refined into gasoline. KiOR spent $200 million to construct its first commercial facility in Columbus, Mississippi, which when fully operational will produce about 13 million gallons a year. Ineos Bio, a division of European oil and chemical company Ineos, completed a $130 million facility in Vero Beach, Florida, next to a county landfill that will convert wood waste and woody garbage into a sludge that will then be combined with engineered bacteria to produce ethanol. When fully operational, the plant will produce 8 million gallons of ethanol to meet Florida’s ethanol demand.

### Table: Who’s Writing the Checks?

<table>
<thead>
<tr>
<th>FINANCER</th>
<th>INDUSTRY</th>
<th>PLANT LOCATION</th>
<th>INDUSTRIAL BIOTECH</th>
<th>CAPACITY (MYD)</th>
<th>FEEDSTOCK TYPE</th>
<th>EXPECTED START DATE</th>
<th>PRODUCT</th>
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<tbody>
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<td>Abengoa Bioenergy</td>
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*Source: Biofuels Digest; Silicon Valley Bank; Burrill & Company*
**SOUTH AMERICAN HARVEST**

**Betting on Brazil**

Major oil companies are placing their bets on Brazil for their initial advanced biofuels and bio-based chemicals commercialization efforts. The lure: sugarcane bagasse—the stuff left after the stalk has been crushed and the sugar extracted; the mechanization of the harvest, which provides a means to aggregate the biomass that is usually left on the field and burned off; a mature market for ethanol where blend ratios range from 20 percent to 25 percent; and a growing interest worldwide in bio-based specialty chemicals commanding higher margins than ethanol.

Fears of a poor sugarcane harvest due to drought at the end of 2011 caused the price of sugar to soar in the global market and led mills to process their harvest as sugar instead of converting it to ethanol. The Brazilian government lowered the blend rate for ethanol in the country’s fuel supply to 20 percent in January to cover shortfalls. Investment in new plantations has dropped precipitously, estimated at $700 million in 2011 compared to $7.8 billion in 2008, according to Bloomberg New Energy Finance. With the sugarcane industry saying that it would need $80 billion in new investment over the next ten years to meet demand, Brazil’s state development bank BNDES said in January 2012 that it would lend $2 billion to the industry to increase its sugar harvest and boost ethanol production by up to 17 percent. But it wasn’t enough.

Under these circumstances, the industry agreed to give the Brazilian government regulatory authority over ethanol, much the same as it already had over gasoline and diesel, in exchange for its help modernizing the industry and expanding ethanol production. Now the mill operators must meet regulatory obligations to produce a certain amount of ethanol, but they will also need to attract capital to expand production.

“The government doesn’t want to subsidize gas prices but also doesn’t want to expose its citizens to the ups and downs of gasoline prices, so they want to see ethanol used,” says Biofuels Digest editor Jim Lane. “The only way to resolve all those needs—the industry’s need for capital, the government’s desire for ethanol, and the companies’ desire to sell a lot more sugar—is to increase production.”

Less than 20 percent of the available agricultural residues in Brazil could produce 45 billion gallons of ethanol every year, according to Bloomberg New Energy Finance. At the same time, biorenewables technology, developed primarily in North America and Europe, has advanced to the commercialization stage and a handful of projects are beginning to come online. Brazil is where the major oil companies and other strategic industries are placing major bets on commercializing the technologies, locating them next to existing sugarcane mills and developing them to be able to take advantage of both bagasse and other feedstocks like sorghum and straw that can enhance the production cycle.

The Brazilian state oil company Petrobras, Dutch oil major Shell through its joint venture Raizen, BP, and French oil major Total through its investments in advanced biorenewables company Amyris, have all committed to advance the commercialization of the industry in Brazil. Both BP and Shell abandoned biorenewables projects in North America in 2012 and shifted their focus to Brazil and sugarcane bagasse. BP, which has projected that biofuels will make up 30 percent of the gasoline pool by 2030, cancelled a planned $300 million cellulosic ethanol project in Florida in late October to place its full attention on such projects in Brazil.

“The decision simply says that BP isn’t going to build the physical ethanol production facilities in the United States,” said BP media spokesman Matt Hartwig in an email to allies concerning it was abandoning the sector. “We are going to be looking for ways to commercialize our cellulosic ethanol technology, while continuing to run our operations in Brazil and the United Kingdom and developing biobutanol technology via our joint venture partner DuPont.”

In 2011, BP invested more than $750 million in three operating Brazilian plantations with sugarcane mills producing sugar and ethanol and has spent close to $200 million to expand their production capacity. At the end of 2012, BP said it would invest $350 million at one of its Brazilian facilities to double its capacity, controlling not only ethanol production but also bagasse feedstock supply for when it decides it will be commercially opportune to add cellulosic technology to its mills.

Shell, in May 2012, ended a long-time partnership with Genogen Energy to commercialize cellulosic ethanol in Canada. But it wasn’t because the oil major didn’t believe in logen’s technology, a few months later in October, Raizen said it would invest to develop a commercial cellulosic ethanol project in Brazil using logen’s technology that would be ready for production in 2014. Raizen is Shell and Cosan’s $12 billion joint venture in Brazil and the country’s largest ethanol producer and retail fuel distributor, including aviation fuels.

Brazilian state oil company Petrobras has also placed a stake in Brazil’s ethanol industry. In November, Petrobras said it planned to invest more than $1 billion in existing ethanol projects over the next four years. Petrobras has an ongoing co-development agreement for cellulosic ethanol with U.S. biorenewables company Blue Sugar. Petrobras has licensed Blue Sugar’s technology for its Brazilian sugarcane mills with the first facility expected to begin production in 2015, producing cellulosic ethanol from bagasse at a cost of about $2 a gallon, according to Blue Sugar CEO Peter Gross.

French oil major Total renewed its commitment to U.S. industrial biotech Amyris for the development of renewable fuels and chemicals using its engineered microbes to convert sugar into usable hydrocarbons. Amyris was one of the earliest U.S. companies to venture into Brazil, setting up a subsidiary to bolt-on its technology to existing sugar mills. After a false start in early 2012 that almost tanked its stock, Amyris began producing Biofene at its Paraíso Bioenergia production facility in December. Biofene is Amyris’ bio-based farnesane, a compound that can be processed into many specialty chemicals.

Brazil is also a desired destination for other major industrial players. Agribusiness Bunge has an ongoing partnership there with Solazyme that uses engineered algae feeding on sugar to make specialty oils.

Demand for sustainable packaging materials has also attracted chemical giants Dow and Mitsui, which finally secured government approval to formalize a 50/50 joint venture in Brazil that plans to make biopolymers for packaging, hygiene, and medical uses. It will be Dow’s largest investment in Brazil and perhaps the world’s largest biopolymers facility.

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Drought at the end of 2011 caused the price of sugar to soar in the global market and led mills to process their harvest as sugar instead of converting it to ethanol.
Many other first commercial projects will come online in 2013 and 2014, including Europe’s largest commercial cellulosic ethanol facility in Crescentino, Italy that will showcase Beta Renewables’ technology and be capable of producing 20 million gallons of ethanol a year. Another project, the Maabjerg Energy Concept, is an integrated design to create a total sustainable local energy solution by co-locating a power plant, a biogas plant, and a bioethanol plant in the Jutland area of Denmark. The idea was developed after DONG Energy (Danish Oil and Natural Gas) said in 2010 that it wanted to close its biomass-fired cogeneration power plant. Instead, it will be revamped to mostly use lignin from the bioethanol plant and the waste stream from the biogas plant. The bioethanol plant, which will be built by DONG, will use straw and other agricultural biomass to produce cellulosic ethanol, molasses, and lignin. The biogas plant, Maabjerg BioEnergy, became operational in late spring 2012 to convert 550,000 tons of biomass to biogas annually.

These are just the first of many plants that will begin producing renewable fuels and chemicals over the next few years, financed by the oil and gas companies, chemical companies, airlines, agribusinesses, enzyme producers, and food companies that are interested in buying their products [SEE FIGURE 7.25]. It is estimated that about 1,300 biorefineries will be needed to address existing global renewable fuels and chemicals targets. As with most commercial projects, the capital costs will come down as more of them come on line.

Optimizing crops

The new refineries will need a stable supply of feedstock ranging from biomass to industrial waste gases. While sugarcane is the opti-
mal feedstock because it doesn’t need to be transformed before it is fermented into ethanol (many forms of biomass need to be processed to be usable, which raises their cost), sugarcane’s price fluctuates with food prices, and, in 2012 when the price of sugar was high, many sugarcane processors in Brazil chose to sell sugar instead of converting it into ethanol.

In order to have a stable and secure supply of feedstock, companies are looking to develop a variety of fast-growing, non-food crops that can be grown in areas not well suited to food crops. Agbiotech Ceres has developed a sweet sorghum requiring less water and other inputs that can be processed by sugarcane mills during their down time, increasing their facilities’ ethanol production season by up to 60 days in Brazil.

Due in part to increased demand for ethanol and sugarcane shortages, Brazil’s government recently announced in its annual agricultural plan for 2012 and 2013 that sweet sorghum would be considered a strategic crop. In order to expand its coverage, Ceres entered into a market development agreement with Syngenta in November in which the companies will work together to support the introduction of sweet sorghum as a source of fermentable sugars at Brazil’s 400 or more ethanol mills. The companies will collaborate on small-scale trials as well as larger demonstration field evaluations with mills before rolling out the program.

Chromatin is also developing sweet sorghum for use as a feedstock for the biorenewables industry. In December 2012 the agricultural biotech entered into a collaboration with green building materials company Chlorophyll to harvest its sorghum for the production of Chlorophyll’s building products. In a test run, Chromatin’s 2012 trial sorghum crop produced a high yield despite record drought conditions. (Burrill & Company, the publisher of this report, is an investor in Chromatin.)

The drive for food security

While industrial biotech is using the tools of biotechnology to develop sustainable sources of fuel and chemicals, agricultural biotechs are using the tools of biotechnology to improve crops to both feed and fuel a growing world population that has surpassed 7 billion and is expected to reach 9 billion by 2050 [See Figure 7.27].

Not only is the global population growing, but a rising middle class in developing countries has also increased the demand for meat. It takes 3 kilograms of grain and 16,000 liters of water to produce 1 kilogram of meat. An estimated one-third of cropland today is used for livestock. The United Nations says agricultural production will have to increase by 70 percent by 2050 to meet global needs.

There is also the ongoing food-versus-fuel debate, exacerbated by severe drought conditions in the United States that led to soaring prices for staple crops such as corn and soybeans that are used for food, fuel, and animal feed [See Figure 7.26]. The food and livestock industry in the United States called for a moratorium on biofuels mandates, while the European Union has proposed limiting the use of food crop-based biofuels to no more than 5 percent of liquid fuel consumption.

With arable land at a premium, many countries have moved to both lease and acquire farmland, mostly in Africa, to meet their agricultural and energy needs. According to United Nations’ Food and Agriculture Organization and the International Food Policy Research Institute, Saudi Arabia, India, China, and South Korea have invested billions of dollars in African land to grow both food crops and biofuels crops destined for their home countries [See Figure 7.28 A AND 7.28 B].

But arable land is limited. As the rate of food consumption outstrips the rate of staple crop productivity, improving crop yields will be critical to assuring global food security in the years ahead. While organic farmers have said their practices are sufficient to meet the world’s growing food needs, an analysis published in Nature in early 2012 found that, in most cases, conventional farming methods that used chemical fertilizers and pesticides produced higher yields than organic farming methods. Researchers reviewed 66 studies comparing the yields of 34 different crops using conventional and organic farming practices. They found that organic farming worked equally well for some fruits and vegetables, but for most crops, especially cereal grains, the yields were significantly lower than conventionally produced crops.

A 2010 U.K. Royal Society report warned that current agricultural practice would not be sufficient to feed the world in the face of climate change, land and water scarcity, and environmental degradation. The report called for the practice of ‘‘sustainable intensification,’’ generating greater yields using less water, fertilizer, and pesticides. The report notes that biotech innovation has a role to play in order to reach the sustainable intensification of agriculture and secure global food supplies.

R&D investments inadequate

The global challenges of food security, energy security, and climate change highlight the need for increased investment in agricultural research and development. Most of this research has taken place in the United States and Europe, but the sums invested are paltry compared to investments in biomedical sciences. The research budget of the U.S. Department of Agriculture stood at $2.3 billion in fiscal 2012 compared to $31.2 billion for the National Institutes of Health.

A December 2012 report issued by the President’s Council of Advisors on Science and Technology recommended increased funding for agricultural R&D by $700 million a year. It also called for the creation of a network of public-private agricultural innovation institutes to leverage the strengths of government scientists and commercial interests. The report identified seven key scientific challenges facing agriculture: measuring new pests and pathogens; increasing the efficiency of water use; reducing the environmental impact of agriculture; adapting to a changing climate; and accommodating demands for bioenergy—all while continuing to produce safe and nutritious food for domestic and global consumption.

The report found that U.S. public and private research in agriculture and food totaled more than $14 billion in 2009, of which $3.8 billion came from federal funds. Private sector R&D accounted for the majority of research funding, $8.7 billion, most of which went to industry-managed internal research. States contributed $1.9 billion disbursed to land grant universities and experiment stations, in the form of state
Biorenewables Companies Focus on ASEAN

Southeast Asia is quickly rivaling Brazil as a desirable location for companies looking to set up advanced biorefineries. The countries that make up ASEAN, the Association of Southeast Asian Nations, have growing economies, a strong agricultural focus and abundant biomass resources, and a shortage of fossil fuels. At the same time, their governments are trying to transition their economies to knowledge-based industries such as biotechnology in order to sustain growth and provide for the social, economic, and environmental well-being of its citizens. As such they are prime targets for integrating advanced biorenewable technologies into an existing infrastructure of established oil-palm plantations and a supply chain capable of producing the biomass needed to support a robust biorenewables industry.

Malaysia, for one, has launched an initiative to support development of a sustainable biomass feedstock supply. As the focal point for biomass feedstock aggregation and supply, MyBiomass will act as a long term purchaser of oil palm biomass and help bring it to facilities that will convert it to higher value products. The region is also in close proximity to large downstream markets for its products in China, India, and the Middle East. The bio-based chemical market is expected to grow at over 20 percent per year over the next five years, according to the European Forum for Industrial Biotechnology, with a total market value expected to exceed $500 billion by 2017.

The chemicals industry and large industrial conglomerates in the region are partnering with advanced technology developers in the United States and Europe to set up facilities in the region to produce biorenewables that can be substituted for their fossil fuel equivalents and provide a hedge against volatile and rising oil prices.

Gevo is another company with plans to develop biorenewables in ASEAN. In June, Gevo signed a collaborative agreement with the Malaysian government’s economic development council and Malaysian Biotechnology Corp to place a cellulosic biomass isobutanol facility in Malaysia that will be operational by 2016. (Burrill & Company, the publisher of this report, is an investor in Gevo.) The collaboration offers a diversified feedstock, organized approach, and the opportunity to develop an economically advanced business plan to meet this expanding market.

“We’re excited to follow the demand, especially since Southeast Asia is one of the fastest growing chemical markets, and Malaysia provides an excellent growth opportunity for Gevo,” said Chris Ryan, president and chief operating officer of Gevo. Gevo is currently seeking industrial partners to help it commercialize its technology in the region.

Advanced biorenewables technologies can also help reduce industrial greenhouse gas emissions. Malaysia’s national oil company, Petronas participated in the $55.8 million series C financing for LanzaTech that include an agreement to work together to accelerate the development and commercialization of LanzaTech’s platform to produce sustainable chemicals from coal, natural gas, and biomass. LanzaTech will use its fermentation process to convert waste gas streams from refineries and natural gas wells to acetic acid, a high-value chemical with applications in the polymers and plastics markets. (Burrill & Company, the publisher of this report, is an investor in LanzaTech.)

“Rather than trying to sequester carbon deep into the earth, we will “bury” it in a chemical,” said LanzaTech CEO Jennifer Holmgren. “In this way, companies cannot only comply with emissions reduction requirements, but also generate revenue along the way.”

LanzaTech’s agreement with Petronas follows a similar agreement in China where the industrial biotech and Chinese steel manufacturer Baosteel where the technology was demonstrated and LanzaTech’s first commercial facility is being built that will convert the steel mill’s waste gas into ethanol.

Thailand’s state oil, gas, and chemical company PTT has invested heavily in biorenewables, including a $60 million strategic investment in Myriant in 2011. The companies have entered into a joint venture to explore building a facility in Southeast Asia to produce bio-succinic acid. PTT also has a 50/50 joint venture with Mitsubishi Chemical aimed at producing bio-succinic acid and polybutylene succinate from sugar using Myriant’s technology. In October 2012, PTT partnered with U.S. biobased material producer NatureWorks, saying it would invest up to $150 million to help build a production facility in Thailand to produce NatureWorks’s Ingeo fiber for use in fabric and packaging. The new plant is expected to begin production in 2015.

Singapore’s Wilmar, an Asian agribusiness giant, has also been actively involved in advancing biorenewables in ASEAN. Wilmar said in April 2012 that it would invest $80 million in a palm-oil based aviation biofuel plant to be built in Indonesia with U.S. biorenewables company Elevance Renewable Sciences.
Brazil ranks second behind the United States in its adoption of GM crops, with more than 30 million hectares (74.1 million acres) planted with soybeans, corn, and cotton. The country reached a milestone in 2011 with the marketing approval of a virus-resistant soybean, developed in-house by Embrapa, a public agricultural research institution. It also approved the first soybean with both insect resistance and herbicide tolerance for commercialization in 2012.

GM crops still in the crosshairs

Both China and India grow transgenic cotton but have hit speed bumps on the road to commercializing other biotech crops, even ones developed domestically. With 22 percent of the world’s population and less than 10 percent of its arable land, China has made agricultural reform a top priority. “Food security remains our biggest concern,” said China’s then premier Wen Jiabao, in a 2011 interview published in China’s Seeking Truth Magazine. “There is no other way to address the challenge than relying on technologies to transform traditional agriculture, such as high-yield variety breeding and GM technology.”

China’s government, in 2008, had allocated $3.8 billion over 10 years toward research and development of transgenic crops and animals. Biogene Transgene, China’s largest GM seed company, supplies the GM cotton seed used by 90 percent of China’s cotton growers and sells its seeds in India. By 2011, China had developed two varieties of insect-resistant rice and a high-phytase corn designed to reduce methane production in the livestock that consume it. They had passed bio-safety standards and were awaiting permission from regulatory authorities. The results of that experiment, published online in August in the American Journal of Clinical Nutrition, showed that the modified rice was indeed an effective way to combat vitamin A deficiency, a problem in many areas of the world that leads to blindness in half a million children each year. In response to public concerns, the government has pulled back. The Chinese Ministry of Agriculture has yet to issue permits to begin commercial production of rice in 2013. Syngenta, Monsanto, and Pioneer Hi-Bred, all have rushed to set up research centers in the country.

But protests from environmental groups, fearful that biotech rice would be approved, and public concern about the safety of GM foods have derailed efforts to advance commercialization. The public was outraged at reports in the summer of 2012 that Chinese children had been “guinea pigs” in an experiment testing golden rice, modified to be a source of vitamin A, without permission from regulatory authorities. The results of that experiment, published online in August in the American Journal of Clinical Nutrition, showed that the modified rice was indeed an effective way to combat vitamin A deficiency, a problem in many areas of the world that leads to blindness in half a million children each year. In response to public concerns, the government has pulled back. The Chinese Ministry of Agriculture has yet to issue permits to begin commercial production of rice in 2013. Syngenta, Monsanto, and Pioneer Hi-Bred, all have rushed to set up research centers in the country.

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GMO Labeling a No-Go, for Now

California’s Proposition 37 was the first attempt in the United States to require labeling of foods made from genetically modified crops. The measure was defeated by voters in a close call, 47 percent to 53 percent, after having gained widespread support in the state earlier in the election cycle. Proponents of Prop 37—mainly organic farmers, natural foods grocers, and environmental groups—argued that people had the right to know what was in their food, pointing to Europe and other countries with GMO labeling laws.

Opponents of the measure, big food processors, seed companies, and agribiotech, did not argue against consumers’ right to know. Instead, they said the wording of the proposition was so broad and would result in unnecessary lawsuits and a rise in food costs. If it had passed, the measure would have required that all raw or processed food products on California grocery shelves be labeled if they contained genetically engineered ingredients or processes. Groceries already in stores would have had to be repackaged to be sold. It also allowed individuals to sue food manufacturers that violated the measure’s labeling provisions. Certain foods were exempted, including meat from livestock fed genetically engineered grains, food sold at restaurants, and alcoholic beverages.

In the end, opponents outspent proponents five-to-one and helped defeat the measure with a barrage of television advertisements in the last weeks before the election. The real issue, a conflict between organic producers and big agribiotech companies, such as Monsanto and DuPont, was masked in the food fight.

The U.S. Food and Drug Administration requires the labeling of a food only if the absence of a label poses a health or environmental risk. In the weeks just before the November election, the American Association for the Advancement of Science issued a statement on the labeling of genetically modified foods, criticizing labeling efforts. “These efforts are not driven by evidence that GMO foods are actually dangerous. Indeed, the science is quite clear: crop improvement by the modern molecular techniques of biotechnology is safe,” the organization said. “Rather, these initiatives are driven by a variety of factors, ranging from the persistent perception that such foods are somehow ‘unnatural’ and potentially dangerous to the desire to gain competitive advantage by legislating attachment of a label meant to alarm. Another misconception used as a rationale for labeling is that GM crops are untested.”

The AAAS reiterated that “GM crops are the most extensively tested crops ever added to our food supply” and that numerous studies have found them nutritionally equivalent to conventional crops. “Legally mandating such a label can only serve to mislead and falsely alarm consumers,” AAAS said in the statement.

Misperceptions about genetic modification are likely to persist without a massive education program. Even then, human emotional involvement with food could trump science. In a surprising turn of events, just before the end of 2012, the FDA released its environmental assessment of genetically modified salmon, a fast-growing version developed by AquaBounty Technologies, concluding that the salmon would have no significant impact on the environment and was “as safe as food from conventional Atlantic salmon.”

The assessment was finalized in April 2012, one and a half years after an FDA guidance that gave a go-ahead for the salmon’s approval, but was held back from release for undisclosed reasons by the administration. After a comment period, it will likely receive formal approval and could be on the dinner table by the beginning of 2014. The path to likely approval for the first transgenic animal for human consumption took 17 years. If it becomes available at the grocery store, it will be interesting to see if people eat it.

by the Supreme Court of India recommended a 10-year moratorium on all field trials of GM crops. The report was widely condemned by many scientists and the industry. “We observe that there is a lack of focus and balanced scientific analysis in the report and there are numerous broad and sweeping recommendations regarding GMOs,” said the industry trade group ABLE-AG. No formal decision had been made on the status of a moratorium as of this writing, but already companies must obtain a “no objection” certificate from state governments before conducting field trials of transgenic crops. This has already put a virtual halt to GM crop research in the country.

Study inflames GM fears

Fears about the safety of genetically modified foods were inflamed following the publication of a French study in the journal Food and Chemical Toxicology that claimed rats fed a diet of a variety of Monsanto’s herbicide resistant corn together with a low level of the herbicide Roundup Ready developed tumors. Although anti-GM activists picked up on it right away as confirming their worst fears, scientists derided the study, conducted by an avowed opponent of GMOs, as flawed and lacking in merit. France, which has attempted to ban the growing of GMO crops even after they have been approved by EU regulators, came out against the validity of the study. France’s High Council of Biotechnology, an independent panel that advises the government, issued a statement saying that study results could not be supported because the study itself was flawed. After reviewing the study, six French scientific academies also issued a joint statement saying that no reliable conclusion could be drawn from the study and that it “spread fear among the public.” Both the French food safety regulator and the European Food Safety Authority also decided the study was flawed and in late November, France decided that there was no reason to ban the GM corn used in the study.

Efforts to commercialize GM crops in Europe have met with failure. Although the European Food Safety Authority has approved every GM product it has reviewed, the European public has been reticent to accept the technology. Efforts to commercialize GM crops in Europe have met with failure. Although the European Food Safety Authority has approved every GM product it has reviewed, the European public has been reticent to accept the technology. Bioavailability of GMOs and its most recent report finds that after 25 years of research, “GMOs are not per se more risky than conventional plant breeding technologies.” In the United States, GM products have also met with public concern. Californians put a measure that would have required the labeling of genetically modified foods on their November 2012 ballot, but the proposition was ultimately defeated.

Patents expiring

The first generation of biotech traits, which focused on herbicide tolerance and insect resistance, are set to expire over the next few years. Chief among these is Monsanto’s Roundup Ready soybean, the most widely used GM crop. This will leave the door open to generic seed companies. Chinese manufacturers already make generic versions of Monsanto’s Roundup Ready.

But Big Ag companies are moving away from the traditional genetic modification methods that involve inserting foreign genes into a plant in favor of exploiting new technologies made available through advances in genomic and biological knowledge. These technologies are blurring the line between GM and conventional breeding methods to induce desired traits into plants. And the desired traits are more complicated, involving a molecular pathway rather than one genetic modification. Besides the introduction of stacked traits that confer the traditional modifications for herbicide tolerance and pesticide resistance, companies are using both biotech and advanced molecular breeding methods to confer traits that increase tolerance to drought and soil salinity, increase efficiency of nitrogen use, and a host of other desirable qualities.
A Taste of Things to Come

New biotech crop breeding technologies without inserting foreign DNA

As the world population swells to a projected 9 billion people by 2050, food production will need to increase by 70 percent, according to the United Nations Food and Agricultural Organization projections. At the same time, farmers will need to reduce their greenhouse gas emissions, increase the water use efficiency of their crops, and assure the healthfulness of the foods that are produced. Plant breeders, therefore, need to use all the technologies available to hasten the crop improvement process.

Traditional genetic modification technology will continue to play an important role in crop improvement, in spite of high regulatory hurdles. But as biological and genomic knowledge advances, new crop technologies are being developed that, in some cases, may find an easier entrance to market. That’s because they may not fall under the present regulatory rules, which focus on transgenic technologies involving foreign DNA insertion. Most of the new techniques work by modifying plant genes directly rather than by inserting foreign DNA.

A study on new plant breeding techniques, sponsored by the European Union’s Joint Research Centre, was conducted to elucidate current technologies under development and their prospects for commercialization. Results of the study were published in the March 2012 issue of Nature Biotechnology.

New technologies covered in the study include: zinc-finger nuclease technology, designed to cut DNA at specific sequences to cause a desired effect; oligonucleotide directed mutagenesis, another way of inducing a site-specific mutation in a plant gene; cisgenesis and intragenesis, transformations done by introducing DNA from the same species that can include silencing techniques such as RNA interference; RNA-dependent DNA methylation, a way to modify gene expression in plants epigenetically; and grafting a non-genetic scion plant onto a genetically altered rootstock so that the fruit of the scion does not contain any genetically altered DNA. With grafting, the rootstock can be modified by gene silencing with RNA interference technology. The small RNAs introduced can move through to the graft to affect gene expression in the scion.

Analyzing scientific publications on new plant breeding technologies between 1991 and 2009, the Nature Biotechnology study authors found that while the majority of publications were arising out of public European institutions (See Figure 7.B), the majority of granted patents and patent applications on new crop technologies were assigned to private North American institutions (See Figure 7.B). The top patent grantees were Sangamo Biosciences with 11 patents on zinc-finger nuclease and Dow Agrosciences with five patents on zinc-finger nuclease (See Figure 7.C). Many of these new techniques give breeders the ability to target the gene of interest and avoid introducing unintended and unwanted changes elsewhere in the genome. Plant breeders have not yet commercialized a product derived from any of these technologies but some are at a late stage of development, already being tested in field trials ahead of building a dossier for submission to regulatory authorities. But commercialization of the most advanced crops is still two to three years away.

It is not yet clear how regulators will treat these new technologies. Indeed, regulatory uncertainty may limit the establishment of new techniques, say the study authors, as they are generally used in the early stages of the breeding process. Companies will be wary of committing to the high costs of developing new breeds without knowing whether they will fall under the GM umbrella and whether or not consumers will accept them. Regulators, too, must develop new ways for identifying the final products of these technologies, especially for risk assessment, and standard methods for identifying GMOs are insufficient for detection.
Many of these advanced breeding technologies go beyond traditional genetic modification in order to develop superior hybrids without policy hurdles faced by genetically modified crops in many parts of the world. For example, Cibus Global, a privately held San Diego-based agricultural biotech, uses a process known as directed mutagenesis that works through the cell’s own DNA repair mechanism, directing DNA repair enzymes to correct and repair the targeted gene in a specific way in order to produce a desired trait. It has applied to Canadian regulatory authorities for marketing approval of its first product, a herbicide-tolerant canola. DuPont’s Pioneer Hi-Bred introduced a new drought-resistant corn to the market in January 2011, developed through the use of molecular markers rather than genetic modification to produce a desired trait. Monsanto was an early investor in DNA sequencing company Pacific Biosciences. In 2011, Monsanto partnered with Atlas Venture, an early-stage venture capital firm based in Cambridge, Massachusetts, to explore investment opportunities in early-stage life sciences technology companies, especially those that support their toolkit. Monsanto was an early investor in DNA sequencing company Pacific Biosciences.

In 2012, a wave of partnering and acquisition activity focused on harnessing the natural capabilities of microbes, and genomic and biologic tools to produce new biological crop protection products. Bayer CropScience anticipates demand for biological pest management using natural microorganisms will become a multi-billion dollar market in the decade ahead. In July 2012, the company acquired Davis, California-based AgraQuest for $425 million plus milestone payments. From powdery mildew to loopers and armyworms, the subsidiary of German drugmaker Bayer AG expects AgraQuest’s biotech-based solutions will help farmers increase their yields.

“The growing fruits and vegetables market, which today accounts for more than 25 percent of our sales, is of strategic importance for us,” outgoing Bayer CropScience CEO Sandra Peter-son said when the deal was first announced. Bayer expects to achieve $3.9 billion (€3 billion) in annual sales in the segment by 2020. The acquisition of AgraQuest simply underlines “our growth ambitions,” she said.

The AgraQuest acquisition reflects a broader interest among Big Ag companies to use biotechnology not only to improve crop yields, but also to address crop-destroying diseases and pests. These products reduce the need for toxic pesticides, fungicides, and herbicides that protect crops, but also carry environmental consequences.

### SELECT AGRICULTURAL BIOTECH M&A IN 2012

<table>
<thead>
<tr>
<th>ACQUIRER</th>
<th>TARGET</th>
<th>DEAL VALUE (USD M)</th>
<th>PRINCIPAL FOCUS</th>
<th>DEAL DESCRIPTION</th>
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<tbody>
<tr>
<td>Monsanto</td>
<td>Precision Planting</td>
<td>250.0</td>
<td>Crop yield improvement technology</td>
<td>Monsanto acquires planting technology developer Precision Planting, a leader in improving yields through on-farm planting performance, and will integrate its team into its Integrated Farming Systems unit, which utilizes advanced agronomic practices, seed genetics and innovative on-farm technology to deliver optimal yield to farmers while using fewer resources. Monsanto will pay $210 million for the business, plus a performance-based payment of up to $40 million.</td>
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<tr>
<td>Bayer CropScience (Germany)</td>
<td>AgraQuest</td>
<td>500.0</td>
<td>Biopesticides</td>
<td>Bayer CropScience acquires California-based biopesticide developer Agragen for $425 million upfront and up to $75 million in milestones. The acquisition enables Bayer CropScience to build a leading technology platform for green products and to strengthen its strategically important fruits and vegetables business, while also opening new opportunities in other crops and markets.</td>
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<tr>
<td>Syngenta (Switzerland)</td>
<td>Pasteuria Bioscience</td>
<td>113.0</td>
<td>Biopesticides</td>
<td>Syngenta acquires Pasteuria Bioscience for $86 million in aggregate payments, plus up to $27 million in deferred payments. In 2011 Syngenta and Pasteuria Bioscience entered into a global exclusive technology partnership to produce nematode control products based on Pasteuria spp., a naturally-occurring soil bacteria long recognized as a promising biological control agent against nematodes. The first products resulting from this relationship will be available in 2014.</td>
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<tr>
<td>Syngenta (Switzerland)</td>
<td>Devgen (Belgium)</td>
<td>523.0</td>
<td>Agbiotech</td>
<td>Syngenta acquires Devgen, a developer of hybrid rice seeds and RNAi technology, enabling Syngenta to combine its crop protection portfolio with Devgen’s best-in-class rice hybrids and broad germplasm diversity and expertise in RNAi-based insect control, for which the two companies signed a global license and research agreement to develop spray applications in May 2012. Syngenta has offered €16 for each outstanding Devgen share and a price for the warrants set according to market practice, representing a total consideration of around €403 million.</td>
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<tr>
<td>BASF (Germany)</td>
<td>Becker Underwood</td>
<td>1,020.0</td>
<td>Crop protection</td>
<td>German chemical giant BASF acquires U.S. crop-technology company Becker Underwood for $1.2 billion (€785 million), continuing consolidation in the seed-treatment market and bolstering BASF’s existing business in crop protection, including chemical coatings and other treatments applied to seeds before they are planted, to protect crops from pests and other harm. The deal strengthens BASF’s presence in biopesticides. Becker Underwood produces beneficial nematodes, which are tiny worms that can help control pests such as weevils and moths.</td>
</tr>
<tr>
<td>Dow AgroSciences</td>
<td>Cal/West Seeds</td>
<td>N/A</td>
<td>Crop seeds</td>
<td>Dow AgroSciences acquires the assets of Cal/West Seeds, leading supplier of alfalfa, clover, and other crops to seed companies and growers globally. Dow AgroSciences will acquire substantially all of Cal/West Seeds’ assets including Cal/West and Producer’s Choice brands, Cal/West SRL, Argentina, the R&amp;D technologies and genetics programs, as well as the production facilities located in California, Washington, and Wisconsin</td>
</tr>
</tbody>
</table>

Source: Burrill & Company
One product Bayer acquired in the deal, Seranade, is a fungicide employing live bacteria to fight fungal crop infections. The bacteria destroy harmful fungus directly and make them more vulnerable to other fungicides by puncturing thousands of tiny holes in the membranes of fungal cells. Another, Requiem, employs an extract from a plant long used to treat parasites in animals and humans to break down insects' exoskeletons, which disrupts their vital function and ability to navigate.

Development of beneficial bio-based compounds and microbes in agriculture is becoming big business for agricultural biotechs, much the same way as it has become a mainstay for industrial biotechnology companies. Bayer’s AgraQuest acquisition bodes well for the industry, suggested Novozymes executive Thomas Videbak, during an earnings call for the Denmark-based industrial biotechnology company. “We see that as a good example of other people also realizing the long-term, mid-term opportunities in this market,” said Videbak, the company’s executive vice president of BioBusiness. “We think that more people working on solutions in this area is going to bring new innovative ideas into the marketplace and we’re certainly happy that the other people are pulling in that direction.”

That pull toward innovation is becoming an all-out push as agricultural diseases and pests develop resistance to a growing number of marketed pesticides and herbicides. The need to address the growing problem of resistance is at the heart of Bayer CropScience’s September 2012 announcement of a new multi-year collaboration with Mendel Biotechnology to jointly identify herbicides through novel modes of action. “There is a major need in agriculture for herbicides acting through novel modes of action,” said David Nicholson, Bayer CropScience’s global head of research and development. To meet that need, Bayer will rely on Hayward, California-based Mendel’s expertise in working with plant genetic regulatory networks, as well as its suite of proprietary genetic tools and assays for understanding plant development. Financial details of the collaboration were not released.

Mendel is also actively pursuing the development of biopesticides. In September 2012, the Swiss agricultural giant said it would acquire Florida-based biopesticide developer Pasteuria Biosciences for approximately $86 million, plus up to $27 million in deferred payments. In 2011 Syngenta and Pasteuria entered into a global exclusive technology partnership to produce nematode control products based on Pasteuria sp., a naturally occurring soil bacteria long recognized as a promising biological control agent against nematodes. The first products resulting from this relationship will be available in 2014.

Biochemical players are also establishing closer ties with companies better known for their drug development expertise and assays for understanding new drug development. “We think that more people working on solutions in this area is going to bring new innovative ideas into the marketplace and we’re certainly happy that the other people are pulling in that direction.”

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Big Ag embraces RNAi

RNA interference, a naturally occurring process for regulating genes within the body, has been the focus of the biopharmaceutical industry in recent years as a potential new class of therapeutics. But Big Ag companies are also embracing the technology through a series of acquisitions and licensing agreements as a potentially powerful tool in the agricultural arena to control pests and improve crop yields.

Building its RNAi portfolio under the BioDirect name, Monsanto in September 2011 acquired Israel-based Beelogics for an undisclosed amount. Beelogics has been working on a biologic to address colony collapse disorder in honey bees using RNAi technology. The deal not only gives Monsanto access to its RNAi expertise, but also provides critical manufacturing capabilities. Monsanto followed that deal in May 2012 with an exclusive licensing agreement with Bothell, Washington-based Marina Biotech for its RNAi delivery and chemistry technologies for an undisclosed amount. In August, Monsanto entered into a ten-year licensing agreement and collaboration with Alnylam Pharmaceuticals, which includes $29 million in upfront payments, as well as potential milestones and royalties. What’s more, Monsanto has said it now has submitted more than 100 patent applications around RNAi technology.
For Monsanto, RNAi represents a new push within the area of agricultural biologies, a $1.7 billion market today that it forecasts will grow at a rate of 10 percent a year. The market includes such things as biopesticides, biofungicides, and nutrients. What makes the technology additionally intriguing for a company often vilified for its work with genetically modified organisms is that RNAi-based products represent a non-transgenic, non-GMO approach—leaving the DNA of an organism unaltered.

Monsanto is not alone in its interest in applying such technology to agriculture. The Belgium-based agricultural biotech Devgen announced in May that it had signed a research partnership and licensing agreement with Syngenta. Under the agreement, Syngenta will develop and commercialize sprayable RNAi-based crop protection products developed from Devgen’s technology. That deal provided Devgen with a $28.3 million ($22 million) upfront payment and annual research fees of $6.2 million ($4.8 million) during the six-year agreement.

Syngenta decided in September 2012 that it wanted to buy Devgen outright, offering to pay $523 million ($403 million) for the Belgian biotech, also a leading developer of hybrid rice. The offer for Devgen represented a 70 percent premium to Devgen’s closing price prior to the announcement and came a week after Syngenta announced its acquisition of Pasteuria Bioscience. “There is immense potential in combining Devgen’s pioneering research in both GM and conventional plant solutions into our offer we can increase the options and capabilities we provide to our customers.”

Other companies, such as DuPont, are pursuing micro RNAs or miRNAs in such applications as enhancing the drought resistance of crops. miRNAs are short RNA molecules that can be used to silence genes. The company entered into a strategic alliance with Rosetta Green at the end of 2011. Rosetta Green is also working with Bayer CropSciences on applying miRNA to crops.

BioDirect leverages Monsanto’s expertise in plant genomics, but uses chemistry to enable new products that could provide options for sustainable pest or virus control. Agricultural biologies are typically topical or seed treatment products produced from natural materials and used to complement or replace agricultural chemical products. Robert Fraley, executive vice president and chief technology officer for Monsanto, discussed the company’s BioDirect platform during an investor presentation at the Goldman Sachs Basic Material Conference in May. "It’s now possible to spray these RNA molecules to control the expression of genes,” said Fraley at the conference. “Through advances we’ve been able to make in manufacturing and formulation, it is now possible to spray these targeted biologicals at an agricultural scale. ‘That gives us a strong discovery effort, a strong IP position, and a strong manufacturing position.’

Monsanto believes its BioDirect technologies eventually could be used to identify new opportunities for current herbicides, create better insect control options, and offer new virus-control tools. "BioDirect technology has the potential to be one of the most exciting advancements for agriculture that I’ve seen in my career,” Fraley said. “By building complementary biological insect control solutions into our offer we would increase the options and capabilities we provide to our customers.”

Laurence Reid, Chief Business Officer, Alnylam

“We don’t know what the rules are for plants yet. Some of them are going to be similar and some of them are going to have to be different.”

“Delivering value”

DuPont, one of the largest chemical companies with a thriving biotech seed business, took a giant leap into the biorenewables space first in a joint venture with Danisco to develop cellulosic ethanol, followed a year later in early 2011 with the $6 billion acquisition of the Danish ingredients and enzymes maker to establish DuPont Industrial Sciences. It was an early indication of a future where the products that deliver value will be the ones that will secure nations’ food and energy supplies with minimal environmental impact.

The biorenewables industry is young and agricultural technology has only recently embraced the power of genomics. For biorenewables, the industry needs to see some commercial successes at scale that can convince investors and the market that biorenewables can be a significant replacement for fossil fuels. Companies that are nimble and flexible will be able to access capital and become acquisition targets.

Success will also depend on the aggregation and conversion of biomass from non-food sources at massive scale. This has not yet occurred and is still a future challenge. But energy and food prices are only going up, land is only becoming more scarce, demand on natural resources is only intensifying. In a finite world, biotechnologies that can move us to a low-carbon future will eventually gain in value, and deliver it to the benefit of mankind.
8
M&A and Partnering

With capital markets still difficult for emerging growth biopharmaceutical companies, Big Pharma showed self-restraint in 2012. In fact, 2012 was notable for the small number of multi-billion dollar deals. Life sciences M&A transactions totaled $109.4 billion globally, a 31 percent drop compared to 2011. On the partnering front, leading pharmaceuticals sought to strengthen their pipelines and sought access to new markets through creative dealmaking that often required their partners to shoulder substantial risks. That will continue in 2013. But as Big Pharma absorbs past acquisitions, it might be ready to dive back into the M&A pool and make a big splash in the near term. Many of these companies are sitting on large stores of cash and it is likely that there will be a pickup in acquisitions in 2013.
At the beginning of 2012, Bristol-Myers Squibb agreed to buy Inhibitex, a maker of hepatitis C treatments, for $2.5 billion in cash. The deal was focused on Inhibitex’s lead drug INX-189, an experimental hepatitis C therapy that at the time of the acquisition had only completed early-stage trials. Inhibitex benefited from the rich $11 billion price tag that Pharmasset had commanded from Gilead Sciences just a month before for its portfolio of hepatitis C drugs. The acquisition valued Inhibitex at $26 per share and marked a 163 percent premium to the company’s pre-announcement market close. It capped an active year for the hepatitis C market spurred by the success of Merck’s Victrelis and Vertex’s Incivek—both oral protease inhibitors—winning U.S. Food and Drug Administration approval in early 2011. BMS’s aggressive play in the hot hepatitis C market—a space it was less familiar with compared to others—exemplified pharmaceutical companies’ efforts to access new sources of revenue by tapping into new innovative therapies in potentially lucrative markets where patients needs are not well met.

But the premiums innovative assets command come with risk. For BMS, its $2.5 billion bet ended up an investment bust. Just months after the acquisition, the drugmaker suspended a mid-stage trial of the compound it acquired from Inhibitex due to safety concerns among patients raising major questions about its future development. BMS eventually abandoned the experimental hepatitis C compound after one patient died of heart failure and nine others were hospitalized during the clinical trial.

Critics faulted BMS for paying so much for the early-stage therapy but the company believed that its rationale was sound at the time since hepatitis C was becoming such an important therapeutic indication and because it already had another hepatitis C compound in its pipeline. Following the clinical failure, the company took a pre-tax impairment charge of $1.8 billion in the third quarter of 2012. It is now in the midst of defending itself against lawsuits from plaintiffs seeking as much as $500 million in damages, alleging that it pushed the compound through development despite serious safety concerns.

In recent years, the pressure drugmakers faced to replenish depleting pipelines led to a surge in acquisitions and partnerships. Pharmaceutical companies have often addressed their R&D deficiencies by buying rather than building from within, but they have sometimes suffered a series of failures that turned gold into straw. Bristol-Myers’ acquisition of Inhibitex turned out to be such a deal. However, the industry has also demonstrated that while it is still willing to pay for access to early and mid-stage assets, buyers are increasingly structuring deals to mitigate their risk and play to each party’s strengths. The evolving M&A model demonstrates an attempt not only to seek innovation, but also to minimize risk.

The sobering Inhibitex deal may have spurred BMS to reconsider its approach to growing its non-R&D presence. Shortly after the Inhibitex blowup, BMS struck a $7 billion deal to acquire the diabetes drugmaker Amylin Pharmaceuticals. In one of the more unusually structured deals of the year, BMS utilized an existing alliance with AstraZeneca to help pay for Amylin. BMS acquired Amylin for $31 per share in cash, or approximately $5.3 billion. The total value of the deal, including Amylin’s net debt and obligation to Eli Lilly, was about $7 billion. To help pay for the transaction, after the merger was completed, AstraZeneca paid BMS’ Amylin subsidiary $3.4 billion for a 50 percent stake in Amylin’s diabetes pipeline in a deal based on the framework of its existing diabetes alliance with BMS in which profits and losses arising from the collaboration will be shared equally. Additionally, AstraZeneca has the option, exercisable at its discretion, to establish equal governance rights over key strategic and financial decisions regarding the collaboration, upon the payment of an additional $135 million to BMS.

The deal marked a rare instance in which two Big Pharmas came together to acquire a biotech company. BMS and AstraZeneca have been in a partnership to develop diabetes drugs since 2007 with limited success. Both needed to strengthen their pipelines. Their first partnered drug, Onglyza, has had limited success competing against Merck’s Januvia. Their most recent diabetes compound, dapagliflozin, failed to win approval from the FDA in January 2012, although it did win European approval in November 2012.

The Amylin deal gives BMS and AstraZeneca three FDA-approved type 2 diabetes drugs. They include Byetta, a twice-daily injectable, and Bydureon, a once-weekly version of Byetta that was approved in early 2012. Byetta is derived from a hormone in the saliva of the Gila monster, a poisonous lizard found in the deserts of North America. Both drugs are GLP-1 receptor agonists, which act to increase the production of insulin in the presence of high blood sugar.

In addition to the GLP-1 franchise, the deal gave the two drugmakers the already approved Symlin, an amylin analog injection approved to treat both type 1 and type 2 diabetes patients with inadequate glycemic control of meal-time insulin, as well as metreleptin, an experimen-
tal leptin analog currently under review at the FDA for the treatment of diabetes and/or hypertriglyceridemia in patients with rare forms of inherited or acquired lipodystrophy.

At the time of the acquisition, BMS CEO Lamberto Andreotti noted the importance of Amylin’s assets to the company’s already strong diabetes portfolio: “Amylin’s innovative diabetes portfolio complement our long-standing leadership in metabolics,” he said.

Unlike the Inhibitex deal where BMS paid a hefty 163 percent premium to bolster its hepatitis C pipeline, the offer for Amylin came at just a 10 percent premium to its closing price the day before the offer was announced. Although that was more than double a previous offer that was made privately and rejected by Amylin’s board in February 2012, BMS mitigated its risk by waiting to buy Amylin until after the FDA approved Bydureon, when Amylin’s share price reflected its improved outlook.

For Wall Street, the structure of the deal represents a marked change from traditional M&A transactions. If the easier-to-use Bydureon becomes a blockbuster product—as it is currently expected to become—there is ample opportunity for the deal to reap rewards for all parties involved. As ISI Group analyst Mark Schoenebaum said at the time of the acquisition, “We saw a lot of interest in Amylin because it’s diabetes, and there aren’t a lot of diabetes assets out there. It is increasingly strategic to be in that market...it will create value for shareholders.” Though BMS may have limited its overall margins by striking the follow-on agreement with AstraZeneca, it had already taken precautionary steps against repeating its earlier mistake by sharing in both the profits and losses Amylin’s assets may bring forth.

Big deals curbed

Overall, 2012 was notable for the smaller number of multi-billion dollar deals. Life sciences M&A transactions totaled $309.4 billion globally, a 31 percent drop compared to 2011. In 2012, Nestle’s $11.8 billion acquisition of Pfizer’s infant nutrition business was the only transaction greater than $10 billion [See Figure 8.1]. By comparison, 2011 saw major transactions that included Sanofi’s $20.1 billion acquisition of Genzyme, Johnson & Johnson’s $21.6 billion Synthes buy, Takeda’s $13.7 billion acquisition of Nycomed, and Gilead Sciences’ $11 billion purchase of Pharmasset.

In addition to BMS’ $7 billion acquisition of Amylin Pharmaceuticals and $2.5 billion acquisition of Inhibitex, other top deals of 2012 included GlaxoSmithKline’s $3 billion acquisition of its partner Human Genome Sciences. The deal gave GSK full control of lupus drug Benlysta and other promising compounds. Other deals of note include AstraZeneca’s acquisition of Ardea Biosciences for $1.3 billion for its gout drug and Amgen’s $1.2 billion acquisition of Micromet for its BiTE technology platform and pipeline.

Overall, deal values for therapeutic M&A deals fell considerably in 2012. After the surge in M&A deal values seen in the second quarter of the year, buoyed by the acquisition of Pfizer’s nutrition business ($11.6 billion) and Amylin ($7 billion), far fewer multi-billion dollar deals were closed in the second half of the year. [See Figure 8.2]. The average value for therapeutic M&A deals in 2012 with disclosed deal values in excess of $20 million was $638 million, a 36.4 percent drop compared to the $1 billion average deal value for such deals in 2011. The number of transactions, however, rose 22.4 percent in 2012 compared to 2011 [See Figures 8.3-8.5].

The hunt for innovative therapeutics continued to fuel activity as companies sought out acquisition targets that had clinical-stage candidates, rather than preclinical or marketed products. Acquisitions of clinical-stage companies...
jumped to 37 percent in 2011, from just 8 percent in 2010. And in 2012, clinical stage companies were the target in nearly half of all disclosed deals, sparked mostly by an uptick in the acquisitions of companies with mid-stage products [See Figure 8.6].

A year of restructuring

Big Pharma no doubt will continue to seek to replenish its pipeline via mergers and acquisitions. But doing so in the midst of restructuring has made the path more challenging. That’s given rise to more creative deals—and in many cases more complex ones that can better ensure our aspirations in dermatology, we have been looking at Medicis for some time,” said J. Michael Pearson, chairman and CEO of Valeant. “This acquisition represents a significant next step” in Valeant’s plan to strengthen its products for acne, actinic keratosis, aesthetic injectables, and antivirals, he said.

Valeant sees a lot to like in the U.S. dermatology market, which it views as fragmented explaining the company’s rationale for the acquisition. “In terms of coverage, there is fairly low government reimbursement for these products, and a growing self-pay component.”

Consider too the Big Biotechs Amgen and Celgene. Both companies announced important acquisitions of companies with promising therapeutic candidates in hematology. Amgen acquired the biotech Micromet for $11 per share in cash, or $1.16 billion; while Celgene paid $350 million in cash upfront for privately held Avila Therapeutics, with further payments that could bring the total payout to $925 million.

Amgen’s acquisition of Micromet comes less than a year after the two companies signed a billion-dollar partnering agreement to discover and develop anti-infectives against undisclosed tumor targets. With the acquisition, Amgen not only gets the whole program, but also Micromet’s mid-stage leukemia therapeutic blinatumomab, a bispecific T cell engager, or BiTE antibody. It will also get potential milestone and royalties from all the companies that have licensed Micromet’s BiTE technology, including Bayer HealthCare Pharmaceuticals, Boehringer Ingelheim, MedImmune, Merck and a relationship-oriented and industry-friendly environment,” Pearson told analysts on a call explaining the company’s rationale for the acquisition.

Amgen acquired a top clinical stage company, with the potential to be a leader in the mid-stage hematologic area where pricing pressures are not as great. In fact, over the last two years, Big Biotech in 2011, and specialty phamas, especially in 2012, have been active acquirers [See Figures 8.8 AND 8.9].

Consider the specialty pharma, Valeant Pharmaceuticals, which in August bought the largest U.S. dermatology company, Medicis Pharmaceutical, for $2.6 billion. The deal allowed Valeant to leapfrog Galderma as the leading prescription skincare company in terms of sales. “The transaction, in which Valeant acquired all outstanding Medicis shares for $44 per share in cash, represented a 39 percent premium to Medicis’ previous day’s closing price and gave Valeant access to Medicis’ extensive portfolio. Among some of the products Medicis offered were the oral acne treatment Solodyn, and the injectable wrinkle remedies Restylane, Perlane, and Dysport, a competitor to Botox.

“Given the complementary nature of our portfolios, and our aspirations in dermatology, we are very excited about this opportunity,” Pearson said. “With a focused target list of prescribers, it is...
be due to more purchasing power—Ernst & Young’s “Firepower Index,” for example, found that between 2006 and 2012 Big Biotech’s capacity to acquire new assets has increased 60 percent while specialty pharma’s firepower has increased 20 percent [See Figure 8.10]. But another reason Big Biotechs and specialty pharma’s may be looking more to M&A is that timelines for developing new drugs are getting compressed. Investors expect results faster than many companies can deliver them. It may be easier to buy potential pipeline candidates rather than develop them in-house. Current business models also play into a larger pool of acquisition candidates since an IPO route is no longer a viable exit for investors in most circumstances. One new business model favored by venture investors involves setting up a company to advance an asset to proof-of-concept and then selling it.

Still a preferred exit

While public markets came back to life in 2012 as the U.S. economy clawed its way out of the deep recession of the last few years, mergers and acquisitions remained the preferred exit for venture backed private companies. In fact, of the 484 total U.S. venture-backed exits tracked by the National Venture Capital Association and Thomson Reuters in 2012, 435, or 90 percent, were via M&A [See Figure 8.11]. It was true that the biotech sector performed well in 2012. The Burrill Biotech Select Index, for example, finished the year up more than 40 percent, and the biotech IPO class of 2012 outperformed IPOs from other industries. But while biotech IPO aftermarket performance was impressive—sparked by the likes of Intercept and Kythera—it didn’t afford their venture backers optimal returns because of the continued difficulties life sciences companies have had pricing their shares. M&A transactions of private companies continued to outnumber those of public companies. While 2011 saw more public companies acquired than in anytime over the last five years, 2012 saw the number of private companies being acquired climb back up to nearly 60 percent of the total, as was the case in past years [See Figure 8.12].

In looking at the types of premiums life sciences M&A deals are attracting, biotech and diagnostics companies are much more prized than specialty pharmaceuticals. Median biotech premiums reached about 42 percent, while median diagnostics premiums stood at 27 percent, rising in lock step as companies seek novel targeted therapeutics that benefit specific populations identified by diagnostics [See Figure 8.14].

Offshore activity growing

Companies continue to look beyond their own backyard and seek attractive acquisitions overseas. For U.S. buyers, higher tax rates in the United States, and higher demand for acquisitions domestically are making the use of offshore cash reserves to buy non-U.S. companies more attractive. While North America continues to be the hottest region for both therapeutic acquirers and targets, there was incremental growth seen globally. Acquirers based in North America grew to 22 in 2012, from 18 in 2011, and acquisitions of North American targets grew to 58 from just 40 in 2011. At the same time, targets outside the United States also increased to 15 companies from 13 in 2011. Japanese companies, especially Takeda Pharmaceuticals, continued their recent trend toward overseas acquisitions [See Figure 8.13]. Japanese companies have been actively buying overseas firms to expand their market reach.

by target region

- North America
- Europe
- Japan
- Rest of World
- Total

Source: Burrill & Company, M&A Capital IQ, Windhover
Acquisitions by both overseas and domestic pharmaceutical companies in emerging markets had reached $20 billion in the first 11 months of 2012, up two-thirds on the 2011 total.

Drug companies also spent record amounts on acquisitions in emerging markets, with China the most attractive target nation. Overall, acquisitions by both overseas and domestic pharmaceutical companies in emerging markets had reached $20 billion in the first 11 months of 2012, up two-thirds on the 2011 total, according to an analysis by law firm Freshfields Bruckhaus Deringer using Thomson Reuters data. China attracted $6.8 billion of that amount. The growth in emerging markets acquisitions, especially in China, is expected to continue for the foreseeable future because of their fast-growing markets for pharmaceuticals. China’s market for medicines is projected to grow by 15 to 18 percent annually to between $155 billion and $165 billion by 2016, making it the world’s second-largest market after the United States, according to consultancy IMS Health.

Going hostile
Pharmaceutical companies, while more anxious than ever to gain access to novel development-stage products, have nevertheless been tightened with upfront payments. Because such transactions are not tied to the known sales of a product, the calculation for determining the terms of the deal are overshadowed by degrees of risk. The competition for assets in certain indications, such as hepatitis C, diabetes, or metabolic disease, has led to larger premiums as Big Pharma has fueled a seller’s market in these areas [see Figure 8.15].

But a few companies in 2012 resisted tender offers in the belief that their assets were more valuable than what the offers reflected. GlaxoSmithKline declined Human Genome Sciences’ offer to participate in its strategic alternatives review process and instead went directly to shareholders in an effort to acquire the biotech for $2.6 billion. Its $13 per share cash offer represented a premium of 81 percent to HGS’s closing share price of $7.17 on April 18, 2012 the last trading day before HGS publicly disclosed GSK’s private offer, which it rejected. The two companies had been partners for a long time, co-sharing profits from HGS’s approved lupus drug Benlysta. They were also partnered on two late-stage drugs to treat diabetes and heart disease, albiglutide and darapladib.

In a statement during the initial take-over attempt, GSK said its offer was fair and it did not need to participate in HGS’s strategic alternatives review process because its offer was not conditional on due diligence and could be completed quickly. “There is clear strategic and financial logic to this combination and HGS shareholders should have the opportunity to decide for themselves on the merits of the offer,” the Big Pharma said at the time.

Eventually though, the partners came to terms, partly due to the fact that GSK hiked its offer price an additional $1.25 a share, which valued HGS at $3 billion, and represented an impressive 99 percent premium over HGS’s closing price the day before the initial tender offer was made, but also because with its existing GSK partnership, the company had little value for other potential acquirers. HGS went looking for a white knight and couldn’t find one. The premium was a negligible victory considering the struggle it had capturing value from its lupus drug Benlysta and the fact that it had turned down a $7 billion bid from Amgen in 2010.

In yet another instance of a take-over turning hostile, Roche made a $5.7 billion bid for Illumina in January 2012, in an attempt to bolster the revenue of its gene-mapping equipment sector. The $44.50 a share bid was quickly rejected by Illumina’s management, who instigated a poison pill provision so as to make Roche’s unwanted bid prohibitively expensive and less attractive. Roche responded by raising its offer by about 15 percent to $51 a share, or about $6.7 billion in total, but Illumina’s management again rejected the deal. Roche’s CEO Severin Schwann responded to the second rejection by saying that he found the share bid “full, fair, and extremely attractive.” And though
Roche hinted that it might raise the bid further, it eventually decided that making a higher bid would not be in the interest of its shareholders.

Partnering deals evolving too

In much the same way that M&A transactions are being structured to limit the risk for the buyer, partnering deals are also undergoing an evolution. In the very first month of the year, Constellation Pharmaceuticals, a small biotech startup, announced a partnership with Roche’s Genentech that, while not nearly one of the biggest partnering deals of the year at only $95 million, exemplifies an evolving partnering model.

Constellation was founded with a focus on epigenetics, a newer field of drug discovery that targets the molecular changes in cells that activate and deactivate genes without actually affecting or altering the genetic make-up of the cell. Constellation’s focus has been on utilizing its research to create cancer treatments. The partnering deal Constellation struck with Roche’s Genentech subsidiary melds its focus on using epigenetics to optimize cancer therapies with Genentech’s expertise in oncology.

The partnership provides a built in exit where Genentech has the opportunity to either acquire Constellation or break up the partnering agreement depending on how the deal evolves. Genentech agreed to provide the biotech $95 million over a period of three years to assist the company in the development programs of the products chosen by the partners. Constellation is also provided the ability to maintain its strategic focus and rights to the programs that aren’t specifically a part of the collaboration. But the agreement also gives Genentech an exclusive future option to acquire all of the company’s shares at pre-negotiated terms that would include the products developed both within and outside the partnership. The price includes an unspecified initial acquisition payment plus contingent value rights payments that are based on the success of the products created through the partnership.

The partnership allows Constellation to independently pursue its strategic endeavors while still being afforded financial security and the know-how from an industry veteran like Genentech. On the other hand, Genentech is provided access to complimentary technology it can either choose to further pursue or discontinue depending on how development goes. The creative collaboration allows all parties to utilize their specialties to help streamline the development process and hedge against potential failures.

Early-stage and proof-of-concept assets

Partnering deals in 2012 were defined by Big Pharma’s focus on both early- and proof-of-concept-stage assets, as well as forging industry-academic alliances as these companies sought to respond to lagging R&D productivity by continuing a push to externalize discovery and early-stage development. The year was also notable for a number of cooperative pre-competitive alliances with global initiatives as part of the growing effort to attack the high cost of R&D.

Overall, there were fewer deals and lower potential deal values seen in partnering deals in excess of $20 million in 2012. In fact, the total number of partnering deals—120—and total deal value—$36.7 billion—seen in 2012 was the lowest in five years. [See Figures 8.16 and 8.17]. Part of the reason for the lower numbers may be due to a much higher volume of deals with undisclosed terms in 2012 relative to years past.

All in all, Big Pharma, specialty pharma, and biotech companies spent less partnering dollars in 2012 than they did in 2011. While Big Pharma and specialty pharmaceutical companies decreased their partnering activity in 2012, activity among biotechs and biotech companies was essentially flat with an increase of just one deal [See Figure 8.18]. While the lower partnering activity could in part be due to the fewer number of disclosed deals, a number of partnering deal terminations signaled that companies were still trying to adjust their strategic focus and unburden themselves of existing partnerships that no longer fit their goals.

Partnering deals remained centered on the usual suspects of cancer and central nervous system disorders, but interest in platform-based companies intensified in 2012. There were 10 alliances focused on technology platforms last year, the highest such amount in five years and the total dollar value for those platform deals—$3.1 billion—was also the highest level seen in the past five years. Life sciences companies are looking for platforms that could feed multiple product candidates into their pipelines in a cost efficient manner.
Infectious disease-focused partnering deals fell dramatically in 2012, but that likely had to do with the fewer attractive hepatitis C assets after 2011's deal-making thinned the offerings. There were only seven alliances formed around infectious disease in 2012, compared to 15 in 2011 [See Figures 8.19 and 8.20].

Research-stage and pre-clinical agreements attracted the most deal activity in 2012. Though deal volume fell for both research and preclinical stage assets, they still proved to be the most sought after stage of assets in 2012 [See Figure 8.22]. Research-stage agreements accounted for 26, or nearly 30 percent, of the total deals with disclosed phases in 2012. And there were 18 pre-clinical stage deals. That accounted for a 20 percent drop from the previous year’s 23 deals, but remained in line with the five year average for pre-clinical stage partnering deals. Total deal value for research-stage assets reached $11.7 billion, surpassing last year’s total by $1.3 billion, more than double as much other asset phase for 2012.

Research-stage assets also commanded large upfront payments. In fact the average upfront payment for research-stage assets was $23 million, the highest it has been in five years. Those upfront payments surpassed both the average upfront payment for both pre-clinical and early-stage assets. But mid-stage assets were also in high demand last year. The average upfront payment for mid-stage assets was up 21 percent from the previous year’s average of $20 million. But mid-stage assets were also in high demand last year. The average upfront payment for mid-stage assets was up 21 percent from the previous year’s average of $20 million.

**Figure 8.19**  **Partnering: Deal Values by Therapeutic Category**

**Figure 8.20**  **Partnering: Number of Deals by Therapeutic Category**
in 2012 to $51 million and nearly matched the average upfront value for late-stage assets [See Figure 8.23].

While Big Pharma was striving to gain access to earlier stage assets, other segments of the industry were still making plays for marketed assets. Both the total value and average value of deals for marketed assets were up more than 50 percent in 2012, and in fact were the highest deal values seen for marketed assets. Both the total value and average deal values range for marketed assets were up more than 50 percent in 2012, and in fact were the highest deal values seen for marketed assets in more than five years [See Figure 8.23].

Academic and government alliances

While there were still plenty of corporate alliances in 2012, there were far fewer than in years past. Partnerships between pharmaceutical companies and academic, non-profit, and government entities took precedence in 2012 and probably contributed to the fewer solely corporate partnerships struck in 2012. Total global partnering dollar value in 2012 was $37.6 billion, down 1.3 percent from 2011, but U.S. partnering dollars for therapeutic companies in 2012 dropped 10 percent. And while there were more partnering deals with total deal values either above $1 billion or in the $500 to $999 million range [See Figure 8.26]. Fewer were of the pharma-biotech variety.

Academic and government alliances with pharmaceutical companies are starting to eat into that once reliable tranche of funding. Consider the global research and licensing agreement that Novartis and the University of Pennsylvania announced in early 2012 aimed at bringing a new personalized immunotherapy approach to patients with various forms of cancer. Novartis will invest approximately $20 million for the construction of a new research center in Philadelphia as part of the pact, and gain exclusive worldwide license to technology developed at Penn that uses manipulated immune-system cells to stave off cancer. Though the full financial details of the collaboration are confidential, a statement from Novartis said that it will provide an up-front payment, research funding, funding for the establishment of the Center for Advanced Cellular Therapies, and milestone payments for the achievement of certain clinical, regulatory and commercial milestones; and royalty payments.

Penn scientists, led by Carl June, used genetic engineering, or chimeric-antigen-receptor immunotherapy, to manipulate T-cells extracted from leukemia patients into recognizing and attacking leukemia cells. These altered T cells were re-injected—using de-activated HIV-1 virus—into the patients where they proliferated until they destroyed the cancer cells. Novartis and Penn believe they will be able to apply the new immunotherapy approach to patients with a variety of cancers by combining the research prowess of a medical school with the commercial expertise of a pharmaceutical company.

Novartis wasn’t the only Big Pharma betting on a new personalized immunotherapy approach. Two other unnamed companies were also involved in negotiations. “I never thought this would happen, that the Pharma industry would get into ultra-personalized therapy,” said June in an interview with Bloomberg. “We had lots of venture capital interest, but it’s hard to be a new company and it takes time to get set up. The fastest route to widespread availability is to use an existing company.”

Big Pharma is becoming more inclined to seek access to early-stage assets through academic institutions. But the potential pay-off for Big Pharma remains to be seen. The gamble may come at a substantial price, since an estimated 35 percent to 40 percent of R&D costs for a drug candidate are incurred prior to mid-stage clinical trials. For academic institutions, however, these burgeoning relationships provide much needed funding and may be their best way to bring promising technologies to market sooner and cheaper.

In addition to embracing academic partnerships, Big Pharma has also been engaging in pre-competitive alliances with each other, as well as with governments, to tackle issues of mutual concern in a cost effective manner. Consider for example the $235 million corporate-academic partnership struck in May 2012 that was part of an effort by five European pharmaceutical companies—GlaxoSmithKline, AstraZeneca, Sanofi, Janssen, and Basilea Pharmaceutica—to combine with leading academic institutions to develop new antibiotics to combat the growing problem of drug resistant microbes.

The collaboration, called Drugs 4 Bad Bugs, is the first formed under the European Commission’s Action Plan announced in November 2012. 

Source: Burrill & Company, S&P Capital IQ; Windhover

“I never thought this would happen, that the Pharma industry would get into ultra-personalized therapy. We had lots of venture capital interest, but... the fastest route to widespread availability is to use an existing company.”

Carl June, Geneticist, University of Pennsylvania

Source: Burrill & Company, S&P Capital IQ; Windhover
2011 to address the rising threats from drug-resistant bugs and is part of Europe’s Innovative Medicines Initiative, the world’s largest public-private partnership in healthcare. The initiative intends to improve the environment for pharmaceutical innovation in Europe by engaging and supporting networks of industrial and academic experts in collaborative research projects. The research program will initially focus on sharing information, supporting potential antibiotics already in the pipeline through new research and improved clinical trial design, and continuing research and discovery on new antibiotics.

A separate agreement in the United States between Pfizer, Eli Lilly, AstraZeneca, and the National Institutes of Health’s National Clinical and Translational Sciences seeks to award grants to fund pre-clinical feasibility studies for new uses of more than 20 compounds shelved by the pharmaceutical companies because they failed to work in the diseases for which they were initially being pursued.

Global initiatives

While many of the alliances struck in 2012 were structured as a means for pharma companies to share risks in the development of treatments in large therapeutic areas, there were also many corporate–academic/non-profit/government alliances aimed at attacking major global concerns.

In the largest collaborative effort towards the elimination of neglected tropical diseases, The Bill and Melinda Gates Foundation, biopharma companies including Abbott, AstraZeneca, Bayer, Bristol-Myers Squibb, Eisai, Gilead, GlaxoSmithKline, Johnson & Johnson, Merck, Merck KGaA, Novartis, Pfizer, and Sanofi, as well as the governments of the United Kingdom, United States, and United Arab Emirates, the World Health Organization, and others agreed to try to eliminate or control ten neglected tropical diseases by 2020. The infections the collaborative effort aim to tackle, include schistosomiasis and African sleeping sickness. Together, such infections affect 1.4 billion people, mostly in developing countries. In all, $785 million has been pledged to improve drug distribution and support the research and development process. The Gates Foundation donated $363 million to the effort and 11 of the biopharma companies will help by sustaining or expanding existing drug donation programs to meet demand, and by sharing expertise and compounds to accelerate R&D of new drugs and strengthen drug distribution and implementation programs.

In another example of such dealmaking, GlaxoSmithKline, UCB, and Eisai formed a joint venture with NHS Dumfries and Galway and Epilepsy Scotland to help improve the management of the 1,500 or so patients that suffer from epilepsy living in the area. The proposal will allow the research savvy pharmaceutical companies to work closely with partners to improve the delivery of healthcare and focus on improving outcomes for patients at a time of significant financial challenge.

Global dealmaking opportunities

But global initiatives weren’t solely delegated to alliances struck between non-profits and pharmaceuticals. Life sciences companies are also looking to align themselves in emerging markets with major prospects for growth. Consider the Asian-Pacific market, which is fertile ground for large pharmaceutical companies seeking markets and smaller biotechs seeking to fund and accelerate the development of their compounds. Smaller companies are teaming up with Asian companies to take advantage of the clinical development strengths and opportunities in the Asian market and to address their rapidly rising unmet healthcare needs.

In order to accelerate the global clinical development of its lead drug candidate, the NBTXR3, Paris-based nanomedicine company Nanobiotix entered into a strategic partnership with PharmaEngine, a Taiwanese specialty drugmaker focused on the development of in-licensed oncology drugs. PharmaEngine will receive exclusive rights to develop and commercialize NBTXR3 in the Asia-Pacific region, including Australia, China, India, Japan, Korea, Taiwan, and other countries, while Nanobiotix will retain exclusive rights for the rest of the world. Nanobiotix also has an option to re-acquire the Asia-Pacific rights except for China and Taiwan, under pre-defined terms.

Under the agreement, Nanobiotix will get a $1 million upfront payment and will be eligible for up to a total of $56 million in milestones, plus tiered royalties on net product sales in the Asian-Pacific region. NBTXR3 is a nanoparticle formulation of hafnium oxide crystals that is designed to enhance the efficacy of radiotherapy. It is currently being tested in an early-stage trial in patients with soft tissue sarcoma in Europe, where it is classified as a class 3 medical device. Preliminary data were expected by the end of 2012 and further clinical trials were in prepara-
tion in Europe and in the United States, where it is classified as a drug.

In another deal, French biotech Transgene and Chinese specialty pharmaceutical Tasyi commenced operation of their Chinese joint venture to develop four Transgene investigational biologics for the Chinese market, including an HCV therapeutic vaccine currently in mid-stage clinical trials. The joint venture will initially focus on technology transfer from Transgene so the compounds can be developed in China. It also intends to develop additional in-licensed products, including non-Transgene products. Most research and development activities serving the venture will be subcontracted to Tasyi and to third parties so Transgene can focus on project management as well as on medical and regulatory development. A first clinical trial is expected to start in 2015. “We are convinced that China is soon going to become one of the largest markets for biopharmaceuticals, and the products selected for development address large local unmet medical needs, such as HCV or HBV,” said Philippe Archinard, chairman and CEO of Transgene at the time of the agreement.

**Companion diagnostics a growing target**

As personalized medicine continues to evolve and advance, drug companies are increasingly turning to diagnostics companies as partners while tools companies have been actively acquiring them. Drugs that prove effective for a certain genetically defined subset of cancer patients, for instance, can be even more effectively marketed along with a diagnostic that reliably identifies the subset of patients for whom a drug will benefit most. The year has seen several high-profile acquisitions, including Agilent’s $2.2 billion acquisition of Denmark-based Dako in May, Thermo Fisher Scientific’s $923 million acquisition of One Lambda in July, and even Illumina’s acquisition of the British diagnostics developer BlueGnome, which provides solutions for screening genetic abnormalities associated with developmental delay, cancer, and infertility.

**Life Technologies** and BMS entered into an agreement in 2012 covering current and future companion diagnostics projects between the two companies. It is their second collaboration and represents another step in Life Technologies’ strategy to develop its diagnostics business through internal development, partnerships, and select acquisitions. The agreement covers an initial project for oncology and provides for a long-term partnership across a potentially broad range of instrument platforms and therapeutic areas. Financial terms of the agreement were not disclosed.

“The pharmaceutical industry is increasingly turning its focus to discovering and delivering targeted, personalized medications,” said Ronnie Andrews, president of medical sciences at Life Technologies in a statement. “As more and more targeted drugs come onto the market in the next decade, there will be a growing need for diagnostics that can help predict which patients will benefit from which drugs.”

There have been at least 25 deals that involve companion diagnostics so far this year (though mostly all with undisclosed deal values). With hundreds of compounds currently in clinical trials for oncology indications alone, Life Technologies sees a strong market opportunity for expansion in the companion diagnostics space. To take advantage of the market opportunity, the company has been steadily beefing up its offerings in the space.

In July, it acquired the personal genetic testing company Navigenics, gaining a genetics platform and support services, plus an established CLIA-certified laboratory that Life Technologies will use to design and validate new diagnostics assays. It also acquired Pinpoint Genomics and its early-stage non-small cell lung cancer test that can help doctors identify those early-stage patients at high risk for progression to late disease. That acquisition gave it another CLIA-certified lab. These technologies supplement the company’s wide array of platforms that include its Ion Torrent line of DNA sequencers, all of which it can leverage to develop new diagnostics.

**Potential uptick in M&A**

With capital markets still difficult for emerging growth biopharmaceutical companies, Big Pharma showed self-restraint in 2012. It streamlined internal initiatives and pursued innovative drugs and access to new markets through creative deals that often required its partners to shoulder substantial risks. That will continue in 2013, but the ongoing cost cutting means that many of the Big Pharma companies that have been absorbing prior acquisitions or restructuring their internal R&D strategies might be ready to dive back into the M&A pool and make a big splash in the near term. Many are sitting on a lot of cash. According to a report by Bloomberg, five of the largest U.S. drugmakers, including Pfizer and Merck, had more than $70 billion in cash at the end of the third quarter 2012. As Big Pharma continues to refine its focus, it is likely that there will be a pick-up in acquisitions in 2013, with a strong likelihood of a few deals in excess of $10 billion as a recent upswing in new drug approvals and a growing interest in companion diagnostics projects.

The rumors have already started to fly.
One of the biggest challenges for life sciences companies is access to capital. Approaches to address unmet medical needs remain complex and expensive to develop, and there is no single path to financing a company today. The traditional path from venture financing to IPO that characterized the biotechnology industry in the early days served it well, but is no longer a reliable model for most companies. Instead, companies need to consider new and creative approaches to funding. Non-dilutive sources of capital are available to those that think globally about funding opportunities and seek out a range of new funding sources that play an increasingly important role, particularly for early-stage companies. These sources include not only government grants, but also the non-profit patient advocacy, disease-focused, and philanthropic groups. Public and private capital is still available to fuel growth, just more expense and challenging to obtain.
CHAPTER 9:
Changing Perspectives on Value

Companies tap a broad pool of capital to advance their programs

The global life sciences industry enjoyed a successful year in 2012, raising a total of $310.2 billion in public and private equity, debt financings, and partnering dollars. The industry was boosted by the best year of new drug approvals in the United States in 16 years, renewal of legislation critical to funding U.S. Food and Drug Administration reviews, including new mechanisms to accelerate reviews of rare disease drugs, removal of uncertainty about healthcare reform, and the passage of the JOBS Act, intended to make it easier for emerging growth companies to go public. Although the U.S. economy continued to recover, slowing growth in emerging markets, budget battles in the United States, and the debt crisis in Europe still made austerity the watchword of the day. The rising cost of healthcare worldwide, and governments struggle to pay for it, have placed growing pressures on pricing of new drugs, diagnostics, and devices. At the same time, the effects of the financial crisis that peaked in 2008 continue to make capital to fund product development more expensive and challenging to obtain. But public and private capital is still available to fuel growth for companies with innovative technologies. It’s not the venture-to-IPO model of the past, but new and creative approaches are emerging that include built-in exits, and funding from government, disease advocacy groups, angel investors, and crowdsourcing.

**Biotech stocks score in 2012**

Public life sciences companies enjoyed a successful year in 2012, as the record number of new drug approvals and regulatory decisions buoyed the industry. The biotech industry in particular scored sizable gains with the Burrill Biotech Select Index closing 2012 up 40.5 percent, compared to a 7.3 percent gain in the Dow Jones Industrial Average, a 15.9 percent rise in the NASDAQ Composite Index, and a 13.4 percent gain in the S&P 500 Index. An improving economy, clinical advances, new product approvals, and M&A activity drove the gains. Sarepta Therapeutics was the year’s biggest winner with shares skyrocketing 477 percent as the company’s mid-stage experimental muscular dystrophy therapy demonstrably improved boys’ ability to walk. Arena Pharmaceuticals’ share price skyrocketed and ended the year up 382 percent when the company received U.S. regulatory approval in June 2012 to market the obesity drug Belviq, which the FDA had rejected when it was first submitted for approval.

There were also some notable company failures in 2012 that sent shares plummeting. Anthera Pharmaceuticals was the biggest decliner as shares plunged from more than $6 at the start of the year to less than $1 at the end of 2012 after its lupus drug, blisibimod, showed little efficacy in a clinical trial. The Canadian biotech Cardiome Pharma lost 94 percent of its value in March after Merck ended a development pact for the oral heart medication vernakalant, which was under evaluation as a maintenance therapy for the long-term prevention of atrial fibrillation. Cardiome had to reduce its workforce and cut its spending in half. Its shares ended the year down 85 percent. Large-cap stocks outperformed their mid-cap and small-cap peers with Gilead Sciences, the top performer in terms of increased market capitalization gaining nearly $25 billion in total value.

All in all, of the 486 life sciences companies tracked by Burrill & Company, half, or 243 companies, finished 2012 higher than where they were at the beginning of 2012, while 240 companies ended the year lower than where they began the year. Three companies’ values...
remained unchanged. For all of the advancers in 2012, 62 percent posted gains greater than 25 percent. Similarly, for all decliners in 2012, 64 percent fell by more than 25 percent. Among the advancers, 36 percent rose more than 50 percent, while an equal number of decliners ended the year down more than 50 percent—an even breakdown.

Big winners obscure weak IPOs

A total of 16 life sciences companies completed initial public offerings in the United States in 2012 to raise a total of $1.1 billion. Although an equal number of companies completed initial public offerings in 2012 as they did in 2011, the total raised was 21.6 percent below the $1.4 billion raised the previous year. IPO volume and total capital raised fell globally, too, from 2011 numbers. Companies raised $2.1 billion through 37 IPOs in 2012, a 44.1 percent drop over the $3.8 billion raised worldwide through 45 offerings in 2011 [See Figure 9.3]. Shares of U.S. life sciences IPOs returned an average of 15.3 percent from their initial offering price through the end of 2012. Of the 16 issues, 12 came in below their target range. Overall, these companies sold their shares at an average of 23.2 percent below the median of their target price. The 12 therapeutic companies that debuted in public markets in 2012 outperformed life sciences IPOs as a whole, rising 25.9 percent for the year [See Figure 9.6]. However, that was largely due to the strong performance of Kythera Biopharmaceuticals and Intercept Pharmaceuticals.

Financing up in the U.S., down globally

Life sciences companies, a universe that includes therapeutic, diagnostic, tools/technology, industrial and agricultural biotech, medical devices, and digital health and information technologies, raised $92.5 billion of new capital globally through financings in 2012 [See Figure 9.8]. It fell short of the $93.4 billion raised in 2011, but as debt offerings fell, the amount of capital raised through equity financings rose [See Figure 9.9]. In all, life sciences companies raised $29.3 billion in global equity, a 7.6 percent increase over 2011. Overall, that represented 31.6 percent of the total capital raised in 2012 compared to 29.1 percent of the total raised in 2011 [See Figure 9.10, 9.11, and 9.12].

Venture and private financings grew almost 23 percent globally, with a 22 percent increase in investments in U.S. companies driving the growth. Global IPO activity fell 44 percent, largely a reflection of a weaker market in China. Global follow-on activity fell 20 percent over the previous year as slower than expected economic growth in emerging markets and a weakened economy in Europe dampened investor appetite. Global debt offerings fell to $63.3 billion, down 4.4 percent. The decrease was primarily due to the relative lack of large M&A deals in the life sciences in 2012, which normally necessitate considerable debt issues by Big Pharma and Big Biotech. The biggest debt issue was completed by Abbott Labs’ biopharmaceutical division AbbVie, which raised $14.7 billion ahead of its market debut in January 2013.

In the United States, life sciences financings were flat in 2012 compared with 2011, at $71.1 billion in debt and equity [See Figures 9.13, 9.14, and 9.15]. U.S. life sciences companies raised $20.1 billion in equity capital, a 21 percent increase over 2011. While the total amount of debt offerings and loans for U.S. life sciences companies fell 6.5 percent compared to 2011, debt capital remained the bulk of capital raised, accounting for a little more than three quarters of the total. Capital raised through equity offerings rose in every category except for initial public offerings, which were down 21.6 percent in 2012 compared to 2011 in terms of dollars.

Companies already public took advantage of improving U.S. public markets and their own positive clinical events to raise capital, as follow-on offerings rose 24.5 percent in 2012 compared to 2011. For example, on October 18, 2012, six drug developers priced offerings to raise a total of $304 million. The deals were a reminder that despite a difficult environment for initial public offerings, already public companies were able to access capital in the improving market. Puma Biotechnology led the pack with a $120 million offering of 7.5 million shares, a 1 million share increase over its original plans. The development-stage biotech’s lead experimental drug is an oral treatment for HER2-positive metastatic breast cancer. With the funds, Puma moved from the OTC Bulletin Board to begin trading on the New York Stock Exchange.

Venture financings up 22 percent

Venture financings—a category that includes equity and venture debt capital raised by private mation technologies, raised $92.5 billion of new capital globally through financings in 2012 [See Figure 9.8]. It fell short of the $93.4 billion raised in 2011, but as debt offerings fell, the amount of capital raised through equity financings rose [See Figure 9.9]. In all, life sciences companies raised $29.3 billion in global equity, a 7.6 percent increase over 2011. Overall, that represented 31.6 percent of the total capital raised in 2012 compared to 29.1 percent of the total raised in 2011 [See Figure 9.10, 9.11, and 9.12].

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with $9.5 billion raised by private companies in the United States. Categories that saw the biggest increases compared to 2011 included digital health (63.7 percent), therapeutics (up 31.9 percent), and diagnostics (up 57.1 percent) [See Figure 9.16 and 9.17]. U.S. health biotechs (therapeutics, diagnostics, and tools/technology companies) received $5.2 billion of total investments, but two thirds of that total was raised in the second half of the year. Three deals that closed just before the 2012 Christmas holiday exemplified the diverse pools of money. They were joined by the biopharma corporates Sanofi-Genzyme BioVentures and Shire. Existing investors TPG Biotech, Fidelity Biosciences, HealthCap, and Pappas Ventures also participated in the transactions. The new capital will be primarily used to advance development of Ultragenyx’s lead clinical-stage programs, UX001 and UX003, both in mid-stage development.

Nuron Biotech, a specialty biologics and vaccines company, got $80 million in funding from Healthcare Royalty Partners, including a $30 million equity investment and a $50 million royalty agreement tied to future sales of Nuron’s products. The financing will support the commercialization and expansion of Meningitec, an already-marketed vaccine for the prevention of a certain type of meningitis, which the Pennsylvania biotech recently acquired from Pfizer. It will also advance clinical development of the company’s pipeline of novel biologics and vaccines for infectious and neurodegenerative diseases, including a treatment for multiple sclerosis in late-stage development.

New Jersey-based cardiovascular disease drug developer Regado Biosciences secured $51 million in a series E funding round led by new investor RusnanoMedInvest, a subsidiary of Russian government-backed investment firm Rusnano, and Baxter Healthcare, with participation by existing investors Edmond de Rothschild Investment Partners, Domain Associates, Quaker Partners, Aurora Funds, and Caxton Advantage Life Sciences Fund. The financing will support Regado’s late-stage global study of REG1, a member of a class of compounds called aptamers, in an anticoagulant system that consists of two agents both administered intravenously to patients experiencing arterial thrombosis while undergoing heart surgery.

Of the top ten private company financings in 2012, all but one had significant backing from private equity firms or strategic investors. These large deals also suggest that as companies have felt little ability to leverage the value of their assets through M&A, partnering, or IPO negotiations, some were unwilling to leave substantial value on the table. Instead, investors ponied up additional financing for promising companies in late-stage development to realize the full value of their investments. Intarcia Therapeutics, for example, decided to keep control of its asset and instead of partnering, raised $210 million in November 2012. That represented the largest private financing of 2012. The biotech raised $160 million in equity through a preferred stock private placement and $50 million in a private debt placement. Intarcia’s TCA 650 is a once-yearly injection-free treatment for type 2 diabetes that provides subcutaneous delivery of the already-approved drug exenatide.

**JOBS Act eases rules for going public**

The JOBS Act, was signed into law by President Barack Obama in April 2012, in an attempt to spark the economy by making it easier for emerging growth companies to access the public markets and create more jobs. The consensus among those familiar with the law was that while it is a step in the right direction, it is not a game changer. It does lower the costs of going public and maintaining status as a public company, but it won’t start a rush of IPOs. “That incremental change might bring a few more IPOs to market..."
Life Sciences Financings Up in Europe

But biotechs struggle to raise capital

The European economy experienced a deep slowdown as austerity measures took their toll in 2012. Economic growth was -0.6 percent in 2012 for European Union member states and life sciences companies were hard hit as far as access to capital was concerned. While regional governments worked to support startup companies and governments initiated measures to help them, it was generally a tough year all around.

Even Britain’s medicines watchdog, the National Institute for Health and Clinical Excellence, or NICE, got into the act saying at the end of June that it would meet with early-stage venture investors to provide advice about which experimental treatments the National Health Service would be most likely to purchase. The agency is hoping that more transparency about what it needs to demonstrate value can help direct money into experimental treatments that are most likely be deemed cost effective.

Funding for European life sciences companies rose 5 percent in 2012 to $7.2 billion, compared to $6.9 billion in overall funding in 2011. Nevertheless, it was 30 percent below the $10 billion raised by the European industry in 2010. The sector was boosted by a 132 percent rise in equity financings solely as a result of a private placement in which $1.3 billion was raised by German medical device maker Fresenius. In fact, medical device and biorenewables companies accounted for most of the gains in 2012.

Biotech companies engaged in drug development, diagnostics, and tools/technology raised $5.1 billion in 2012, down 22.7 percent compared to the $6.6 billion raised by this group in 2011. The drop in funding was partially due to the deep slowdown of the European economy, with economic growth of the collective members of the European Union off by 0.6 percent in 2012 and eurozone countries off by 0.9 percent.

Five public drug developers raised significant funding in the public markets, including Vernalis, which raised $103.8 million in a placing and open offer; and private placements by ThromboGenics raising $103.1 million, Genmab raising $83.6 million, Veleox Pharmaceuticals raising $73.3 million, and Algeta raising $49.7 million. Elan spun out its drug discovery unit as the standalone company Neotope and funded it with $125 million.

French companies commanded European life sciences initial public offerings with six companies completing IPOs in Europe and one, medical device maker EOS Imaging, going public on the New York Stock Exchange in an offering that raised $51.1 million. French biotech DBV Technologies made its public debut at the end of April through an IPO on the Euronext Paris Exchange and a concurrent private place-

Privately held European life sciences companies raised $1.8 billion in 143 venture and private capital rounds 2012, a 7 percent increase over in the $1.7 billion raised in 150 deals in 2011. However, the top 10 percent of financing rounds accounted for half of the total amount raised.

The company raised $53.6 million through the sale of 4.6 million shares at $11.80 a share, the low end of its target range, valuing the company at $157.1 million. DBV is developing allergy treatments that are delivered through the skin. Its investigational treatment for peanut allergies is in mid-stage testing in children and adults. U.K.-based specialty pharma Clinigen also completed an initial public offering, raising $16.2 million to begin trading on London’s AIM Exchange.

Privately held European life sciences companies raised $1.8 billion in 143 venture and private capital rounds in 2012, a 7 percent increase over the $1.7 billion raised in 150 deals in 2011. However, the top 10 percent of financing rounds accounted for half of the total amount raised. Of those 14 companies, three are in the bio-industrial sector, two are medical device developers, three are diagnostics companies, two are tools/technology companies, and only four are biopharmaceutical developers.

One of the biggest financings was completed by Dutch molecular cancer diagnostics developer Agenda, which raised $65 million in a series F capital round led by Debiopharm Group with participation of all its current investors and new investors. The company had filed to go public in 2011, but pulled the IPO after a few months due to unfavorable market conditions.

Based in the Netherlands and in Irvine, California, Agenda develops and markets genomic-based diagnostic products, including the Symphony suite of breast cancer tests that analyze a person’s genome to help physicians determine a patient’s individual risk for metastasis, which patients will benefit from chemo, hormonal, or combination therapy, and which patients do not require these treatments and can instead be treated with other less arduous and less costly methods. Besides the breast cancer assays, Agenda’s pipeline includes a test for stage 2 colon cancer prognosis and prediction, and other genomic products in development. Agenda also collaborates with drugmakers, cancer centers, and academic groups to develop companion diagnostic tests in the area of oncology.
that were not able to go to market before,” said Allen Sussman, corporate and securities partner with the law firm Reed Smith, “but it’s not going to open the floodgates because there are so many other gates to pass. Namely, the bankers have to be willing to underwrite the company. They have to believe it has a sustainable growth model, a good IP portfolio, or a track record for the last five years.”

The JOBS Act doesn’t address getting to the point of being ready to go public, said Gordon Empey, partner in the emerging companies practice group at the law firm Cooley. He calls this the “grinder”—the real challenges facing life sciences companies. “Most companies can get started in what they call the virtual model, with token funding coming out of a university,” he said. “A good life sciences company can get rolling on not a lot these days, but it’s what happens next. Without the venture capital funds being able to show returns and hence raise additional venture funds—that’s a challenging area, and the JOBS Act doesn’t touch that.”

Still, the new law does offer advantages for emerging growth companies, a new category of public companies with less than $1 billion in annual revenue in their most recent fiscal year. Companies under this category, which includes most small life sciences companies, have five years, or until they reach the $1 billion annual revenue threshold, to comply with Sarbanes-Oxley, the financial reform legislation put into place after a spate of corporate scandals including the Enron debacle. “It gives companies some leeway at a time they really need it to grow,” said Mark Heesen, president of the National Venture Capital Association and a strong supporter of the new law.

The JOBS Act also has provisions that make it easier for a private company to go public as an emerging growth company, easing certain disclosure rules, such as requiring only two years of audited financial statements rather than three, and permitting companies to file an initial registration statement, called an S-1, confidentially with the U.S. Securities and Exchange Commission. Traditionally the S-1 statement would be public the minute it is filed. The S-1 can remain confidential up to 21 days before the start of the roadshow, a series of meetings with potential investors. During the confidentiality period, underwriters can see if there is interest in a company while companies can respond to SEC comments without having to disclose sensitive information, such as clinical trial results, to the public. “This means if investors view it as not the right time for this company to go public, it’s not like they are suddenly viewed as a bad company by the public as a whole,” Heesen said. “Getting this ‘scarlet letter’ on them that they have to wear for years has really been an impediment for many companies.”

Equity-based crowdfunding is perhaps the provision in the JOBS Act that has gotten the most attention in the media. Under this provision, rules for which the SEC has yet to finalize, new companies will be able to raise up to $1 million annually in equity capital from unaccredited investors, individuals with limited net worth. “This is a sum that is not likely to have much effect on emerging life sciences companies, given the cost of drug and device development.”

What the JOBS Act doesn’t do is create a market for small, publicly traded life sciences companies. There has been a massive decline in venture-backed IPOs across technologies, according to Empey. He said entrepreneurs have gotten to the point where they are questioning the idea of going public at all and M&A has become the typical exit path for venture-backed companies. At the same time, the venture community is concerned that IPOs are necessary for a vibrant industry.

Improving IPO market still not an exit path

When two biopharmaceutical companies went public on October 10, 2012, they did something that caught the attention of industry watchers. They completed successful initial public offerings at the top of their expected ranges. Not only did they both increase the size of their offerings because of demand, they also both proceeded to trade at premiums after their debut. That sparked excitement about the prospects for a more robust IPO market for biopharmaceutical companies and speculation in the trade press about when venture investors would be replenishing their coffers with big profits from newly exited investments.

Intercept Pharmaceuticals raised $75 million in its IPO after increasing the size of the offering to 5 million shares from its planned 4.3 million. It came at $15 a share, the top of its range. It ended the year at the top of the list of venture-backed biotechs that went public in 2012, on average, did so with venture investors and other insiders purchasing 31.5 percent of the initial public offering. That compares to 28.1 percent for the IPOs in the same sector in 2011 and 26.7 percent in 2010. It’s also in line with what others have found. In fact, an earlier study of deals in 2011 by Needham &
Companies went public with an average step-up in valuations between previous venture rounds. That's an improvement over the 1.2 times previous venture rounds, more than twice what companies going public commanded as step-ups in the same period.

The good news about IPOs is that public market investors and companies appear to be closing a gulf in the perceived value of the companies. In 2012, biopharmaceutical companies that went public did so at an average of 25 percent below the midpoint of their expected ranges. That may not sound good, but it does represent a steady improvement over the past two years. In 2010, biopharmaceutical companies that completed initial public offerings did so at 39.4 percent below the midpoint of their expected ranges. The participation of venture investors in many cases has become essential for public market investors who otherwise might be unwilling to buy biopharmaceutical IPO shares. For the venture investor, these offerings may not only provide an attractive valuation at which to purchase additional shares, but also a path to liquidity since they will be able to sell stock once any lock-ups expire. It’s interesting to note that the level of participation of existing investors in biopharmaceutical IPOs does not appear to function as an indicator of whether deals get completed within their target ranges, or how deeply they needed to cut their prices in order to complete public deals, or how they perform in the aftermarket.

Where there is a correlation is between the 2.6 times earlier valuations.

Mergers and acquisitions have become the preferred exits for venture investors, not only because of the expediency these transactions provide, but because the valuations are generally far more favorable. The average step-up in valuations from previous venture rounds in M&A transactions has grown steadily over the past three years. In 2012, the average step-up reached 37 times previous venture rounds, more than twice what companies going public commanded as step-ups in the same period.

The lack of returns for investors has made taking on risk more difficult to reward, a scenario that is playing out across the life sciences ecosystem from Big Pharma to public market investors all looking for less risk and more value. During a panel at the BIO Investor Forum in San Francisco in October 2012, several venture capitalists and one fund manager gave their views on what lies ahead in the life sciences. “We have a very steep curve, between risk and value that we’re playing on all the time in the private side,” said Akkaraju. “We’re willing to wait until that time to go up that curve but as steep as the curve is, there is only a short period of time to turn that curve—make that inflection.”

Nevertheless, venture investors still say they are willing to invest in early-stage companies, especially if it is for an innovative product targeting an unmet need. “We get paid for taking risk at the end of the day,” said Bryan Roberts, a partner at Venrock. “The way you really create value here is to get through risk gates that create a product that people thought if it could be made, there would be eight people making it.”

Companies—those with $200 million or less of market value. None of the BIO Investor Forum panelists expected to see an out-performance of small-cap stocks. One reason, they said, is that pharma is waiting for companies to be de-risked before acquiring them. That’s what happened with Amylin. Its stock sat at $10 a share for a long time before Bristol-Myers Squibb wanted to buy it for $22 a share. Venture capitalists are building companies that they hope to partner with or sell to Big Pharma, but Big Pharma today holds the cards. “The dynamics of what we think about for where we put money in biotechs have much more to do with where our ultimate customer is going to be,” said Srimi Akkaraju, managing director of New Leaf Venture Partners. “And that customer is Big Pharma.” But Big Pharma is only buying a small percentage of the companies backed by venture capitalists. They want access to early innovation, but they want to share the risk. The VCs see lots of opportunity, but they are playing in a difficult space themselves. “We have a very steep curve, between risk and value that we’re playing on all the time in the private side,” said Akkaraju. “We’re willing to wait until that time to go up that curve but as steep as the curve is, there is only a short period of time to turn that curve—make that inflection.”
“We get paid for taking risk... The way you really create value here is to get through risk gates that create a product that people didn’t think could be made for a big unmet need.”

Bryan Roberts
Venture Partner, Venrock

Experimenting with different models

As 2012 began, venture investors were buoyed by several acquisitions of privately held companies that provided them with good returns on their investments, such as Celgene’s acquisition of Avila Therapeutics and Biogen Idec’s acquisition of Stromedix. These returns boosted investor enthusiasm for the sector and it seemed the long period of difficult fundraising that began with the global economic recession in 2007 was ending. In January 2012, Flagship Ventures announced the closing of a $270 million life sciences fund that exceeded its $250 million fundraising goal. Most of the new fund will be allocated to budding greentech and biotechnology companies, though it stated that some of the new fund would go to late-stage investments.

Flagship’s announcement came a day after Canaan Partners said that it had raised $600 million for a new fund, $200 million of which will be allocated to healthcare and the life sciences. Vivo Ventures, a healthcare investment firm, also announced the close of a $375 million fund in late-stage pharmaceutical and medical device companies in the U.S. and in revenue-stage healthcare companies in greater China. Burrill & Company, publisher of this report, announced a $125 million close for its Burrill Brazil Fund I in January and a second close of its Burrill Capital Fund IV in August 2012 for a total of $585 million. These fund closings came amid increased worries over venture investors pulling out of the sector. A survey conducted by the National Venture Capital Association in late 2011 found that 39 percent of the 150 venture companies surveyed said they would be decreasing their investments in the life sciences sector over the next three years. Many cited the increased risk and higher costs of drug development, regulatory issues, the weak IPO market, and the difficulty of finding exits.

To overcome these challenges, venture capitalists were formulating an exit strategy at the time of investment and experimenting with various business models in order to provide returns to their own investors. With less capital to work with, companies being built today need to have differentiated, transformative science, but also a capital efficient plan for translating that science into products or attracting a Big Pharma/Big Biotech acquirer. When MPM Capital led a $23 million series A financing round for Selexys Pharmaceuticals in September 2012, it included an agreement with Novartis that granted the Big Pharma an exclusive option to acquire the company and its lead asset, the anti-P-selectin antibody SeGlI, following a proof-of-concept trial in patients with sickle cell anemia—an indication that could be worth as much as $665 million if exercised. Novartis also participated in the financing through its option fund managed by MPM.

Another emerging model involves placing an initial big bet on a promising company by committing a large sum of capital at the launch so that the company can advance rapidly to proof-of-concept without worrying about raising more capital to get there. The idea is to get to a stage where the technology can be sold or partnered without giving up value or needing to raise more private capital at a higher valuation. For example, Third Rock Ventures launched Global Blood Therapeutics in June with a commitment of $40.7 million to develop treatments for genetic blood-based diseases for which there are no effective cures. Its first focus is on sickle cell disease, which is caused by a single mutation and affects more than 15 million worldwide.

The asset-centric model currently favored by many venture investors, including Atlas Venture, Versant Ventures, Avalon Ventures, and others, involves forming a company around an asset or technology that can be developed quickly and efficiently so that it can be partnered or sold to Big Pharma. Such is the case with Avalon Venture’s portfolio company A fraaxis, which was set up in 2007 to develop technology focused on PAK1 inhibition as a potential treatment for Fragile X, an inherited form of mental retardation and autism. The clinical development path was accelerated because Fragile X can be classified as an orphan indication. As Avalon developed a library of compounds targeting PAK, it realized that the PAK group of proteins also showed promise for treating not only other central nervous system disorders, such as schizophrenia and Alzheimer’s disease, but also had potential for treating cancer and inflammatory conditions. Avalon’s investment thesis, said Jay Lichter, president and CEO of Affraxis and managing partner of Avalon Ventures, is to invest just enough in an early-stage company—on the order of less than $15 million—to make enough progress to license or sell the technology. You can look at that angel series A, you can look at the average exit, which is somewhere on the order of $130 million to $150 million, and you will be investment heroes and will have advanced the science,” said Lichter.

In January 2013 Roche’s subsidiary Genen-tech agreed to pay up to $187.5 million in upfront, research, and milestone payments for an exclusive license to Affraxis’s technology. The licensing agreement was essentially the same as selling the company as Genentech took control of all of its intellectual property. “Afraaxis has secured this relationship with Genentech only five years after founding the company as part of Avalon’s life sciences portfolio,” said Lichter.

Pressure builds to sell companies

With only $477 million in venture capital raised by U.S. drug developers in the first quarter of 2012, which included very little for first funding rounds, some venture investors felt the industry was headed for a 30 percent year-on-year drop in funding that was not likely to level out until 2015. Speaking at the 2012 Allicense conference in San Francisco, the end of April, Patrick Herron, a partner at Frazier Healthcare, said his limited partners had told him that before they put more money into venture funds they wanted to see some distributions. At the time, that meant through a strategic sale rather than an IPO. Such pressures have been driving venture investors to steer their portfolio companies away from the IPO market and instead toward strategic sales where they can get better multiples and lock in returns on their investments.

“As we think about investing the first dollar into a company, we want to see a path to liquidity/sale in less than five years,” said Herron. “That’s dramatically different than seven or eight years ago. Now you’ve got to find a partner that you need to know who your buyer is, and do that...
work before you write a check.”

All the venture capitalists on the panel agreed that the industry is undergoing an inevitable contraction in biotech venture financing that will last for several years—inevitable because the rate at which venture capitalists have been funding companies has outpaced the rate at which they have been able to raise new funds, leading to a multibillion dollar gap that Abingworth Management’s Jon MacQuitty, at the same conference, said is “one of the hidden disasters of the industry” of which many people are unaware. He likened it to a potential biotech equivalent of “The Hunger Games,” in which only one company will get funding for every 25 that are trying to raise money.

M&A transactions of venture-backed biotechs have generated some good returns, even though most deals are structured so that a full payout is based on meeting contingencies. While the total upfront value of such transactions was about $5.3 billion in 2011, according to a BioCentury analysis, there still is a backlog of companies that need to find exits in order to provide liquidity to their investors. While venture capitalists and their limited partners may still be able to generate attractive returns, it will become more difficult for entry level biotechs to find money needed to develop their technologies, the panel members said. Most of them conceded that investing in the first round would not get them the multiples they needed to satisfy the demands of limited partners. “The only time it’s the A round is when it is the only round to be done,” said Herron. “Right now it really is a ‘have and have not’ deal.”

The emphasis on build-to-sell: a big initial funding with the hope that the company will be sold before needing another round of private investment. This was the idea behind the creation of Warp Drive Bio, which was launched at the beginning of 2012 to develop a genomics platform that will mine microbes for potential therapeutic agents. Third Rock Ventures, Greylock Partners, and Sanofi committed up to $125 million in capital, a partnership with Sanofi that does not limit Warp Drive Bio’s ability to form partnerships with other companies, and an agreement whereby Sanofi will acquire it if it meets certain objectives. The financing included an initial $75 million in a tranched equity investment with the remaining $50 million tied to the achievement of specified milestones. Although the amount of the initial funding was not disclosed, Sanofi CEO Chris Viehbacher said that it had only put in $5 million initially, which he called a small bet when he spoke on a panel at the BIO International Conference in Boston in June 2012. If Warp Drive Bio succeeds, the built-in exit strategy may limit Third Rock’s return on its investment, but the trade-off of assured liquidity ameliorates the risk.

Corporate venture on the rise

Speculation ran high that Big Pharma, rich with cash and in need of bolstering its pipelines, would step up and acquire promising biotechs. However, with the exception of a handful of transactions in 2012, this did not happen. Big Pharma continued to externalize its R&D, but it looked to share risk wherever it could. It also dove more deeply to access innovation at a much earlier stage, setting up global innovation centers, partnering with venture capitalists and academia, and entering into risk-sharing collaborations with each other to address high-risk, chronic disease areas in open innovation partnerships.

This theme played out during 2012 as biopharmaceutical dealmaking saw a preponderance of drug discovery and preclinical R&D collaborations. In many cases announced deals did not include disclosure of financial terms, but for those that did, most were highly risk-abetted with much of the potential deal value tied to development and/or milestones. Whether or not these deals will advance the goals of therapeutics startups remains to be seen. In some cases, partnerships were abandoned altogether. Indeed many venture capitalists welcome corporate participation both for its financial resources and pharmaceutical market expertise. Analysis by Burrill & Company suggests that having a corporate partner can also improve exit opportunities for venture capitalists.

The goals of corporate venture firms vary widely with some focused strictly on investing in companies of strategic interest to the parent, such as Abbott Biotech Ventures and Pfizer Ventures, while others such as SR One, the corporate venture arm of GlaxoSmithKline, and Novo Ventures make investments that are not tied to their backers’ strategic interests.

Pharma partners with venture capital

Multinational drugmakers seeking a window on innovation are relying not only on their corporate arms, but also directly on partnerships with venture capital firms. In April 2012,
Merck said it would invest in a new $270 million life sciences fund raised by Flagship Ventures, committing money from its $250 million strategic Merck Research Ventures Fund. Merck will be not be able to choose the companies for investment but will be able to offer its expertise to the companies that receive funding.

GlxoxsmithKline and Johnson & Johnson invested in European firm Index Ventures newest $200 million, asset-centric fund that will make investments in early-stage life sciences companies with just one or two compounds. The strategy is to make efficient use of capital by focusing on developing assets rather than infrastructure and building a company. Index will choose each asset to invest in and help develop them to be sold or partnered. GSK and J&J are just limited partners that can offer their expertise and will be on scientific advisory boards, but their financial return is the same as all the other limited partners.

Merck and J&J also joined the ranks of Pfizer and others by establishing research centers. Merck committed $90 million in March 2012 to fund the establishment of Calibr to help translate academic drug development projects to the stage where commercial partners can take them over for further development.

In September, J&J said it would open innovation centers in Boston, San Francisco, London, and Shanghai to identify promising early-stage technology and augment its collaboration and investment opportunities in life sciences around the world. In addition to housing science and technology experts, each center will have local deal-making capabilities with flexibility to adapt deal structures to match the early-stage opportunity. J&J hopes the new centers will also provide scientists, entrepreneurs, and emerging companies focused on early-stage opportunities with one-stop access to experts within the company who can facilitate collaborations across its pharmaceutical, medical device, diagnostics, and consumer companies. “The innovation centers allow us to be closer to where the innovation occurs, to access and invest in the best early-stage science and technology, and to fuel our business, as well as the health of the innovation ecosystem overall,” said Paul Stoffels, J&J’s global chairman of pharmaceuticals.

Funding through an alternative route

In February 2012, Celgene made a strategic investment in the Boston-based biotech Acetylon Pharmaceuticals, which was developing promising treatments for multiple myeloma and other diseases. The Big Biotech paid $15 million for preferred shares of Acetylon. The investment did not include any technology rights or license option rights. By then, the barely four-year-old startup had already raised $40 million to finance its programs without taking any money from traditional venture capital sources.

Acetylon was started in 2008 by a group of angel investors, hired some staff, and advanced its research and development. When its lead drug candidate was ready for testing, it decided to get it into the hands of a pharma, in return for co-development and royalties. Acetylon’s president and CEO, as its only employee to run it. By July 2009, Acetylon received its 5.25 millionth check from a group of angel investors, hired some staff, and advanced its research and development. When its lead drug candidate was ready for human testing, Acetylon turned to the Leuke-

### Filling a Gap

Companies backed with corporate venture capital more likely to succeed

Corporate venture capital has stepped in to fill the gap in biotech startup funding with traditional venture capitalists moving toward later-stage investments or backing away completely from the life sciences. In fact, many venture capitalists welcome a pharmaceutical corporate as a syndicate partner, especially for an early-stage investment, and with good reason.

While corporate venture investors come with deep pockets and industry expertise, they also may represent an indicator of future success. A May 2012 analysis by Burrill & Company suggests that therapeutics companies backed by corporate venture participation are more likely than other ventures backed by major life science firms or corporate investors to enter into licensing or collaborative deals, and be acquired or complete an initial public offering.

The analysis examined all therapeutics venture investments made between January 1, 2000 and December 31, 2011 in the S&P Capital IQ database. A total of 2907 companies received disclosed venture capital funding through 5,100 rounds of financing during that period. Of those companies, 9.9 percent (286 companies) received funding in part from a corporate venture fund.

Of the companies that received corporate venture funding during the analysis period, 24.5 percent (70 companies) were acquired, compared to 14.4 percent (380 companies) for those that did not receive funding from a corporate venture investor. But while having corporate venture funding was a greater predictor of an eventual acquisition, it wasn’t because the parent of the corporate venture fund was likely to buy the company. While it is likely that a corporate venture arm of a Big Pharma is created to provide a strategic advantage to the parent company, only six of the corporate venture funded companies that were eventually acquired were acquired by the parent of that corporate venture arm.

Companies that received corporate venture funding were also far more likely to enter into licensing or collaboration agreements. A total of 48.4 percent (39 companies) that received corporate venture funding during the period entered into at least one licensing or collaboration agreement. That compared to 29.9 percent of the non-corporate venture funded companies (782 companies) that entered into licensing or collaboration agreements during the period.

Corporate venture funding was also a greater predictor of an eventual IPO for a company. A total of 12.2 percent of corporate venture backed companies (35 companies) successfully completed IPOs. That compared to 7.8 percent, or 205 companies, in the analysis that did not receive corporate venture backing.

Finally, there was not a significant difference between the two groups in terms of the time from first venture funding to an M&A or IPO for the companies in the analysis that achieved exits. The companies backed with corporate venture capital achieved exits, on average, at four years, compared to 4.25 months for non-corporate venture backed companies.

The numbers bear out the premise that the increased participation by pharmaceutical and biotech corporate venture funds is paying dividends for emerging companies in the life sciences sector as their backing signifies a greater likelihood of providing an exit for its investors and also seems to provide validation for such companies.

Though unclear from the research, the data suggests that one benefit of having corporate venture funding is that it may guide companies to work on projects that are strategically aligned with the longer term priorities of Big Pharma and Big Biotech. In doing so, these corporate venture funds are supporting the lagging venture capital universe while still improving the position of their parent companies for the long haul.
Hedge Fund Manager Pitches Cancer Megafund

Diversified investments, massive scale could mitigate risks, fund innovation

A debt- and equity-financed megafund of up to $30 billion could generate handsome returns for investors backing speculative early-stage cancer drug research and development, says MIT professor of finance and hedge fund manager Andrew Lo and his colleagues in a paper published in the journal Nature Biotechnology in October 2012.

By creating large, diversified portfolios of as many as 150 projects at all stages of development, and structuring combinations of equity and securitized debt financing, larger than normal capital pools could support costly R&D portfolios, Lo and his colleagues suggest. Simulating returns based on historical data, Lo estimates a $5 billion to $15 billion megafund may yield average returns of 8.9 percent to 11.4 percent for equity holders and 5 percent to 8 percent for “research-backed obligation” holders, owners of securitized early-stage clinical and preclinical biomedical assets. While those returns are lower than typical venture capital hurdle rates, they may be attractive to pension funds, insurance companies, and other large institutional investors, Lo suggests.

“Consensus is growing that the bench-to-bedside process of translational biomedical research into effective therapeutics is broken,” Lo and his colleagues write. A “trend of increasing complexity and risk implies that the traditional financing vehicles of private and public equity are becoming less effective for funding biopharma because the needs and expectations of limited partners and shareholders are becoming less aligned with the new realities of biomedical innovation.”

Using securitization to finance preclinical or early-stage drug development would set the megafund apart from strategies pursued by venture capitalists and biopharma companies already investing in the sector. A megafund on the order of $5 billion to $15 billion could also differentiate itself by investing in speculative early-stage R&D in exchange for a percentage of future royalties or proceeds from any subsequent sale of the intellectual property, the authors suggest.

Lo and his co-authors partially dismiss worries raised by the role of securitization in the recent financial crisis, writing, “securitization was, and continues to be, an effective means of raising capital.” They model a variety of scenarios by which capital could be raised and deployed, concluding that if implementation issues could be addressed, the financing techniques they suggest could “greatly expand the current scale of biomedical innovation.”

Lo would like to draw together scientists, investment managers, and potential investors to explore the megafund idea in greater depth. “Proposing to raise billions of dollars for biomedical research in the current economic climate may seem ill-timed and naïve,” the authors concede. However, they argue, the cost of cancer’s burden must be balanced against the risk of failure.
They will also jointly establish a drug and medical device manufacturing facility in Russia that meets cGMP standards.

Rusnano’s efforts are aimed at advancing Russia’s Pharma2020 plan to modernize its healthcare industry. "We are working hard to spur development of innovative technologies in the Russian healthcare industry," said Anatoly Chubais, CEO of Rusnano. The joint venture will leverage the technology of portfolio companies, and obtain exclusive rights to manufacture and market products based on these technologies in Russia and the Commonwealth of Independent States. It will also manage advanced-stage clinical trials in Russia and manufacture and market products based on technologies in Russia and the Commonwealth of Independent States. It will also manage advanced-stage clinical trials in Russia and the Commonwealth of Independent States. It will also manage advanced-stage clinical trials in Russia and the Commonwealth of Independent States. It will also manage advanced-stage clinical trials in Russia and the Commonwealth of Independent States.

Another Russian fund looking to source promising new drugs from the lab to the clinic.

In July 2012, Rusnano made its first investment in the domain portfolio company CoDa Therapeutics, committing $40 million along with current investors, Domain, GBS Ventures, and BioPacific Ventures, to close a series B round that began in 2011. In return, the San Diego-based biotech developing wound-healing products will license rights to its technology in Russia and the Commonwealth of Independent States to the joint venture. CoDa has agreed to establish R&D operations in Russia.

Rusnano is also an investor in Burrill Capital Fund IV, committing $200 million to the $905 million fund, to access technologies from around the world that could benefit Russia. Investments will facilitate the transfer of Western biomedical and nanotechnologies to Russia and the placement of contract production and services in the country through the establishment of joint ventures.

Another Russian fund looking to source new compounds for development in Russia is the Maxwell Biotech Venture Fund, a $100 million fund looking to invest in biotech and pharmaceutical companies with preclinical or early-stage compounds that could benefit from being developed and commercialized in Russia for the Russian market. MBVF is a public-private partnership between private investors and the Russian Venture Company, a government fund of funds, set up to build the country’s innovation economy. MBVF supports a portfolio of Russian companies it has helped set up. In 2009, it began to look abroad for innovative compounds it could bring into Russia for development, and in 2011, it partnered with four U.S. biotechs, including AtheroNova and Sequella for investigational drugs to be developed by MBVF portfolio companies and first commercialized in Russia. The U.S. companies can then use the clinical data to commercialize the compounds internationally.

Other initiatives include an effort by the Welsh government to create a biotech hub through an $80 million commitment to what is targeted to be a $375 million fund, a $100 million R&D fund backed by Merck Canada, Lumira Capital, and other venture capital firms to attract pharmaceutical companies to Quebec; and a Welcome Trust project to invest $317 million in emerging healthcare and life sciences businesses and technologies in Europe in early-stage development with significant potential to grow.

Among the most unusual efforts is a $250 million initiative from Cleveland’s University Hospitals announced in February 2012, which is establishing a non-profit entity to fund and advise physician-scientists on translational research and a related for-profit accelerator that will develop selected compounds to proof of concept. In September 2012, BioMotiv, the for-profit drug development arm of the Harrington Project for Drug Discovery and Development, secured $21 million in financing from founding investors, University Hospitals and the Harrington family, to speed the development of promising new drugs from the lab to the clinic.

The company plans to raise a total of $100 million in capital.

BioMotiv’s business model is to build a portfolio of innovative compounds in-licensed from academic medical centers associated with the Harrington Project and other sources. The aim is to advance discoveries to a stage where they can be out-licensed to pharmaceutical companies or venture capitalists. As a for-profit enterprise, BioMotiv can leverage the resources of the non-profit Harrington Project, which include an “idea factory,” to help shape a robust portfolio of potential drug candidates.

BioMotiv says its business model bridges the early-stage development gap and “serves as the formerly ‘missing middle portal’ between the upstream academic medical centers and the downstream biopharmaceutical companies and venture firms.”

“The challenge of translating discoveries into clinical development requires an innovative, next-generation business model,” said Ron Harrington, an entrepreneur whose family made a $50 million gift to jumpstart the University Hospitals’ initiative. “BioMotiv’s mission-aligned model and experienced team will enable it to efficiently and effectively manage a portfolio of early-stage drugs.”

All of these efforts reflect a dramatic change in the way drug development is conducted and funded. They represent not only a search for new models to address a system that
Companies Get $1 Billion in U.S. Grants and Contracts

MediVector to boost clinical development of broad-spectrum anti-viral

In a capital-constrained economy, life sciences firms are increasingly looking to governments to provide funding for their clinical programs. In 2012, various government agencies awarded $1.4 billion in contracts and grants to almost 200 companies. In the United States, approximately 140 companies received $986 million in funding from various government agencies ranging from the National Institutes of Health to the U.S. Departments of Defense, Energy, Agriculture, and Health and Human Services.

The Boston-based biotech MediVector received the year’s biggest award, a $138.5 million contract from the Department of Defense’s Joint Project Manager Transformational Medical Technologies program, or JPM-TMT, to advance development of favipiravir, a broad-spectrum anti-viral targeting multiple influenza viruses. The Defense Department says the contract will help bolster the protection of the military against both naturally occurring pandemic flu and bio-engineered viruses.

JPM-TMT is part of a broader initiative that aims to protect U.S. military forces from biological threats through strategic investments and partnerships with innovative biotech firms, pharmaceutical corporations, other government agencies, and academic institutions.

Funding agencies include the National Institutes of Health and the Departments of Defense, Energy, Agriculture, and Health and Human Services.

JPM-TMT looks to invest in later-stage drug candidates to reduce risk of technical failure and quickly deliver U.S. Food and Drug Administration-approved products to its troops in war zones. Investing in drugs that test favorably in early stage human clinical trials reflects the program’s goal to provide promising therapeutics to fight emerging infectious diseases. MediVector’s contract was awarded in mid-March shortly after a controversial decision to publish studies on the development of engineered H5N1 avian viruses.

“Currently available medical countermeasures do not adequately protect the joint forces,” said David Hough, joint project manager of JPM-TMT. “This drug shows promise that it can mitigate flu symptoms by interfering with the influenza replication process. Our contract with MediVector addresses a capability gap in the protection of the joint forces.”

MediVector said its platform reduces development time and improves the economics of drug development by as much as 30 percent over industry standards. Its lead candidate, favipiravir, has already shown positive results in animal studies and early-stage human clinical trials. The funding will be used to support late-stage trials.

**Figure 9.C** U.S. GOVERNMENT FUNDING FOR LIFE SCIENCES COMPANY PROGRAMS

Selected companies funded in 2012

<table>
<thead>
<tr>
<th>COMPANY</th>
<th>AWARD IN USD M</th>
<th>CATEGORY</th>
<th>PROJECT FUNDED</th>
<th>FUNDING AGENCY</th>
</tr>
</thead>
<tbody>
<tr>
<td>MediVector</td>
<td>138.5</td>
<td>Therapeutics</td>
<td>Universal flu therapeutic</td>
<td>Department of Defense</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Joint Project Manager Transformational Medical Technologies</td>
<td></td>
</tr>
<tr>
<td>Battelle</td>
<td>102.0</td>
<td>Tools/Technology</td>
<td>Biodefense testing services</td>
<td>National Institutes of Health</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Preclinical development and cGMP manufacturing for vaccines and biologics</td>
<td>National Institutes of Health</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>National Institutes of Health</td>
<td>institutes of Health</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>of Allergy and Infectious Disease</td>
<td></td>
</tr>
<tr>
<td>Advanced BioScience</td>
<td>102.0</td>
<td>Tools/Technology</td>
<td>Development and cGMP manufacturing for vaccines and biologics</td>
<td>Biomedical Advanced Research and Development Authority</td>
</tr>
<tr>
<td>Laboratories</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elusys Therapeutics</td>
<td>64.7</td>
<td>Therapeutics</td>
<td>Development of anthrax drug</td>
<td>Biomedical Advanced Research and Development Authority</td>
</tr>
<tr>
<td>BioSeek</td>
<td>46.0</td>
<td>Diagnostics</td>
<td>Toxin screening</td>
<td>Environmental Protection Agency</td>
</tr>
<tr>
<td>Life Technologies</td>
<td>45.0</td>
<td>Tools/Technology</td>
<td>DNA identification supplies</td>
<td>U.S. Army</td>
</tr>
<tr>
<td>Cellerant Therapeutics</td>
<td>36.4</td>
<td>Therapeutics</td>
<td>Acute radiation syndrome</td>
<td>Biomedical Advanced Research and Development Authority</td>
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<tr>
<td>BioFire Dx</td>
<td>27.4</td>
<td>Diagnostics</td>
<td>Pathogen detection</td>
<td>Department of Defense</td>
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<tr>
<td>Expression Analysis</td>
<td>27.0</td>
<td>Tools/Technology</td>
<td>Genomic analysis</td>
<td>Defense Logistics Agency</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Philips Healthcare</td>
<td>27.0</td>
<td>Medical devices</td>
<td>Device support services</td>
<td>U.S. Air Force and Army</td>
</tr>
<tr>
<td>Cenusa Bioenergy</td>
<td>25.0</td>
<td>Industrial/Ag</td>
<td>Feedstock production</td>
<td>Department of Agriculture</td>
</tr>
<tr>
<td>Pfenex</td>
<td>18.8</td>
<td>Tools/Technology</td>
<td>Bioprocess for rPA-based anthrax vaccine</td>
<td>Biomedical Advanced Research and Development Authority</td>
</tr>
<tr>
<td>New England Research</td>
<td>18.0</td>
<td>Medical devices</td>
<td>Pediatric clinical trial of circulatory devices</td>
<td>National Institutes of Health</td>
</tr>
<tr>
<td>Institutes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Illumina</td>
<td>17.0</td>
<td>Tools/Technology</td>
<td>Sequencing systems</td>
<td>U.S. Food and Drug Administration</td>
</tr>
<tr>
<td>Arsenal Medical</td>
<td>15.5</td>
<td>Medical devices</td>
<td>Control of intra-abdominal hemorrhage</td>
<td>Department of Defense</td>
</tr>
<tr>
<td>Paragon Bioservices</td>
<td>15.0</td>
<td>Tools/Technology</td>
<td>Mammalian process for vaccine manufacture</td>
<td>U.S. Department of Defense</td>
</tr>
<tr>
<td>TetraPhase Pharmaceuticals</td>
<td>11.5</td>
<td>Therapeutics</td>
<td>TP-434 antibiotic</td>
<td>Biomedical Advanced Research and Development Authority</td>
</tr>
<tr>
<td>Luminex</td>
<td>11.0</td>
<td>Diagnostics</td>
<td>Rapid biothreat diagnostic</td>
<td>Department of Defense</td>
</tr>
<tr>
<td>Cepheid</td>
<td>11.0</td>
<td>Diagnostics</td>
<td>AIDS diagnostics for Africa and Burma</td>
<td>USAID and Centers for Disease Control</td>
</tr>
</tbody>
</table>
“(Foundations) bring capital to the table. They bring scientific expertise. And perhaps most importantly, they bring patients who are eager and willing to participate in clinical research.”

Margaret Anderson
Executive Director, FasterCures

has become too costly to sustain, but also the involvement of a widening range of stakeholders that want to ensure they realize the benefits they have come to see in successfully bringing new therapies to market.

Foundations de-risk early-stage research

Funding from disease-focused foundations has become an important source of capital for advancing new therapies for rare diseases and other areas of unmet need as traditional venture capital funds migrate to later-stage investments. This funding is often non-dilutive and can help de-risk early research even in the development process.

Notable successes, such as the Cystic Fibrosis Foundation’s role in backing development of the cystic fibrosis therapy Kalydeco, approved by the FDA in January 2012, have shown the impact such organizations can play in bringing new medicines to market. Although already spending millions of dollars each year to fund work on developing new medicines for neurological conditions and rare diseases, foundations are taking steps to amplify their efforts.

A partnership program, the Michael J. Fox Foundation’s Vector One approach. In February 2012, the foundation set up a partnering program to proactively showcase promising research on Parkinson’s disease in its portfolio. While several of its grant awardees have later secured follow-on funding from Big Pharma and venture capital firms, the new partnering program is designed to help establish more such relationships, said Sohini Chowdhury, the foundation’s senior vice president of research partnerships. “The $50 million to $60 million we have to invest is a drop in the bucket,” said Chowdhury. “So we focus on de-risking projects enough so other funders can see their potential.”

So far, the program has showcased eight projects, some in preclinical stages and others in clinical development. All of them have been from biotech companies, she said. More than 30 groups, including venture capital firms, pharmaceutical companies, and biotechs have received “pitch packets” from the foundation, highlighting each project’s scientific rationale, latest set of experiments, and likely next steps. That material is also featured on the group’s website to open it up to an even broader audience. “It’s really important that we have pharma remain invested in Parkinson’s disease,” said Chowdhury. “If there’s something that’s really promising, we need pharma to act on it, because we don’t have those deep pockets.”

FasterCures, a group working to improve the medical research system, has been looking at venture philanthropy funding for disease research since its founding eight years ago, said the group’s executive director, Margaret Anderson. “What we have noted is the amount of interest and attention they have garnered because of their successes.” Foundations appear to be one of the bright spots in medical research because they offer one-stop-shop approach to getting results, said Anderson. “They can do that because they bring capital to the table. They bring scientific expertise. And perhaps most importantly, they bring patients who are eager and willing to participate in clinical research.”

A combination grant and credit line of $4.2 million from the French Muscular Dystrophy Association for instance, will help Bluebird Bio support development of LentiGlobin, the company’s development-stage program for the treatment of beta-thalassemia and sickle cell anemia, while also extending a manufacturing process development and scale up collaboration between Bluebird and Génethon, a not-for-profit biotherapy lab funded by the French Muscular Dystrophy Association. In addition, Anderson said, the venture capital community understands the role that foundations are playing in de-risking early-stage research.

One place that work is happening rather directly is at The Myelin Repair Foundation, which in February 2012 announced a partnership with ENDECE Neural to expedite the advancement of myelin regeneration drug candidates for multiple sclerosis patients through preclinical studies and into early-stage clinical studies using the foundation’s own new translational research lab. “Who else is going to de-risk academic discoveries if non-profits don’t?” asks Scott Johnson, the group’s president and founder. “It’s hard for companies to determine what gems there are in the academic space that they should make a bet on.”

Angel investors extend financial runway

Jeffrey Sohl, director at the University of New Hampshire’s Center for Venture Research, notes that since 2007, the venture universe has seen an enormous “culling of the forest” as the number of active venture capitalists has shrunk from roughly 1,200 to around 400. That, along with the hesitance of the remaining firms to invest in early-stage life sciences companies, has left a substantial funding gap that is being addressed by syndicates of angel investors.

Angel investors have long been seen as the first avenue to equity outside of friends and family, providing the $100,000 to $500,000 seed funding that small biotech and medical device companies need to get up and running. With many venture investors shying away from committing first round capital, angel syndicates have also come forward to provide a necessary stop-gap and not only help extend the financial runway for life sciences startups, but also help themselves in spreading the risk. Angel investment in healthcare, biotechnology, and medical devices and equipment startups accounted for 36 percent of total angel investments in the first half of 2012, according to UNH Center for Venture Research.

Avaxia Biologics’ angel syndicate came forward with $6.4 million in a series B financing in December 2012 to fund a first-in-human trial of its oral anti-TNF antibody AVX-470 to treat ulcerative colitis for which it had just received FDA clearance. The drug is designed to act locally in the gastrointestinal tract to suppress inflammation and treat inflammatory bowel disease, which includes ulcerative colitis and Crohn’s disease. Current anti-TNF antibodies work well, but they are injected and suppress the entire immune system, which can lead to serious side effects. Avaxia’s funding round was led by existing investor Cherrystone Angels and new investor Golden Seeds, with participation by nine other angel groups, many of whom are new investors attracted by the potential of its platform and its ability to localize treatment.

Because life sciences angels often have extensive experience in adopting a lean startup methodology, offering low angel valuations, and focusing on capital efficiency using virtualization and other outsourced infrastructure models. They can often help steer a company to early market feedback from strategic partners and high-quality clinical data on comparative effectiveness early in their testing programs.”

Figure 9.23
NEW SOURCES OF FUNDING PLAY GREATER ROLE

Angel investors filling early-stage venture gap in U.S. in 2011 for all industries

Source: University of New Hampshire Center for Venture Research and NVPA
Angel investors in the United States have organizations, such as the Angel Capital Association, that support their activities. Now, the idea has caught hold in the United Kingdom. Angels for Life Sciences launched in October 2012 as the first national angel network focused on helping raise money for early-stage life sciences companies. The group is sponsored by the U.K.’s BioIndustry Association, the Wellcome Trust, international law firm Fasken Martineau, the National Endowment for Science, Technology and the Arts, and business angel network Oxford Investment Opportunity Network. The idea is to hold meetings that bring together expert and generalist angels with companies seeking funding. Companies eligible to participate must already have secured funding from an experienced life sciences angel.

Crowdfunding comes to biotech

The JOBS Act enables private companies to have up to 2,000 investors and still remain private, opening another avenue for startups to access capital. Already popular in tech circles, crowdfunding—using social media to source small amounts of capital from a large pool of investors—has begun to create buzz as a pool of investors has begun to create buzz. Source small amounts of capital from a large pool.

Already popular in tech circles, crowdfunding—using social media to source small amounts of capital from a large pool of investors—has begun to create buzz. Source small amounts of capital from a large pool.

Crowdfunding has already been used by life sciences companies in France with some success. Almost 20 percent of the pre-IPO investment in French biotech Nanobiotix was raised through the Fonds Commun de Placement dans l’Innovation, the French model for crowdfunding. Nanobiotix raised $8.5 million in an IPO in September. The U.K. BioIndustry Association is basing its proposal for a Citizens’ Innovation Fund on the French model.

The world has changed

There is no single path to financing a company today. The paradigm of venture financing to IPO that characterized biotechnology in the early days served the industry well, but it is no longer a reliable model of funding for most companies. Instead, companies need to take a three dimensional approach to thinking about potential funding sources. Though capital remains expensive and difficult to come by today, companies can find non-dilutive sources of capital by thinking globally about their funding opportunities and seeking out a range of new funding sources that are playing an increasingly important role, particularly for early-stage companies. This includes not only government grants, but tapping into non-profit patient advocacy, disease-focused, and philanthropic groups.

Though venture capitalists are moving away from early-stage financing, a new generation of angel capital investors are rising in their place, often veterans of the industry who can provide not just money, but guidance as well. The reality is that rather than having fewer financing options, entrepreneurial companies have a range of funding choices that they can pursue.

Regional differences exist in both the availability and cost of capital. Venture investors in the United States may not be interested in backing a development-stage company working on a new antibiotic but investors in Russia may be interested, as was the case for Cleveland Bio-Labs subsidiary Panacea, which received $4.6 million under Russia’s Pharma2020 program to fund clinical development of its xenoYin program. The only requisite to funding a company today is creativity.

U.K. Biotech Industry Group Turns to Crowdfunding

BioIndustry Association proposes engaging public to fund homegrown innovation

With the outlook for its economy flat and capital constrained for innovative startups, the Biotech Industry Group, the United Kingdom’s biotech industry trade group, in September 2012 invited public investment in advancing homegrown innovation with a proposal to set up Citizens’ Innovation Funds.

The proposal, “Citizens’ Innovation Funds: Engaging the Public with UK Innovation,” details a plan to enable the British public to support the innovative businesses that will drive the nation’s future economic growth. BIA estimates its plan could lead to almost £500 million ($300 million) a year in funding for companies and lead to the creation of more than 1,500 new high tech jobs.

In the foreword to the report, BIA CEO Steve Bates said that British commentators often lament “the lack of a ‘British Google,’ a ‘British Apple,’ or a ‘British Amgen.’” This could be an ideal time to support innovative companies, he said, complementing government initiatives to stimulate the economy, and offering the potential for attractive returns at a time when interest rates on savings is at an all-time low. It is also a chance to be patriotic.

“Citizens’ Innovation Funds provide a practical way of unlocking the patriotic potential of a large number of Britons to crowdfund the innovative businesses which are essential for our nation’s economic future,” said Bates.

The funds would allow members of the public to put up to £23,000 ($35,000) a year and receive a tax break deduction at 40 percent of the amount invested. A Citizens’ Innovation Fund investment would be made for a minimum of five years and the return would be tax free for the investor.

The proposed Citizens’ Innovation Funds would be managed by professional investment managers, rather than by the government, and would carry tax advantages. The model would be based on a successful program adopted in France in 1997 that has raised more than $7.8 billion (€6 billion) since 1997 and invested in more than 1,150 innovative companies by the end of 2010. Almost four fifths of those companies were less than four years old at the time of investment.

The BIA analysis of the French program found that companies backed by these public funds had a lot of advantages over similar innovative companies not receiving such funding. These advantages included greater revenues and job creation, greater propensity to export, greater likelihood of publishing patents, and an increased likelihood of listing on a stock exchange. Indeed, among European life sciences startups, most companies that have successfully completed initial public offerings have been French.

The BIA’s proposal applies the French experience to the UK market, and estimates that its plan could be revenue neutral for the government within three years. “At a time when new ideas are needed to boost the UK economy Citizens’ Innovation Funds are cost effective, practical and timely,” said Bates.
Figure 9.24 PERFORMANCE OF PUBLICLY TRADED LIFE SCIENCES COMPANIES IN 2012

Figure 9.25 CAPITAL RAISED BY U.S. BIOTECHS FROM 1995 TO 2012

Figure 9.26 HISTORICAL U.S. BIOTECH IPOS
### Figure 9.27  Public Biotech Company Performance 2001 to 2012

<table>
<thead>
<tr>
<th></th>
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</thead>
<tbody>
<tr>
<td>Sales/Revenue (USD B)</td>
<td>42.70</td>
<td>47.40</td>
<td>59.50</td>
<td>71.50</td>
<td>82.60</td>
<td>89.60</td>
<td>99.50</td>
<td>91.60</td>
<td>91.40</td>
<td>94.60</td>
<td>88.62</td>
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<tr>
<td>R&amp;D Expenses (USD B)</td>
<td>13.5</td>
<td>14.3</td>
<td>16.8</td>
<td>18.5</td>
<td>21.7</td>
<td>23.7</td>
<td>23.7</td>
<td>19.3</td>
<td>19.5</td>
<td>19.1</td>
<td>16.7</td>
</tr>
<tr>
<td>Net Income (USD B)</td>
<td>(11.6)</td>
<td>(4.1)</td>
<td>(4.4)</td>
<td>(4.1)</td>
<td>(3.2)</td>
<td>(0.6)</td>
<td>3.7</td>
<td>4.3</td>
<td>7.5</td>
<td>9.75</td>
<td>8.5</td>
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<tr>
<td>Cash &amp; Equivalents (USD B)</td>
<td>419</td>
<td>416</td>
<td>45.5</td>
<td>47.7</td>
<td>51.4</td>
<td>71.2</td>
<td>75.6</td>
<td>74.7</td>
<td>112.12</td>
<td>50.3</td>
<td>50.2</td>
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<tr>
<td>Market Capitalization (USD B)</td>
<td>224</td>
<td>344</td>
<td>400</td>
<td>490</td>
<td>492</td>
<td>454</td>
<td>404</td>
<td>346</td>
<td>372</td>
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<td>404</td>
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<tr>
<td>Number of Public Companies</td>
<td>329</td>
<td>315</td>
<td>356</td>
<td>363</td>
<td>360</td>
<td>373</td>
<td>356</td>
<td>318</td>
<td>298</td>
<td>286</td>
<td>294</td>
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Includes ADRs and marketable securities.

Source: Burrill & Company

### Figure 9.28  U.S. Biotech Financings 2007 to 2012 (USD M)

<table>
<thead>
<tr>
<th>Year</th>
<th>2007</th>
<th>2008</th>
<th>2009</th>
<th>2010</th>
<th>2011</th>
<th>2012</th>
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<td>Public</td>
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<td></td>
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<tr>
<td>IPO</td>
<td>2,041</td>
<td>6</td>
<td>1,217</td>
<td>1,199</td>
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<tr>
<td>PIPE</td>
<td>1,618</td>
<td>1,174</td>
<td>1,713</td>
<td>1,802</td>
<td>1,389</td>
<td>1794</td>
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<tr>
<td>Follow-on</td>
<td>6,311</td>
<td>2,081</td>
<td>6,297</td>
<td>3,234</td>
<td>4,895</td>
<td>5907</td>
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<tr>
<td>Debt</td>
<td>6,749</td>
<td>5,273</td>
<td>11,201</td>
<td>17,846</td>
<td>29,239</td>
<td>15691</td>
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<tr>
<td>Other</td>
<td>611</td>
<td>2,580</td>
<td>693</td>
<td>2,146</td>
<td>5,315</td>
<td>849</td>
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<tr>
<td>Total</td>
<td>21,566</td>
<td>16,164</td>
<td>25,504</td>
<td>31,058</td>
<td>46,953</td>
<td>30,949</td>
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<tr>
<td>Private</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>VC</td>
<td>4,236</td>
<td>5,050</td>
<td>4,383</td>
<td>4,831</td>
<td>4,823</td>
<td>5792</td>
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<td>Total Financings</td>
<td>25,802</td>
<td>21,214</td>
<td>31,166</td>
<td>35,336</td>
<td>51,776</td>
<td>36,521</td>
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<td>Partnering</td>
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<tr>
<td>Total</td>
<td>38,834</td>
<td>35,946</td>
<td>59,417</td>
<td>65,059</td>
<td>69,841</td>
<td>51,509</td>
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</table>

Includes Therapeutics, diagnostics, tools/technology, industrial/ag Does not include Digital health, healthcare IT, medical devices; Big Pharma debt raises.

Source: Burrill & Company

### Figure 9.29  U.S. Public Company Reconciliation

<table>
<thead>
<tr>
<th>Year</th>
<th>2008 IPOs</th>
<th>2009 M&amp;As</th>
<th>2008 New or reinstated filings</th>
<th>2008 Delisted and/or traded on bulletin board</th>
<th>2008 Companies added based on biotech focus</th>
<th>2008 Change in biotech focus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Public Companies as of 12/31/07</td>
<td>373</td>
<td>1</td>
<td>-28</td>
<td>31</td>
<td>-22</td>
<td>0</td>
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<tr>
<td>Total Public Companies as of 12/30/08</td>
<td>356</td>
<td>3</td>
<td>-8</td>
<td>1</td>
<td>-42</td>
<td>0</td>
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<tr>
<td>Total Public Companies as of 12/31/09</td>
<td>318</td>
<td>17</td>
<td>-8</td>
<td>1</td>
<td>-30</td>
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<tr>
<td>Total Public Companies as of 12/31/10</td>
<td>298</td>
<td>16</td>
<td>-21</td>
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<td>Total Public Companies as of 12/31/11</td>
<td>286</td>
<td>16</td>
<td>-3</td>
<td>11</td>
<td>-16</td>
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<tr>
<td>Total Public Companies as of 12/31/12</td>
<td>294</td>
<td>16</td>
<td>-3</td>
<td>11</td>
<td>-16</td>
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Includes all Biotechnology companies on U.S. listed exchanges.

Source: Burrill & Company
### Figure 9.30  Top Global Private Company Capital Raises in 2012

<table>
<thead>
<tr>
<th>COMPANY</th>
<th>PRINCIPAL ACTIVITIES</th>
<th>RAISED USD M</th>
<th>FINANCING ROUND</th>
</tr>
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<tbody>
<tr>
<td><strong>THERAPEUTICS</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bicon Pharma</td>
<td>APIs, generics</td>
<td>250</td>
<td>Private equity</td>
</tr>
<tr>
<td>Intarcia Therapeutics</td>
<td>Diabetes drug delivery</td>
<td>210.3</td>
<td>Equity ($164.5M) and debt ($45.8M)</td>
</tr>
<tr>
<td>NantPharma</td>
<td>Biopharmaceuticals</td>
<td>125</td>
<td>Private equity investment</td>
</tr>
<tr>
<td>TauRx (Singapore)</td>
<td>Alzheimer’s disease</td>
<td>111.8</td>
<td>Tranched, receives first tranche of $31.5M</td>
</tr>
<tr>
<td>CureVac (Germany)</td>
<td>mRNA vaccines</td>
<td>104.9</td>
<td>Series D</td>
</tr>
<tr>
<td>Nuron Biotech</td>
<td>Infectious, neurodegenerative</td>
<td>80</td>
<td>Equity ($30) and royalty based</td>
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<tr>
<td>Ultragenyx Pharmaceuticals</td>
<td>Rare genetic diseases</td>
<td>75</td>
<td>Series B close</td>
</tr>
<tr>
<td>Vital Therapies</td>
<td>Bio-artificial liver</td>
<td>60.1</td>
<td>Close of $76M offering</td>
</tr>
<tr>
<td>bluebird bio</td>
<td>Gene therapies</td>
<td>60</td>
<td>Series D</td>
</tr>
<tr>
<td>Intas Pharmaceuticals (India)</td>
<td>Pharmaceuticals</td>
<td>57</td>
<td>PE capital ahead of IPO</td>
</tr>
<tr>
<td><strong>TOOLS/TECHNOLOGY</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Warp Drive Bio</td>
<td>Drug discovery engine</td>
<td>75</td>
<td>Series A, tranched</td>
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<tr>
<td>Triviton Healthcare (India)</td>
<td>Medical equipment and devices distributor</td>
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<tr>
<td>Intrexon</td>
<td>Synthetic biology</td>
<td>75</td>
<td>Series E</td>
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<tr>
<td>Oxford Nanopore (United Kingdom)</td>
<td>Next-gen sequencing</td>
<td>51.1</td>
<td>Series E</td>
</tr>
<tr>
<td>23andMe</td>
<td>Genetic analysis</td>
<td>50</td>
<td>Series D</td>
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<tr>
<td>Novasep (France)</td>
<td>API manufacturing solutions</td>
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<tr>
<td>IntegenX</td>
<td>Sample preparation systems</td>
<td>39.4</td>
<td>Series D</td>
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<tr>
<td>CellTex Therapeutics</td>
<td>Adult stem cellbank and lab</td>
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<td>InViva</td>
<td>Personalized medicine</td>
<td>29.6</td>
<td>Series A</td>
</tr>
<tr>
<td>Roka Bioscience</td>
<td>Pathogen detection</td>
<td>27.5</td>
<td>Series D, first tranche of $47.5 million</td>
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<td><strong>DIAGNOSTICS</strong></td>
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<tr>
<td>Agenda (Netherlands)</td>
<td>Cancer diagnostics</td>
<td>65</td>
<td>Series F</td>
</tr>
<tr>
<td>Magnisense (France)</td>
<td>In vitro bioassays</td>
<td>58.3</td>
<td>Three year investment in joint project in Russia</td>
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<td>CardioDx</td>
<td>Cardiovascular Dx</td>
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<td>Series F</td>
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<tr>
<td>Aria Diagnostics (Tandem)</td>
<td>Prenatal testing</td>
<td>52.7</td>
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<td>Triplex International Biosciences (China)</td>
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<td>Biocartis (Switzerland)</td>
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<td>Foundation Medicine</td>
<td>Genomic profiling</td>
<td>42.5</td>
<td>Series B</td>
</tr>
<tr>
<td>Astute Medical</td>
<td>Biomarker-based Dx</td>
<td>40.4</td>
<td>Series C</td>
</tr>
<tr>
<td>Cell MDX</td>
<td>Stealth mode</td>
<td>40</td>
<td>Series A</td>
</tr>
<tr>
<td>Strand Diagnostics (India)</td>
<td>Dx accuracy systems</td>
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<td>Series A, strategic investment over 3 years</td>
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<td>100</td>
<td>Series D</td>
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<tr>
<td>Best Doctors</td>
<td>Employer sponsored online doctors</td>
<td>45.5</td>
<td>Private equity investment</td>
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<td>Kinnear Software</td>
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<tr>
<td>Americal Well</td>
<td>Telehealth, on-line care</td>
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<tr>
<td>Practice Fusion</td>
<td>Web-based EM</td>
<td>34</td>
<td>Series C, Part of $50M round</td>
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<tr>
<td>Valence Health</td>
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<tr>
<td>Telcare</td>
<td>Wireless glucose monitoring</td>
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<tr>
<td>Withn3</td>
<td>Collaborative tools</td>
<td>20</td>
<td>Equity only</td>
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<tr>
<td>Lazon</td>
<td>Health benefits exchange</td>
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<tr>
<td>Proteus Biomedical</td>
<td>Digestible sensors</td>
<td>17.5</td>
<td>Series F; part of $50 M round</td>
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<tr>
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<td></td>
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<tr>
<td>Gazasia (United Kingdom)</td>
<td>Waste-to-biofuels</td>
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<td>Strategic investment</td>
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<td>Sapphire Energy</td>
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<td>Harvest Power</td>
<td>Waste-to-energy</td>
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<td>Renewable chemicals</td>
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<td>Series E</td>
</tr>
<tr>
<td>Tamar Energy (United Kingdom)</td>
<td>Waste-to-power</td>
<td>102.1</td>
<td>Launch funding</td>
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<td>BRAIN (Germany)</td>
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<td>Joule Unlimited</td>
<td>Renewable fuels/chemicals</td>
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<td>Lanztech</td>
<td>Biorenewables</td>
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<td>Syra Innovations</td>
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<td><strong>MEDICAL DEVICES</strong></td>
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<tr>
<td>ConforMIS</td>
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<td>Series E</td>
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<td>ConforMIS</td>
<td>Orthopedic implants</td>
<td>73</td>
<td>Series F</td>
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<tr>
<td>Sientra</td>
<td>Aesthetics</td>
<td>65</td>
<td>Series C</td>
</tr>
<tr>
<td>TrVascular</td>
<td>Cardiovascular</td>
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<td>Apollo Endosurgery</td>
<td>Surgical tools</td>
<td>47.6</td>
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<tr>
<td>Mevion Medical Systems</td>
<td>Proton beam therapy</td>
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<tr>
<td>ViewRay</td>
<td>Radiation therapy system</td>
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<td>Endosense (Switzerland)</td>
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<td>Amplitude Systems (France)</td>
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<td>40</td>
<td>Syndicated private equity</td>
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<td>Artstasis</td>
<td>Vascular access devices</td>
<td>38</td>
<td>Part of $51.2M round</td>
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</table>

Source: Burrill & Company
## Figure 9.31 Top Global Public Company Capital Raises in 2012

<table>
<thead>
<tr>
<th>IPO</th>
<th>COMPANY</th>
<th>TICER</th>
<th>RAISED USD M</th>
<th>PRINCIPAL ACTIVITY</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Xrang Haisco Pharmaceutical (China)</td>
<td>SHE:002653</td>
<td>127.0</td>
<td>Therapeutics</td>
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<td></td>
<td>Yantai Dongcheng Biochemicals (China)</td>
<td>SHE:002675</td>
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<td>MerinnaPharmaceuticals</td>
<td>MACK</td>
<td>100.1</td>
<td>Therapeutics</td>
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<tr>
<td></td>
<td>Globus Medical</td>
<td>NYSE:GMED</td>
<td>99.6</td>
<td>Medical devices</td>
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<tr>
<td></td>
<td>Hainan Shuangcheng Pharma (China)</td>
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<td>94.0</td>
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<td></td>
<td>Tesaro</td>
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<td>Intercept Pharmaceuticals</td>
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<tr>
<td></td>
<td>Kythera Biopharmaceuticals</td>
<td>KYTH</td>
<td>81.0</td>
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<tr>
<td></td>
<td>Hangzhou TiGERmed Consulting (China)</td>
<td>SHE:300347</td>
<td>80.0</td>
<td>Tools/Technology</td>
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<tr>
<td></td>
<td>Beijing Leadman Biochemistry (China)</td>
<td>SHE:300289</td>
<td>79.3</td>
<td>Tools/Technology</td>
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<tr>
<td></td>
<td>Jinhe Biotechnology (China)</td>
<td>SHE:002688</td>
<td>78.6</td>
<td>Therapeutics</td>
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<td></td>
<td>Durata Therapeutics</td>
<td>DRTX</td>
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<tr>
<td></td>
<td>Greenway Medical Technologies</td>
<td>NYSE:GWAY</td>
<td>77.0</td>
<td>Healthcare IT</td>
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<td></td>
<td>Renewable Energy Group</td>
<td>REGI</td>
<td>72.0</td>
<td>Industrial/Ag</td>
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</tbody>
</table>

### PIPE

<table>
<thead>
<tr>
<th>COMPANY</th>
<th>TICER</th>
<th>RAISED USD M</th>
<th>PRINCIPAL ACTIVITY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fresenius (Germany)</td>
<td>Frankfurt FME</td>
<td>1,310.0</td>
<td>Medical devices</td>
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<tr>
<td>Zhejiang Medicine (China)</td>
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<tr>
<td>Wuhan Humanwell Healthcare (China)</td>
<td>SHA:600079</td>
<td>157.0</td>
<td>Tools/Technology</td>
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<tr>
<td>Zhejiang Conba Pharma (China)</td>
<td>SHA:600572</td>
<td>148.0</td>
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<tr>
<td>Chongqing Huapont Pharmaceutical (China)</td>
<td>SHE:002004</td>
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<tr>
<td>MannKind</td>
<td>MKND</td>
<td>107.4</td>
<td>Therapeutics</td>
</tr>
<tr>
<td>Vernalis (United Kingdom)</td>
<td>LSE:VER</td>
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<tr>
<td>ThromboGenics (Belgium)</td>
<td>EuronextTHR</td>
<td>103.1</td>
<td>Therapeutics</td>
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<td>Acadia Pharmaceuticals</td>
<td>ACAD</td>
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<td>Therapeutics</td>
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<td>Genmab (Denmark)</td>
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<td>MannKind</td>
<td>MKND</td>
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<td>Veloxis Pharmaceuticals (Denmark)</td>
<td>CSX:VELO</td>
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<td>Henan Taloph (China)</td>
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<td>SNTA</td>
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<td>Therapeutics</td>
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<tr>
<td>Cell Therapeutics</td>
<td>CTIC</td>
<td>60.0</td>
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### FOLLOW-ON

<table>
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<th>RAISED USD M</th>
<th>PRINCIPAL ACTIVITY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shanghai Fosun Pharma (China)</td>
<td>HK: 2196</td>
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<td>ALXN</td>
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### DEBT (PHARMA)

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<th>RAISED USD M</th>
<th>PRINCIPAL ACTIVITY</th>
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<tbody>
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<td>Vvus</td>
<td>VVUS</td>
<td>202.5</td>
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<tr>
<td>Idex Pharmaceuticals</td>
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<td>Therapeutics</td>
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<tr>
<td>Infinity Pharmaceuticals</td>
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<td>Ardea Biosciences</td>
<td>RDEA</td>
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<tr>
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<td>Rigel Pharmaceuticals</td>
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<td>Exelixis</td>
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<td>Therapeutics</td>
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<td>Synageva BioPharma</td>
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<td>Synageva BioPharma</td>
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### DEBT (BIOTECH)

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</thead>
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<td>Gilead Sciences</td>
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<td>2,200.0</td>
<td>Infectious diseases, HIV</td>
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<tr>
<td>Biomet</td>
<td>Private</td>
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<tr>
<td>Celgene</td>
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<td>1,500.0</td>
<td>Cancer, autoimmune</td>
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<td>SiNovopharm (China)</td>
<td>HK:1099</td>
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<td>Thermo Fisher Scientific</td>
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<td>Hologic</td>
<td>HOLX</td>
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<tr>
<td>Biomet</td>
<td>Private</td>
<td>1,000.0</td>
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<td>LabCorp</td>
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<td>Elan (Ireland)</td>
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<td>Industrial/Ag</td>
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Source: Burrill & Company
### Biggest Market Movers in 2012 by Share Price

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### Biggest Market Movers in 2012 by Market Cap

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Source: Burrill & Company, S&P Capital IQ
Figure 9.34 A  PERFORMANCE OF TOP GLOBAL PUBLIC COMPANIES IN 2012

Performance of top Australian public companies in 2012

Performance of top Canadian public companies in 2012

Performance of top European public companies in 2012

Performance of top Russian public companies in 2012

Source: Burrill & Company; S&P Capital IQ
Figure 9.34B  PERFORMANCE OF TOP GLOBAL PUBLIC COMPANIES IN 2012

Performance of top Chinese public companies in 2012

Performance of top Indian public companies in 2012

Performance of top Japanese public companies in 2012

Performance of top South Korean public companies in 2012

Source: Burrill & Company, S&P Capital IQ
Table 9.35  **Top U.S. Public Life Sciences Companies**

2012 Total Revenue and Net Income are extrapolated figures

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<th>NET INCOME 2012 (USD M)</th>
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**MEDICAL DEVICES**

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**Finance**

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## Figure 9.35  Top U.S. Public Life Sciences Companies  Continued from previous page

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## Figure 9.36  Top Global Pharma and Biotech Companies

2012 Total Revenue and Net Income are extrapolated figures

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<th>COMPANY NAME</th>
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<th>MARKET CAP 12/31/2012 (USD M)</th>
<th>TOTAL REVENUE 2012 (USD M)</th>
<th>2012 PERCENT CHANGE</th>
<th>NET INCOME 2012 (USD M)</th>
<th>2012 PERCENT CHANGE</th>
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Source: Barron & Company, S&P Capital IQ

Continued on next page
**Figure 9.36**  
**Top Global Public Pharma and Biotech Companies**  
Continued from previous page

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<tr>
<th>COMPANY NAME</th>
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<th>MARKET CAP 12/31/2012 (USD M)</th>
<th>TOTAL REVENUE 2012 (USD M)</th>
<th>2012 PERCENT CHANGE</th>
<th>NET INCOME 2012 (USD M)</th>
<th>2012 PERCENT CHANGE</th>
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**Figure 9.37**  
**U.S. Company Total Capital Raised, 2012 vs 2011**

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<td>Digital Health/IT</td>
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<td>737</td>
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**Type**  
**Category**  
**2011**  
**2012**  
**Change**

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<th>COMPANY NAME</th>
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<td>3,851.8</td>
<td>-13.8</td>
<td>279.8</td>
<td>-15.9</td>
</tr>
<tr>
<td>Daiichippon Sumitomo Pharma</td>
<td>TSE:4506</td>
<td>4,754.1</td>
<td>4,097.7</td>
<td>-13.4</td>
<td>176.0</td>
<td>-13.2</td>
</tr>
<tr>
<td>Hisamitsu Pharmaceutical</td>
<td>TSE:4530</td>
<td>4,248.9</td>
<td>1,713.0</td>
<td>-3.9</td>
<td>227.7</td>
<td>-11.0</td>
</tr>
<tr>
<td>Santen Pharmaceutical</td>
<td>TSE:4536</td>
<td>3,155.0</td>
<td>1,345.8</td>
<td>-10.1</td>
<td>191.1</td>
<td>-25.8</td>
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<td>Tsumura</td>
<td>TSE:4540</td>
<td>2,128.1</td>
<td>1,188.8</td>
<td>-5.1</td>
<td>211.2</td>
<td>211.2</td>
</tr>
</tbody>
</table>

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**Type**  
**Category**  
**2011**  
**2012**  
**Change**

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**Source:** Burch & Company

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**Type**  
**Category**  
**2011**  
**2012**  
**Change**

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**FOLLOW-ON**

| Therapeutics | 3,664 | 5,537 | 50.3% |
| Tools/Technology | 992 | 70 | 92.9% |
| Diagnostics | 168 | 311 | 85.1% |
| Digital Health/IT | - | - | 0.0% |
| Industrial Biotech | 52 | 74 | 42.3% |
| Medical Devices | 148 | 277 | 87.2% |
| TOTAL | 5,044 | 6,269 | 24.3% |

**OTHER EQUITY**

| Therapeutics | 749 | 881 | 17.6% |
| Tools/Technology | 11 | 24 | 118.2% |
| Diagnostics | 16 | 6 | -62.5% |
| Digital Health/IT | 0 | 0 | 0.0% |
| Industrial Biotech | 10 | 253 | 2430.0% |
| Medical Devices | 76 | 92 | 21.1% |
| TOTAL | 862 | 1,256 | 45.7% |

**TOTAL PUBLIC EQUITY**

| 8,809 | 10,599 | 20.3% |

**TOTAL EQUITY (PUBLIC AND PRIVATE)**

| 16,572 | 20,056 | 42.1% |

**DEBT**

| Therapeutics | 2,784 | 3,676 | 32.0% |
| Tools/Technology | 761 | 898 | 18.0% |
| Diagnostics | 406 | 641 | 57.9% |
| Digital Health/IT | 467 | 737 | 57.8% |
| Industrial Biotech | 958 | 1,049 | 9.5% |
| Medical Devices | 2,387 | 2,456 | 2.9% |
| TOTAL | 7,763 | 9,457 | 21.8% |

**TOTAL CAPITAL RAISED**

| 57,424 | 46,215 | -19.5% |

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**Source:** Burch & Company
For much of the history of the biotechnology industry, the practical question faced by therapeutics companies throughout the discovery and development process was, “Will we be able to get this approved?” That has changed. Though companies are no less concerned about their experimental products proving safe and efficacious, the overriding question for executives and investors evaluating a potential product’s worth has become, “Can I get paid for this?”

Healthcare is in the midst of an upheaval. As populations grow and age and chronic diseases affect a greater portion of the world’s population, these intertwined trends are taking a greater toll on the financial wellbeing of healthcare systems. In response, governments around the globe struggle with the seemingly contradictory goals of improving the quality of care while simultaneously cutting costs. The pressures are driving reform efforts around the world and pulling healthcare systems away from a fee-for-service model and towards value-based care, where instead of paying providers for procedures, they are paying for results.

For some, these pressures signal a move toward a dire future in which healthcare is rationed, cost is shifted to individuals, and new technologies are dismissed as nothing more than new opportunities for inflating costs and driving healthcare systems closer to the brink of bankruptcy. It is a world in which power is shifting to payers, and governments are wielding blunt instruments to cut costs, such as price controls, formularies, and penalties for people who practice unhealthy behaviors. For drug and device makers, it represents new barriers to bringing innovative products to market. It is creating a bias against innovation. No longer will drugs and devices need only to demonstrate that they are safe and effective. Now, they will also need to establish they provide superior value through improved outcomes at lower costs compared to what’s already available.

But the dilemma we face today presents new opportunities to address problems with healthcare that extend well beyond costs alone. We are in the midst of the most dramatic shift in healthcare, perhaps in the history of humanity. That transformation is being driven by an unprecedented understanding of the molecular mechanisms of diseases, as well as our emerging understanding of the human genome and the growing list of other omes from the proteome to the microbiome. Scientists are uncovering how molecules within the body interact with genes, and how genes interact with diet and the environment to influence health and wellness.

Clinical practice is moving away from treat-

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“Price is what you pay. Value is what you get.”
Warren Buffett

“I conceive that the great part of the miseries of mankind are brought upon them by false estimates they have made of the value of things.”
Benjamin Franklin

“As one digs deeper into the national character of the Americans, one sees that they have sought the value of everything in this world only in the answer to this single question: How much money will it bring in?”
Alexis de Tocqueville
ing the symptoms of disease to treating the underlying molecular drivers of
disease, and beyond that, to intervening before diseases manifest themselves.
Although the earliest days of personalized medicine were characterized by
the advent of targeted therapeutics, the development of low-cost sequenc-
ing, and a deepening knowledge of the way genes interact with other aspects
of their environment, the trial and error approach of matching a drug to a
patient is giving way to a new era of precision medicine.

Accelerating the pace with which precision medicine takes hold is the
convergence of healthcare technologies with communication and informa-
tion technologies, giving rise to a new world of digital health. Smart-
phones are evolving into health guides, monitors, and an important new
link between patient and providers. The family practitioner is giving way to
accountable care organizations where the first point of contact may not be a
doctor in private practice, but instead a nurse practitioner working out of a
clinic located within a big box retailer or national drug store chain.

The evolving world is altering the way patients access healthcare and
providers deliver it. But perhaps the greatest potential for digital health to
alter healthcare practice lies in tying together disparate streams of data to
guide and interpret the meaning of individual, real-time, biological changes
to optimize health and wellness. The mapping of the human genome, rather
than an end itself, is only a start. The challenge is not only to integrate the
genome with the other omes being cataloged, but also to utilize the enor-
mous computing power available today to overlay disparate datasets, such
as insurance records, electronic health records, clinical data, real-time
patient monitoring, pharmacy records, and more to decode what it tells us
about health and wellness, what works and doesn’t work, and which patients
require intervention.

And though it is in healthcare where the biotechnology revolution is
most visibly played out, its effects touch on virtually all human endeavors
including how we grow our food, fuel our machines, and produce our goods.
The challenges faced in healthcare mirror the challenges faced in other
industries as the pressure from growing populations and prosperity create
demand for food, fuel, and industrial products where scarcity, financial costs,
and societal impacts are growing concerns. Even so, biotechnology holds
the promise to provide solutions to the growing problems we face.

A focus on value is not a bad thing. It should be
embraced. It will help impose discipline in corpo-
rate decision-making and prioritize true innova-
tion. Creating value alone, though, is not enough.
Companies will need to figure out how to capture
value as well, and that will be a greater challenge in
a world where there is increasing cost conscious-
ness, and where comparative effectiveness becomes
a gatekeeper to the marketplace. Though it would
be easy if value were an absolute, it is not. As with
beauty, value is in the eye of the beholder—whether
it is a payer weighing reimbursement for a product
or a company weighing an acquisition. How that
particular entity operates, its particular needs, and
its alternatives will shape its view of the value of an
asset.

**Value is transient**

When **Human Genome Sciences** received an
unsolicited $7 billion bid from **Amgen** in 2010
to buy the company, it had its lead experimental
drug, Benlysta, in late-stage clinical testing. The
drug represented the first new therapy for lupus
in 50 years. Two years later, the company had won
approval for the drug and it was on the market, but
when Human Genome Sciences’ partner **Glaxo-
SmithKline** made an unsolicited bid to acquire it,
offered less than half what the company would
have commanded just two years before. When
Human Genome Sciences went looking for a white
knight, neither Amgen nor anyone else was to be
found.
**Value is geographically dependent**

What is the value of a five-bedroom, four-bathroom house? Well, according to the real estate information website Zillow, a 3,210 square-foot house on Margareta Street in Detroit sold in December 2012 for $55,001. Just three weeks earlier, a 2,840 square-foot, five bedroom, four bathroom house on Austin Avenue in Los Altos, California sold for $2.5 million. There were likely many variables between the two homes, but chief among them was the location. Detroit is the United States’ least expensive housing market and Los Altos is its most expensive.

Differences in the location of a market can have significant impact on the value of an asset. The cost of capital can also vary dramatically from market to market, allowing life sciences companies an opportunity to exploit geographic variations in value. One way this can be seen is in a number of deals involving countries that are seeking to build their own innovation-based biopharmaceutical industry. In these arrangements, the financial partner in the emerging country funds clinical development of the drug in exchange for rights to the drug in their home country. The innovator company can then use the data from those studies, which it owns outright, to seek approval for the drug in the rest of the world. These arrangements provide non-dilutive financing, reduce development risks, and allow companies the ability to develop multiple products simultaneously.

**Value to payers is not a constant**

Life sciences companies must contend with growing cost-consciousness among payers, but what one payer views as an expense, another might view as an opportunity for savings, depending on the nature of the organization. Consider Kaiser Permanente, which ranked highest among 830 insurance plans in a Consumer Reports survey at the end of 2011. Time Magazine noted that Kaiser is both an insurer and provider. As such, it has a larger incentive to invest in preventive care, wellness classes, and free health education clinics. “Many other insurers and health systems avoid sinking money into such programs because patients switch insurers so frequently that such spending winds up benefiting another company,” wrote Time. “But as the Consumer Reports’ ratings show, Kaiser patient satisfaction is high and patient turnover low, so it makes more sense for the insurer to invest for the long haul.”

By contrast, there is high turnover in most employer sponsored insurance plans because employers frequently change health insurers in pursuit of lower costs. As a result, insurers have a disincentive to pay for preventive care. Researchers at Case Western Reserve University and Carnegie Mellon University looked at diabetes management and the lack of preventive care in a 2007 study and found the high rate at which Americans change health plans could be the cause. “It takes about a decade for insurers to recoup their investment in early diabetes treatment, and by then odds are that their customer has moved on to another health plan,” wrote Slate magazine in discussing the study. “Alas, a lot of this turnover may be built in to the way Americans get health insurance. And it’s the doing not of individual patients so much as their employers, who are always on the lookout to switch plans for lower-cost coverage.”

**Value is not a function of sales and earnings**

Multibillion dollar deals for life sciences companies years away from products on the market are a reminder that these companies don’t sell for a multiple of sales or earnings. Consider Gilead Sciences, which paid $11.2 billion to complete its acquisition of Pharmasset at the start of 2012. The bid, announced at the end of 2011, represented nearly a 90 percent premium over Pharmasset’s closing price on the day before the announcement. Pharmasset’s experimental hepatitis C drug, an oral...
therapy that promises to free patients from the use of interferon, which can cause flu-like side effects, represented not only a potential best-in-class drug, but also one with a complimentary mechanism of action to a hepatitis C drug candidate already moving through Gilead’s pipeline. That enhanced Pharmasset’s potential value to Gilead since hepatitis C therapies are expected to follow the path that Gilead so successfully forged with combination drugs for HIV/AIDS. Though Pharmasset’s lead candidate has completed mid-stage testing, it is still undergoing late-stage clinical trials and is not expected to reach the market until 2014 at the earliest.

The Pharmasset acquisition changed the relative value of other hepatitis C drug developers as well. On the cusp of Gilead’s acquisition, its competitor Bristol-Myers Squibb purchased Inhibitex for $2.5 billion, a 163 percent premium over its close the day before the deal was announced. Inhibitex’s lead drug candidate was also in mid-stage testing, but things did not turn out well for Bristol-Myers. In August 2012, just six months after completing its acquisition, the drugmaker announced that it would discontinue development of the Inhibitex drug, leading Motley Fool to declare it “the most epic drug failure ever”—a reminder that value can be fleeting. Bristol-Myers said it would take a $1.8 billion charge related to the drug’s failure.

The challenge for life sciences companies

A world in which companies must evaluate their pipelines by asking whether a drug in development is something for which a payer would reimburse is a fundamentally different one than the world in which this industry has operated during the past. While companies today feel pressure to do more with less, improve their R&D productivity, and find ways to replace revenue lost to generic competition in the face of expiring patents, they also need to reconceive themselves in fundamental ways.

Biopharmaceutical companies that see themselves as being primarily in the business of developing and selling drugs will live in a world in which they will swim against stronger and stronger currents. Intense pricing pressure may lead to the industry producing more diamonds and less coal, but in a world of value-based healthcare, it will be increasingly difficult for drugmakers to capture the value of their gems. Companies that are able to think differently about their assets, the value they can create through leveraging internal expertise, and their approaches to serving the healthcare needs of patients, will find novel ways to capture value outside of their products. Companies from web-based retailers such as Amazon, with its cloud computing services, to grocers such as Safeway, with its capitalizing on loyalty card data mapping the buying habits of its customers, have found ways to do this.

The biotech industry continues to be one driven by vision, optimism, and enthusiasm for what can be, rather than necessarily what is. Such a world provides a perspective to see value differently. It is a world driven by innovation and focused on potential. As a result, it’s also a perspective that is prone to rapid and sharp shifts as science, clinical data, policy, regulation, and competition alter the landscape with the suddenness of a temblor. The world in which these companies operate is changing.

While there is much talk about value defining the new world of healthcare, governments and payers hold the power to determine price. The risk is that under the banner of value, governments and payers rely on the most expedient tools at their disposal to address costs without consideration of the value of a given therapy to a patient. We may be heading toward a world, to borrow from Oscar Wilde’s Lord Henry, where “people know the price of everything and the value of nothing.” Innovation can bridge the gap between need and affordability. But for innovation to matter in this new world, it must create value for the customer, while providing adequate opportunity for industry to capture value along the way.

“Nothing is intrinsically valuable; the value of everything is attributed to it, assigned to it from outside the thing itself, by people.”
John Barth

“Don’t be seduced into thinking that that which does not make a profit is without value.”
Arthur Miller

“Value, like beauty, is in the eye of the beholder.”
G. Steven Burrill
About Burrill & Company

Founded in 1994, Burrill & Company is a diversified global financial services firm focused on the life sciences industry.

With $1.6 billion in assets under management, the firm’s businesses include venture capital/private equity, merchant banking/investment banking, and media. By leveraging the scientific and business networks of its team, Burrill & Company has established unrivaled access and visibility in the life sciences industry. This unique combination of resources and capabilities enables the company to provide life sciences companies with capital, transactional support, financial advisory services, management expertise, insight, market intelligence, and analysis through its investments, conferences, and publications. Headquartered in San Francisco, the company oversees a global network of offices throughout the United States, Latin America, Europe, and Asia.
Overview

Burrill & Company is focused on innovations in biotechnology, healthcare, and biogreentech, from therapeutics, diagnostics, and devices to medical technologies, healthcare delivery, digital health, and nutraceutical/wellness, to agricultural biotechnology and industrial biotechnology.

We have created a unique and highly effective platform for generating deal flow, assessing the scientific, commercial and investment viability of potential transactions, executing transactions, creating value in portfolio companies, and exiting. Our global investment strategy gives us access to best-in-class life sciences deals, foreign capital, and public markets.

Global Financing, Advisory and Media Capabilities

VENTURE CAPITAL

- $1.6 billion under management
- More than 100 investments
- More than 50 board seats
- Healthcare & BioGreenTech

Burrill & Company

MEDI A

- Insight into critical news through podcasts and weekly, monthly, and annual reports
- Intelligence-gathering for investment-focused conferences, custom reports
- Industry-leading conferences
- Books
- Publications
- Social Media

Burrill Securities/Investment Banking

- Strategic Advisory
  - Divestments/spinouts
  - Strategic partnerships
  - Project financings
- Principal Investing
  - Growth capital
- Public and private financings
  - Private placements/PIPS
  - IPO/FO Underwriting
  - Sales and trading
  - Equity research

Burrill Biotechnology Capital Fund

Why Burrill & Company Venture Capital

- Domain expertise unparalleled
- Global innovation window and execution capability
- Powerful network
- Large capital base
- Top-tier track record

VI ENT URE CA PITAL

Burrill & Company invests exclusively in life science-based companies with breakthrough technologies and effective business models to meet the world’s need for better healthcare, food, and energy. We partner with talented entrepreneurs with the vision to grow existing life science opportunities worldwide. The Burrill family of funds was formed to capitalize on our unique investment platform and the global opportunities created by today’s intersection of the genomic/proteomic and biologic revolution with market needs. We have only just begun to capture the value of the DNA age and the power of biotechnology to transform global needs to heal, fuel, and feed the world.

The Burrill Family of Funds

The Burrill family of venture capital and private equity funds, with nearly $1.6 billion under management, includes:

- Burrill Capital Fund IV
- Burrill Life Sciences Capital Fund III
- Burrill Life Sciences Capital Fund II
- Burrill Life Sciences Capital Fund I
- Burrill Agbio Capital Fund
- Burrill Biotechnology Capital Fund
- Malaysia Life Sciences Capital Fund I & II
- Burrill Biogreentech
- Burrill Digital Health Fund
- Burrill Brazil Fund
- Burrill Canada Fund
- Burrill China Fund
- Burrill Europe Fund
- Burrill India Fund
- Burrill Pan-Asia Fund
- Burrill Poland Fund
- Burrill Taiwan Fund
- Burrill ISTCAP Turkey Fund
- Burrill IdVectoR Fund
- Burrill Africa Fund

Investment Platform

Burrill & Company has created a unique and highly effective platform for generating deal flow, assessing the scientific, commercial, and investment viability of potential transactions, executing transactions, creating value in portfolio companies, and exiting. Our capital base has been provided by more than 30 large industrial companies, plus a larger group of financial institutions.
Burrill Securities, LLC provides a broad and complementary range of services to address the needs of our clients at various stages in their growth. These include a comprehensive array of strategic and financial advisory services including mergers and acquisitions, capital raising, and licensing/partnering. Burrill’s investment experience covers a wide range within life sciences including biotechnology, pharmaceutical, diagnostics, drug discovery and enabling technologies, medical devices, agricultural biotechnology, nutraceuticals/wellness, industrial biotechnology, and biofuels/bioenergy.

Since its founding, Burrill has built worldwide capabilities unmatched by other boutique Life Sciences banking firms, including:

- A multicultural, multilingual team spanning the globe
- Extensive international business relationships
- Worldwide pharmaceutical regulatory and marketing experience

These capabilities are particularly important in this ever-shrinking world, as the dynamics of technologies, end-markets, and capital increasingly operate on a global scale.

Ways Burrill can bring its international capabilities to bear include:

- **Capital Access** – Assisting companies worldwide in accessing capital outside their borders
- **Technology Access** – Cross-border buy-side and sell-side activities for companies looking to expand their technology portfolio
- **Market Access** – In-licensing and out-licensing projects to take advantage of emerging global markets
- **Global Arbitrage** – Taking advantage of discontinuities in value and market access

**Life Sciences-Dedicated Investment Banking**

**FINANCING**
- Public company financing
- Late-stage venture financing
- Private equity

**STRATEGIC ADVISORY**
- Sell-side
- Buy-side
- Licensing & partnering
- Strategic options analysis

**GLOBAL ARBITRAGE**
- Global financing
- International joint ventures
- Cross border M&A
- Global advisory

**International Capabilities**

Since its founding, Burrill has built worldwide capabilities unmatched by other boutique Life Sciences banking firms, including:

- A multicultural, multilingual team spanning the globe
- Extensive international business relationships
- Worldwide pharmaceutical regulatory and marketing experience

Why Burrill Securities, LLC

- Unique ability to access capital, deals, and partnerships
- Enables global arbitrage/international deals and financing
- Boutique focus, just life sciences
- Deep industry intelligence (unparalleled media business)
- Highly experienced team (>65 people in Burrill & Company) globally
- Financial capital, network capital, and experience capital
**Life Sciences Partners**

**Our Services**

Life Sciences Partners advises companies on financings and financing strategies and complements Burrill & Company’s investment banking and principal investing businesses.

**Selected Experience**

- **Pfizer**
  - Name: Pfizer
  - Trans. Type: M&A
  - Deal Value: $60 billion
  - Role: Buy-side Advisor

- **Genentech**
  - Name: Genentech
  - Trans. Type: M&A
  - Deal Value: $46.7 billion
  - Role: Sell-side Advisor

- **Synthelabo**
  - Name: Synthelabo
  - Trans. Type: M&A
  - Deal Value: Not disclosed
  - Role: Sell-side Advisor

- **Marion Laboratories**
  - Name: Marion Laboratories
  - Trans. Type: M&A
  - Deal Value: $5.2 billion
  - Role: Sell-side Advisor

**Life Sciences Partners Team**

**Fred Frank, Managing Partner**

Mr. Frank joined Peter J. Solomon Company in 2009 from Barclays Capital, where he was vice chairman. He began his investment banking career at Smith, Barney & Co. in 1958, where he attained the positions of co-head of research, vice president and director. Subsequently he joined Lehman Brothers, in 1969, as a partner. At Lehman, Mr. Frank was vice chairman and provided investment banking services to numerous companies in the pharmaceutical, biotechnology, healthcare services, medical device, and nutraceutical industries, and was involved in hundreds of financings, strategic alliances, and merger and acquisition transactions in the global healthcare industry.

**Mary Tanner, Managing Partner**

Ms. Tanner headed Life Sciences Partners, a company she founded to specialize in healthcare investment and strategic advisory work. Previously, she served as senior managing director at both Lehman Brothers and Bear Stearns. Ms. Tanner has devoted more than 25 years to the global healthcare industry. Her expertise includes the ethical pharmaceutical industry, biotechnology, diagnostics, medical devices, healthcare services, cosmetics and consumer medicine industries. In addition to her well-known work with large companies, Ms. Tanner specializes in domestic and cross-border transactions between large and small companies, including corporate partnering and minority investments.

**Why Life Sciences Partners**

- Storied team
- Experience acting as lead underwriters for more than 125 initial public offerings
- Negotiated more than 75 mergers and acquisitions
- Veteran advisors in hundreds of financings, strategic alliances, and M&A transactions

**International**

Burrill & Company has a multicultural, multilingual team, with extensive international business experience spanning the globe. Given that diseases know no borders, and that science/technology, intellectual property protection, and capital are ubiquitous worldwide with instantaneous communications and a highly mobile workforce, globalization is a requirement, not an option. Burrill & Company is the leader in arbitraging value and integrating the most efficient life sciences resources worldwide.

**Burrill Offices**

San Francisco
Boston
New York
Philadelphia
Zurich
Rio de Janeiro

**Burrill International Teams**

- **Burrill Biogreentech**
  - G. Steven Burrill
  - Roger Wyse
  - Greg Young
  - Kish Kishore
  - Burrill Brazil
  - G. Steven Burrill
  - João Paulo Baptista
  - Paul Freiman
  - Thomas Gerlach
  - Marcus Albernaz
  - Eduardo Mattos
  - Victor A. Hebert
  - Burrill Canada
  - G. Steven Burrill
  - Ann Hanham

- **Burrill China**
  - G. Steven Burrill
  - David Wetherell
  - Bryant Fong
  - Michael Keyvanshenasaie
  - Wen Yang

- **Burrill Digital Health**
  - G. Steven Burrill
  - David Wetherell
  - Dirk Lammerts
  - Sven Rohmann
  - Jack Young

- **Burrill Europe**
  - G. Steven Burrill
  - Sven Rohmann
  - Paul Maruani

- **Burrill India**
  - G. Steven Burrill
  - Tania Fernandez

- **Burrill Malaysia**
  - G. Steven Burrill
  - Roger Wyse
  - Greg Young
  - Kish Kishore

- **Burrill Pan-Asia**
  - G. Steven Burrill
  - David Wetherell
  - Michael Keyvanshenasaie

- **Burrill Poland**
  - G. Steven Burrill
  - Marek Orlowski

- **Burrill Russia**
  - G. Steven Burrill
  - Irena Melnikova
  - Sergey Axenovich
  - Anna Annenko

- **Burrill Taiwan**
  - G. Steven Burrill
  - Marietta Wu

- **Burrill ITSCAP Turkey**
  - (a joint venture)
  - G. Steven Burrill
  - Ahmet Aykac
  - Isil Bayman

**Venture Capital and Private Equity**

Burrill & Company is actively seeking venture capital, growth capital, and private equity investment opportunities globally.

**Media**

We organize global conferences focused on Greater China, Latin America, Europe, India, the United States, and topicaly relevant issues.

**Burrill Securities**

We advise companies on public or private financings and cross-border transactions, including M&A, strategic partnerships, spin-outs, and strategic development.
Burrill & Company's Media Group provides insight, intelligence, and information on life sciences that are unmatched in the industry. The Media Group team is the creator of the Burrill Annual Bio-tech Report, now in its 27th year of publication. As the creator, sponsor, and facilitator of more than a dozen leading industry conferences globally and publisher of a wide range of bio-intelligence reports, the Burrill Media Group has developed a unique and highly effective platform for the industry’s top executives, investors, scientists, and consultants to find and make outstanding life science investments.

**Publications**

**Annual Report on the Life Sciences Industry**

Biotech 2013 - Life Sciences: Capturing Value

With growing pressures on governments to cut spending, new demands from payers for value, and efforts by life sciences companies to reinvigorate their R&D and business models, Biotech 2013 examines what value means in 2013 and where opportunities for life sciences companies and investors lie. Burrill & Company’s 27th annual report on the life sciences industry offers insight and analysis into where the biotech industry is today and where it is heading.

**Monthly: The Burrill Report**

The Burrill Report provides actionable market intelligence on the latest global developments and trends in the life sciences industry. Available monthly, regular features include: venture financings, public financings, grants, partnering and licensing deals, mergers and acquisitions, FDA new product approvals, upcoming PDUFA dates, and more.

**Weekly: The Burrill Weekly Brief**

The Burrill Weekly Brief is an electronic newsletter that analyzes the most important business and finance news stories of the week. Additionally, the newsletter tracks the amount of money invested into the industry from public and private sources and identifies all the partnering and M&A deals announced during the week.

**Daily: BurrillReport.com**

Visit BurrillReport.com for daily news and analysis of the latest developments in the life sciences. The website complements the weekly and monthly editions of the Burrill Report and offers industry data available exclusively from Burrill & Company.

**Burrill Family of Life Sciences Indices**

Burrill publishes indices charting the biotech industry stock market performance on a monthly and quarterly basis.

- Burrill Biotech Select Index
- Burrill Large-Cap Biotech Index
- Burrill Mid-Cap Biotech Index
- Burrill Small-Cap Biotech Index
- Burrill Personalized Medicine Index
- Burrill Diagnostics Index
- Burrill BioGreenTech Index

**Industry Events**

The Burrill Media Group hosts and sponsors more than a dozen major annual industry events that enable attendees to remain on the cutting edge of the industry.

**The Burrill Pan-Asia Life Sciences Meeting**

April 21, 2013 – Chicago, IL

The annual Burrill Pan-Asia Life Sciences Meeting is one of the most important bio-partnering meetings focused on Pan-Asia, and leads to significant strategic partnerships shaping the entire industry.

**The Burrill & Buck Aging Meeting**

May 20-21, 2013

 Lifespans are increasing and populations are aging. This demographic shift presents opportunities for drug and device makers, as well as significant challenges for healthcare systems and payers. There’s also the hope that scientific breakthroughs will slow, or even reverse, the damage that we’ve come to view as part of aging.

**Life Science Innovation Northwest**

July 10-11, 2013 – Seattle, WA

The Pacific Northwest is home to many of the life sciences’ superstars, and many of the industry’s most promising startups. Companies in this enterprising region are developing technology for use beyond healthcare, embracing fields such as agriculture, biomaterials, and biofuels. This meeting focuses on the state of the biotech industry in the Pacific Northwest and worldwide.

**The Burrill Personalized Medicine Meeting**

September, 2013 - San Francisco, CA

Our annual two-day event encompasses the spectrum of personalized medicine—from prediction to prevention—providing attendees with a window into the emerging personalized medicine world and the challenges and opportunities that this new paradigm presents.

**The Biotech Meeting**

October 13-15, 2013 – Laguna Beach CA

This meeting is the premier industry conference exclusively for Chief Executive Officers of biotechnology companies. The Biotech Meeting is held at the Montage Resort & Spa in Laguna Beach. This is an invitation-only event.

**Burrill & Company Annual Reception**

January 7, 2014 – San Francisco, CA

Burrill & Company hosts an annual reception during the JP Morgan Annual Healthcare Conference, welcoming more than 2,000 guests. This event brings together the biggest names in the biotech, pharmaceutical, and healthcare industries in a lively setting with exceptional wines, hors d’oeuvres, and live entertainment. This is an invitation-only event.

**The Burrill Digital Health Meeting**

February 2014 – Burlingame, CA

In the not-too-distant future, nearly all of healthcare will be digitized. Patients will be able to connect with their physicians in real-time, and doctors will be able to practice medicine anywhere and at anytime, with instant access to the information they need. The convergence of wireless technology and the proliferation of mobile devices is giving rise to new practices and products. The Burrill Digital Health Meeting showcases the underlying issues, emerging business opportunities, and cutting-edge innovations.
THE BURRILL TEAM

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G. STEVEN BURRILL
Founder and Chief Executive Officer

G. Steven Burrill has been involved in the growth and prosperity of the biotechnology industry for over 45 years. Mr. Burrill has been Chief Executive Officer of Burrill & Company, a venture capital/private equity, merchant banking/investment banking, and media firm since its founding in 1994.

He currently serves on the Boards of Directors of AliveCor (Chairman), Catalyst Biosciences, Depomed (NASDAQ: DEPO), NewBridge Pharmaceuticals, Novadaq (NASDAQ: NVDQ), Targacept (NASDAQ: TRGT) and XDx. Previously he served as Chairman of the Boards of BioImagene, Abunda Nutrition and Pharmasset.

Mr. Burrill is a founder and currently serves as Chairman of the Board of the National Science and Technology Medals Foundation (NSTMF) and also as Chairman of the Boards of Directors of the Life Sciences Foundation, the World Council for Ethical Standards, the Vilas County (Wisconsin) Economic Development Corporation (VCEDC) and as Vice Chairman of the National Health Museum. He also serves on the Boards of Bay Area Science Infrastructure Consortium, BayBio (Emeritus), Buck Institute for Research on Aging, California Healthcare Institute (Emeritus), The Exploratorium (Emeritus), Gladstone Foundation, Global Virus Network, Kellogg Center for Biotechnology, MIT Center for Biomedical Innovation, BIO Ventures for Global Health (BVGH), Harvard Medical School Genetics Advisory Council, and NIH Scientific Management Review Board.

In 2012 Mr. Burrill received the Richard Bolte, Sr. Award for Supporting Industries from the Chemical Heritage Foundation for his biotechnology industry leadership worldwide. In 2011 he received a lifetime achievement award at Scrip Intelligence’s annual Scrip Award ceremony in London. That same year he received the Breath of Life Award from the Northern California Chapter of the Cystic Fibrosis Foundation to honor his contributions to the life sciences industry. In 2008 he received both the BayBio Pantheon DiNA lifetime achievement award for his biotech leadership worldwide, and the Alan Cranston Living Legend Award for his central role in advancing biomedical research globally. In 2002 he was recognized as a biotech investment visionary by Scientific American magazine (The Scientific American 30), and was also honored that year at the American Liver Foundation’s Annual “Salute to Excellence” Gala, which honors leaders from the medical, biotech and biopharmaceutical industries. In 1995 Mr. Burrill received BIO’s service award for his global biotechnology leadership.

He serves on the editorial boards of Scientific American, the Journal of Commercial Biotechnology, Life Science Leader, and on the advisory boards of the Center for Policy on Emerging Technologies (C-PET) and BioAg Gateway, City of Madison. He is an advisor to the University of Illinois, the University of Wisconsin-College of Agriculture and Life Sciences, the University of Minnesota College of Biological Sciences, University of California, Davis, and Duke University, and is an adjunct professor at University of California, San Francisco. He also serves on the Advisory Boards for the Department of Biology at San Francisco State University and the Biotechnology Master’s Program in the Department of Biology at the University of San Francisco. He serves on the BioNJ Diagnostics and Personalized Medicine Committee.

Prior to founding Burrill & Company in 1994, he spent 28 years with Ernst & Young, directing and coordinating the firm’s services to clients in the fields of biotechnology, life sciences, high technology, and manufacturing worldwide.

Mr. Burrill earned a BBA degree from the University of Wisconsin, Madison.
G. Steven Burrill has been involved in the growth and prosperity of the biotechnology industry for over 45 years. An early pioneer, Mr. Burrill is one of the original architects of the industry and one of its most avid and sustained developers. He currently serves as chairman of AliveCor and sits on the boards of Catalyst Biosciences, Depomed, NewBridge Pharmaceuticals, Novadaq, Targacept and XdRx. Previously he served as chairman of the Boards of BioImagene, Abunda Nutrition, and Pharmasset. Prior to founding Burrill & Company in 1994, he spent 28 years with Ernst & Young, directing the firm’s services to clients in the biotechnology, life sciences, high technology, and coordinating the firm’s services to clients in supply chain management, Wetherell turned his attention to cleantech venture investing and supply chain management, Wetherell turned his attention to the life sciences industry. In 2005, he started GBP Capital, a venture capital company focused exclusively on leading edge life sciences. He has received numerous awards, including Ernst & Young’s New England Entrepreneur of the Year in 2000 and recognition as one of Money Magazine’s Top 25 investors. He obtained his B.A. in Mathematics from Ohio Wesleyan University and an honorary doctorate from Bryant University. He currently serves as chairman of Lentigen and sits on the boards of numerous other companies, including HyperMed, Flexible Stenting Solutions, TMune Therapeutics and Quintess.

David Wetherell has spent more than 20 years as a CEO in high-tech, as well as 17 years in venture capital, the last seven of which have been dedicated to biotech and life sciences. From 1986 to 2006, he served as both CEO and, later, chairman of CMGI, where he helped build the company from $3 million in annual revenues to more than $1 billion and started the first venture capital firm focused on the Internet, i2Ventures. When CMGI, now ModusLink, turned its direction away from the Internet to cleantech venture investing and supply chain management, Wetherell turned his attention to the life sciences industry. In 2005, he started GBP Capital, a venture capital company focused exclusively on leading edge life sciences. He has received numerous awards, including Ernst & Young’s New England Entrepreneur of the Year in 2000 and recognition as one of Money Magazine’s Top 25 investors. He obtained his B.A. in Mathematics from Ohio Wesleyan University and an honorary doctorate from Bryant University. He currently serves as chairman of Lentigen and sits on the boards of numerous other companies, including HyperMed, Flexible Stenting Solutions, TMune Therapeutics and Quintess.

Bryant E. Fong joined Burrill & Company in 1998 and has more than 18 years of experience in the biotechnology industry. Prior to joining Burrill & Company, Fong held positions as a biochemist and molecular biologist with two early stage biotechnology companies located in the San Francisco Bay Area. His first position involved working with eukaryotic recombinant expression systems and he was part of the first research group to publish on the expression of a four-gene system in S. cerevisiae in the production of recombinant human collagen. Later, Fong was hired as the first employee of a genomics company to help develop and validate its high throughput functional genomics platform. Fong’s aggregate research experiences include recombinant protein expression in yeast, development of linear artificial chromosomes for pathway engineering/heterologous gene transfer in yeast, and catalytic RNA technology.

Douglas Lind, M.D. joined Burrill & Company in January 2012 as a Managing Director in the Company’s Venture Group. Previously he served as Managing Director at the venture firm GBP Capital. He has more than 20 years of experience in the life sciences industry, ranging from clinical practice to Wall Street equity research analyst and venture capitalist. His focus is to identify disruptive technologies and visionary leadership that offer high value solutions to pressing medical needs. He served as senior biotechnology equity research analyst at Morgan Stanley from 1997 to 2002 and at PaineWebber from 1995 to 1997. His coverage of large and small capitalization biotechnology companies included Amgen, Biogen, Celera, Centocor, Chiron, IDEC Pharmaceuticals, ImmClone, MedImmune, Agouron, Axsy Pharmaceuticals, and Millennium Pharmaceuticals.

Lind is a graduate of the University of Iowa College of Medicine. He served as an attending physician at St. Elizabeth’s Hospital in Boston, an affiliate of Tufts University School of Medicine, where he completed his residency in internal medicine. He currently serves on the board of directors of Lentigen, MalVax, HyperMed Imaging, and Spectral Image.

Roger Wyse, Ph.D. joined Burrill & Company in 1998 and has led the development of the agriculture, nutracueticals, health & wellness, and industrial biotechnology related activities in venture capital investing. Recently he has championed the virtual corporate venture model for accelerating economic development in emerging economies.

Wyse chairs or serves on numerous boards of private companies. He is founder and co-chairman of the $162 million Malaysian Life Sciences Capital Fund and serves on the International Advisory Panel for Biotechnology for the Prime Minister of Malaysia. He is a member of the Global Science and Innovation Advisory Council for Malaysia, the Civilian Research and Development Fund’s GIST Global Advisory Group, and the International Advisory Board of the EU based Knowledge Economy Network. He was founder and chairman of the Alliance for Animal Genome Research and serves on the Board of the Industrial & Environmental Section of BIO.
Wyse has over 30 years of experience as an internationally recognized scientist and as a Dean at two major research universities: Rutgers and the University of Wisconsin, Madison. Immediately prior to joining Burrill & Company, Wyse served for five years as Dean of the College of Agricultural and Life Sciences at the University of Wisconsin, Madison. From 1986 to 1992 he served as Dean of Research, Rutgers University.

Wyse earned international recognition for his basic studies in plant biochemistry, he has published over 150 scientific papers and in 1982, received the prestigious Arthur Fleming Award as the Outstanding Young Scientist in the U.S. Federal Service. He was elected a Fellow of the American Association for the Advancement of Science, the Crop Science Society of America and The American Society of Agronomy. He has served as a consultant to numerous Fortune 500 companies and is an international advisor to countries seeking access to global innovation to accelerate economic development.

**Greg B. Young**

**Managing Director, BioGreentech, MLSCF**

Greg B. Young is Managing Director, BioGreentech. During his more than twelve year tenure at Burrill working within its venture capital division, Young has developed an extensive network of venture capitalists, entrepreneurs, academics, bankers, attorneys and consultants for sourcing deal flow. His focus areas of investment cover renewable energy and chemicals, as well as biological processes which promote sustainability. He has played a senior or lead role in more than fifteen venture capital financings and has been involved in the early formation of several portfolio companies. He currently serves on the Board of Directors of Cobalt Technologies and Virdia and is an observer on the Boards of Akermun and Giori Energy. Young’s past Board observer positions include Gevo. Since its formation in 2006, Young has served as an investment manager for the Malaysian Life Sciences Capital Fund (MLSCF), a venture fund co-managed by Burrill & Company. Young has been deeply involved in shaping MLSCF’s investment strategy as it pertains to biogreentech investing. Prior to joining Burrill & Company, Young worked as a molecular biologist focused on protein expression at an early-stage biotech company located in San Diego. Young received his B.S. in Biochemistry and Cell Biology from the University of California, San Diego and an M.S. in Biotechnology from Northwestern University.

**Ganesh M. Kishore**

**CEO, MLSCF I**

Prior to joining Burrill & Company, Kishore Ph.D. served as Vice President, Science & Technology and Chief Biotechnology Officer at DuPont. Prior to this he was Vice President, Technology, for DuPont Agriculture & Nutrition. He joined DuPont in June of 2003 and focused on R&D efforts related to biotechnology within the company. Kishore previously served as Co-President, Nutrition & Consumer Sector and Assistant Chief Scientist/Chief Biotechnologist for Monsanto Co., which he joined in 1980. His contributions include the discovery, development and commercialization of agbio products, manufacturing processes for Nutrasweet and the transformation of the chemical company into a leading food and nutrition company.

He is a founder of the plant biotech/informatics company, Metaheka Life Sciences. Kishore also serves as the chairperson for the St. Louis RCGA’s Bioenergy group. He serves on the boards of numerous for profit and not-for-profit institutions including the School of Nutrition and Policy Tufts University, St. Louis RCGA, and the National Research Advisory Board of the Washington University at St. Louis. He has also served as an advisor to National Science Committees in many Asian countries and venture capital groups. Kishore is a member of the American Association for the Advancement of Science, the American Society of Biochemistry and Molecular Biology, the American Society of Plant Physiologists, and the Institute of Food Technology.

Kishore received a B.S. in Physics and Chemistry, an M.S. in Biochemistry from the University of Mysore and a Ph.D. in Biochemistry from the Indian Institute of Science. He completed postdoctoral training at the University of Texas at Austin.

**Dirk Lammerts**

**Managing Director, Digital Health**

Dirk Lammerts, M.D. has more than 20 years of professional experience in healthcare, life sciences, and high-tech industries. Lammerts has a combined medical and computer science background with an M.D. from Dusseldorf University Medical School, and training in Neurology at the University of Cologne Medical Center. He also received Board certification in Medical Computer Science by the German Medical Association. Early in his career, Lammerts developed computer-based training programs for neurological patients suffering from memory and cognitive deficits.

Lammerts worked as a senior engagement manager for McKinsey & Company advising clients across a broad spectrum of industries in the U.S., Europe, and Asia-Pacific. He also held positions as Vice President Molecular Diagnostics at Affymetrix and as Vice President Marketing and Corporate Development at XDs, building businesses in molecular diagnostics and personalized medicine.

Throughout his career, Lammerts has been driving technology convergence through innovative use of computer technologies and online, mobile, and interactive media in medicine, based on the premise that these technologies are providing a platform to fundamentally improve access to and quality of healthcare worldwide.

**Derek Wong**

**Analyst, Digital Health**

Derek Wong, Ph.D. joined Burrill & Company in 2011 as an Analyst in the Digital Health Practice. He was instrumental in the Series A investment in AliveCor, developer of the innovative iPhone ECG device. Prior to Burrill & Company, he taught physics at the University of San Francisco. He was a member of the QB3 New Venture Consulting Group at the California Institute of Quantitative Biology (QB3) and assisted spin-outs from the University of California in commercializing their technologies. Wong participated in the Management of Technology Program at U.C. Berkeley’s Haas School of Business where he worked on various projects including electric vehicle deployment and computer user interface redesign for young children. Trained as an engineer and a scientist, Wong has co-authored several research articles published in top-tier scientific journals including Cell, Proceedings of the National Academy of Sciences, and Physical Review Letters. Wong holds a Ph.D. in Bioengineering from the University of California, Berkeley and San Francisco, a B.S.E. from the University of Pennsylvania, and a B.S. from Haverford College.

**João Paulo Poiares Baptista**

**Managing Director, Brazil**

João Paulo Poiares Baptista is the CEO of Burrill Brasil Gestão de Recursos SA, which is the Burrill Brazil General Partner. Prior to joining Burrill & Company, he served as a Director of Rio Bravo Venture Partners, created by the merger of MVP with the Venture Capital division of Rio Bravo Investimentos. He has served as the
President of the Investment Committee of MVP TECH FUND since the beginning of its operations. Baptista served as board member of several leading technology-based companies in Brazil and served for one mandate as Vice Chairman of the Health Committee of AMCHAM RJ (American Chamber of Commerce in Rio de Janeiro). Baptista graduated in Economy at Universidade de Coimbra, Portugal and began his career as an analyst for the Department of Economy Industry Services (SE) in Macau, where he became Head of Division. In 1987 he joined Pacific Infotech Corp (PIC), an investment group with focus on technology-based companies, to serve as an analyst in Los Angeles, U.S.A. Between 1990 and 1992, as Managing Director of PIC in Europe, he expanded its European business and in 1999 founded MVP – Mercatto Venture Partners, one of the pioneers in venture capital activities in Brazil. He actively participated on the development of Projeto Inovar from FINEP (Brazilian Ministry of Science and Technology), responsible for Venture Forum Brazil. Also under the auspices of Inovar, he created and developed the first forums in partnership with BOVESPA, where as a consultant he performed strategic analysis and enabled positioning and preparation of companies for investor presentations in the program BOVESPA Mais. Baptista was one of the founders of ABR – Brazilian Association of Venture Capital, currently known as ABVCap, where he served as member of the Board for three mandates. Baptista invested privately in several successful ventures in Portugal and Brazil.

Paul Freiman has over 40 years of experience in founding and managing biotechnology and healthcare companies. Freiman, former CEO of Syntex, led the company’s acquisition by Roche Holdings in a $5.3 billion transaction. He has been chairman of the Pharmaceutical Manufacturers of America Association (PhRMA) and has also chaired a number of key PhRMA committees both domestic and international. He served as CEO of a biotech firm based in California and currently serves on three biotechnology boards as well as that of a major Japanese company.

Currently domiciled in Rio de Janeiro, Freiman has extensive experience in Latin America, having also served as Vice President, Latin America, for Burrill & Company.

Thomas Gerlach, Ph.D. joined Burrill & Company in December 2011 after nearly 20 years in the pharmaceutical industry in different positions within multinational companies in Germany, Switzerland and Brazil, where he was involved in drug development, brand management and commercial operations. In 2002 he founded Actelion Pharmaceuticals do Brasil, the Brazilian subsidiary of Actelion Pharmaceuticals and served as general manager until 2010. There he led the foundation for the company’s Latin American operations. He originally joined Actelion as a project manager in Switzerland in 2000. Prior to that, Gerlach held positions with Novartis, Switzerland, Knoll AG, and BASF Pharma, Germany.

He has been a visiting scholar at Michigan State University where he worked on research projects in the field of retinoids. He holds a Ph.D. in Biology and a degree in Chemistry (Staatsexamen) from the University of Mainz, Germany, and a masters in biology from the University of Mainz. He is fluent in German, English, and Portuguese.

Eduardo Marques de Souza Dantas Matsos joined the management team of The Burrill Brazil I Fund as an Associate in 2012. He is focused on the analysis of investment opportunities, financial modeling, and support to deal structuring. He also contributes to the establishment of financial models per sector, market analysis and competitive intelligence, as well as overall strategic partnerships.

Mattos joined Burrill with 12 years of experience in investment analyses and financial market activities. His previous professional activities were as a partner at Mercatto Investimentos where he was portfolio manager of the equity funds investing in companies ranging from blue chips to small caps. He was one of the two partners to initiate the firm’s corporate finance and private equity practice, he acted as a financial advisor in M&A transactions, and helped raise R$250 million for a biodiesel production plant in the north of Goiás, Brazil. He also analyzed clean energy projects and was Senior Associate of the Mercatto Food and Beverage private equity fund.

Mattos earned a bachelor’s degree in business administration from Cândido Mendes University, has a M.B.A from IBMEC-Rio, and is portfolio management certified by CVM (Brazil’s Securities Commission).

Marcus Albernaz focuses on the Brazilian operations and contributes to investor relationships, market analysis, competitive intelligence as well as overall strategic partnerships, investee oversight, and deal flow analysis.

Prior to joining Burrill & Company, Albernaz had seven years investment analysis and financial market experience. His previous professional activities were at Banco UBS (PhRMA) and has also chaired a number of key PhRMA committees both domestic and international. He served as CEO of a biotech firm based in California and currently serves on three biotechnology boards as well as that of a major Japanese company.

Currently domiciled in Rio de Janeiro, Freiman has extensive experience in Latin America, having also served as Vice President, Latin America, for Burrill & Company.

Alexandre Augustus Batista de Oliveira joined Burrill Brazil Gestão de Recursos Ltda. on March 1, 2012 as Office Manager. He is in charge of the office administration, IT, and the back office activities of the Burrill Brazil I Fund. Alexandre has 16 years of experience with financial and administrative activities. He started his career at Banco Noroeste, then he joined ING Bank, and most recently served as an administrative assistant for Rio Bravo Investimentos for its Rio de Janeiro office.

Konstantin G. Skryabin focuses on special projects for Burrill & Company (digital health, biofuels, nanobiotechnology). As a leader of Russian biotechnology and nanobiotechnology innovations, he founded and headed the Centre Bioengineering, Russian Academy of Sciences (1991) and organized...
and headed the Biotechnology Chair at the Lomonosov Moscow State University (2007).

His more than thirty years experience in biotechnology includes Secretary General/ Treasurer of COBIOTECH (Committee on Biotechnology of International Council of Scientific Unions) and co-chairman of several key Russian and international biotechnology committees. In addition, he has consulted for many pharmaceutical and biotech companies in Russia. Together with Bioprocess Holding and other partners, he founded Bioprocess Capital Partners, which managed the first Russian venture capital fund focused on life sciences.

Through his pioneering research, Skryabin established genomic sequencing in Russia, developed systems for the production of a variety of biologically active compounds, and enhanced the elucidation of biosafety and ethical issues posed by genetic engineering. He has published more than 500 scientific papers and been assigned 59 patents and inventions.

Skryabin is a full member of the Russian Academy of Sciences and the Russian Academy of Agricultural Sciences. He was a member of the Council of the President of the Russian Federation on Science, Technologies and Education (2001-2012) and currently serves as a Chairman of the Russian Academy of Sciences’ Scientific Council on Biotechnology and a member of Presidium (Executive board) of the Russian Agricultural Academy. Among his many distinctions, he has been recognized in the Order for Services for Motherland in Russia. Prior to joining Burrill & Company, Skryabin was a member of the biopharma investment banking team at Leerink Swann. She also produced and launched a new series of syndicated reports for the firm, entitled Future in Focus, that provided clients with insight and analysis of business and technology issues shaping corporate and R&D strategies, pipelines and alliances.

Prior to Leerink Swann, Melnikova was a Research Manager at Life Science Insights, a subsidiary of IDG, the leading technology market research company. As a project leader at TransForm Pharmaceuticals (acquired by Johnson & Johnson), she was responsible for running several programs, including Engineered Tissue Constructs, funded by DARPA, and Amyloidoses.

Melnikova has published over 20 manuscripts in peer-reviewed journals and is a regular contributor to the “Analyst Coach” section of Nature Reviews in Drug Discovery magazine. She holds an M.S. in chemical engineering from the Mendeleev University of Chemical Technology of Russia and a Ph.D. in molecular medicine/molecular biology from the University of Texas Health Science Center at San Antonio.

**IRENA MELNIKOVA**
Managing Director, Russia

Irena Melnikova, Ph.D. joined Burrill & Company in October 2012 as Managing Director, Russia. Prior to joining Burrill & Company, she served as Director of Strategy and External Innovation at Sanofi.

Previously, Melnikova was a Principal in the Life Science team of TVM Capital, a global venture capital firm. At TVM, she was involved in deal origination and new investment opportunity evaluation and actively participated in the management of TVM Capital investments in the United States. Prior to TVM Capital, she was a member of the biopharma investment banking team at Leerink Swann. She also produced and launched a new series of syndicated reports for the firm, entitled Future in Focus, that provided clients with insight and analysis of business and technology issues shaping corporate and R&D strategies, pipelines and alliances.

Prior to Leerink Swann, Melnikova was a Research Manager at Life Science Insights, a subsidiary of IDG, the leading technology market research company. As a project leader at TransForm Pharmaceuticals (acquired by Johnson & Johnson), she was responsible for running several programs, including Engineered Tissue Constructs, funded by DARPA, and Amyloidoses.

Melnikova has published over 20 manuscripts in peer-reviewed journals and is a regular contributor to the “Analyst Coach” section of Nature Reviews in Drug Discovery magazine. She holds an M.S. in chemical engineering from the Mendeleev University of Chemical Technology of Russia and a Ph.D. in molecular medicine/molecular biology from the University of Texas Health Science Center at San Antonio.

**SERGEY AXENOVICH**
Director, Russia

Sergey Axenovich, Ph.D. joined Burrill & Company in 2007 and has more than 12 years of experience in the biotechnology industry. Axenovich currently focuses on sourcing and evaluating healthcare investment opportunities and is actively involved in the development and operations of Burrill venture funds in Russia. Prior to joining Burrill & Company, Axenovich managed the cancer drug discovery program at Pharmaceutical Product Development, PPD, and led strategic collaborations with two major pharmaceutical companies. He began his research career as part of the cancer functional genomics team at Genome Therapeutics. Axenovich is an observer on the board of NEOS Therapeutics. He received his Ph.D. in Molecular Genetics from the University of Illinois, Chicago and his M.B.A. from the University of California, Berkeley Haas School of Business. Axenovich has an undergraduate degree in Microbiology from M.V. Lomonosov Moscow State University.

**ANNA G. ANNENKO**
Operations and Business Development Manager, Burrill Russia

Anna G. Annenko serves as Operations and Business Development Manager in the Moscow branch of Burrill Russia, an affiliate of Burrill & Company. Annenko graduated from Moscow Institute of Oriental Studies in 1999 as a specialist in the region of Southeast Asia, with a focus on Thailand. Annenko obtained solid experience in operations management, customer relation services, logistics, and business development in large international companies in Russia and abroad, in particular Southeast Asia. Her career developed further in foreign economic relations under the Malaysian Diplomatic Mission in the Russian Federation, where Annenko held the position of Marketing Officer of the Commercial Section of the Embassy of Malaysia from 2003 to 2010. During her seven years in the commercial section of the embassy, she was deeply involved in a range of activities, including enhancement of bilateral government-to-government and economic relations, international trade operations, development of business links at the government-to-government and business-to-business levels, handling of high level government delegations and missions, and event management.

**ANNA F. HANHAM**
Managing Director, Canada

Ann F. Hanham, Ph.D. joined Burrill & Company in February 2000, and has utilized her background in clinical and regulatory affairs to lead deals in diagnostic, device and therapeutic opportunities. Prior to joining Burrill & Company, Hanham was a Senior Manager and Vice President of Clinical & Regulatory Affairs at InterMune Pharmaceuticals, and prior to that, the Senior Director for Oncology Product Development at Otsuka Pharmaceuticals and the Medical Director for Celnix Pharmaceuticals. She has also worked for Becton Dickinson in both regulatory and clinical affairs in their monoclonal antibody program, and as a regulatory toxicologist with the Health Protection Branch of Health and Welfare Canada. She holds a Ph.D. from the University of British Columbia, an M.Sc. from Simon Fraser University, and a B.Sc. from the University of Toronto. Hanham was also Board Certified in Toxicology in 1986. She is currently the CEO of Adlyfe, and a member of the Board of Directors of Adlyfe, Endocyte, SCYNEXIS, and Waterstone. Hanham is a charter member of the C100, a group dedicated to assisting Canadian entrepreneurs.

**SVEN ROHMANN**
General Manager Europe / Managing Director, Digital Health

As the General Manager in Europe, Sven Rohmann, M.D., Ph.D. manages all Burrill & Company activities (Venture Capital, Private Equity and Merchant Banking) out of Zurich, Switzerland, and is also part of the global digital health team. He joined Burrill & Company in 2010 with a background in clinical medicine and basic research. He spent 10 years at Merck Serono, which provided him with a strong...
THE BURRILL TEAM – Life Sciences Venture Capital

foothold in the pharmaceutical industry. His career exposed him to pre-clinical and clinical development, as well as marketing, business, and corporate development. During his tenure at Merck, he was involved in the successful licensing of Erbitux from ImClone and the establishment of Merck Oncology.

Prior to joining Burrill & Company, Rohmann worked as Venture Capital Fund Manager for Novartis Pharma, and as Managing and General Partner at Nextech Venture, both in Switzerland. In addition, Rohmann served as CEO of two European biotech start-ups and gained board experience at several SME’s in Germany, Austria, Liechtenstein and the U.S.

Rohmann brings a thorough knowledge of European research and regulatory policies and a unique blend of scientific, pharma/biotech and venture knowledge to Burrill. He maintains an extensive network of contacts among academic and government research administrators and healthcare providers and has significant experience in global, as well as European, partnering. Rohmann received his M.D. from the University of Mainz, Germany, and his Ph.D. from the Erasmus University, Rotterdam, Netherlands.

Michael Keyoung
Managing Director, Pan-Asia

Michael Keyoung, M.D., Ph.D. has more than 15 years of healthcare and life sciences experience through his role as scientist, surgeon, consultant and investor. At Burrill & Company, Keyoung oversees Burrill’s U.S., Asia and European public portfolio companies and leads cross-border transaction business across all of Asia and North America. Previously, Keyoung was co-founder of a life sciences healthcare investment partnership in New York. Keyoung also served as an advisor and consultant to leading life sciences venture capital firms, medical device, pharma, and biotechnology companies. Keyoung was a Howard Hughes Medical Institute fellow and received his clinical surgical training at University of California, San Francisco and biomedical fellowship at Memorial Sloan Kettering Institute and Rockefeller University in New York. Keyoung performed preclinical drug discovery research for Aventis (now Sanofi-Aventis) and Merck while at Cornell and participated in translational clinical trials. A National Institute of Health-Medical Scientist Training Program scholarship recipient, Keyoung received both his M.D. and Ph.D. in Neuroscience and Neurology from Cornell University Weill Medical College and Memorial Sloan Kettering Cancer Center. Keyoung has over 35 articles, book chapters and presentations in publications such as Nature Biotechnology and Nature Medicine.

Keyoung has served on the Board of Directors at New York County Medical Society and Board of Overseers at the Cornell University-Weill Medical College in New York and currently serves on the boards of private biopharma companies and organizations in the U.S. and in Asia.

Marietta Wu
Managing Director, Taiwan

Marietta Wu, M.D., Ph.D. has experience in fields ranging from clinical medicine and medical research to finance and entrepreneurship. In her current role at Burrill & Company, she leads Burrill’s operation in Taiwan and focuses on venture capital investing in China and Taiwan related life sciences opportunities. She currently serves on the board of Taiwan Liposome Company and Waterstone Pharmaceuticals (observer). She also served as acting COO of Waterstone, a specialty pharmaceutical company with key operations in China. In addition, she assists companies seeking trans-Pacific partnerships. Wu is a frequent speaker and author on China and Taiwan life sciences topics, and a founding member of the China Healthcare Investment Conference.

Prior to joining Burrill, Wu was Director of Strategy at Edwards Lifesciences. She also held various financial and business development positions at Eli Lilly & Company. In the past few years, she has been active in cross-border ventures and value creation in the life sciences industry.

Wu received a medical degree from Shanghai Jiaotong University School of Medicine (formerly Shanghai Second Medical University), a Ph.D. in Medical Sciences from Medical College of Ohio, and an M.B.A. from the University of Michigan Ross School of Business.

Tania Fernandez
Director

Tania Fernandez, Ph.D. has more than 15 years of experience in the fields of oncology and molecular biology. She secured her doctorate at the Cancer Research Institute (Tata Memorial Centre), India, with an Indo-U.S. scholarship from the National Institutes of Health and won both the Young Scientist Award and the most outstanding doctoral thesis award at Bombay University for her doctoral work. She gained operational experience at Hoechst Pharmaceuticals, Mumbai, India.

After completing her doctorate, Fernandez specialized in the fields of protein chemistry, protein delivery systems, and genetic engineering at the College of Medicine, Texas A&M University. In 1999, she joined the National Cancer Institute at the NIH as a post-doctoral associate and was appointed staff scientist in 2000.

Her work at the NIH resulted in two awards for excellence in biomedical research. Her research has been published in scientific journals and she has been an invited speaker at national and international conferences. She is an active member of the National Institutes of Health BioScience Business Interest group, The NIH Stem Cell Group, LARTA and the Women’s Technology Cluster (now Astia) where she assists with mentoring biotech companies and evaluating them.

Fernandez sits on the Board of Strand Life Sciences and Adlyfe and holds/held Board Observer seats with WhiteGlove Health and BioImagene (acquired by Roche). She also sits on the Editorial Advisory Board of Express Pharma, India. She has authored several articles on biotech and the evolving life science landscape both in the U.S. and in India.

Joshua Zelig
Director

Joshua Zelig joined Burrill & Company as a Director in the Venture Group in 2011. Prior to joining the Company, Zelig was an Associate Partner at GBP Capital, a Greenwich, Connecticut-based healthcare venture firm. In that capacity he was responsible for sourcing, evaluating, and executing investment transactions and new business opportunities. Additionally, Zelig managed the firm’s intellectual property portfolios, oversaw the company’s operations, and worked closely with portfolio companies in setting and delivering on strategic objectives.

Previously, Zelig was an Equity Research associate at Morgan Stanley where he covered biotech and consumer stocks. He later worked in real estate management, acquisition, and due diligence capacities on behalf of a number of large private real estate companies as well as public REITs.

Zelig is a graduate of Yeshiva University, Sy Syms School of Business, where he received a B.S. in Finance. He is currently a member of the board of directors of Flexible Stenting Solutions.
GARRETT VYGANTAS  
ENTREPRENEUR-IN-RESIDENCE

Garrett Vygantas, M.D., joined Burrill & Company in 2006 as a member of the Venture Group and is involved in the sourcing, evaluating and structuring of new investment opportunities across the life sciences spectrum. In 2007, Vygantas founded NewBridge Pharmaceuticals; he was President & CEO until 2010. NewBridge is a Dubai-based specialty pharmaceutical company commercializing therapies to treat diseases of increasing incidence in the emerging markets of the Middle East, Africa, Turkey and Caspian regions. Vygantas raised $20.4 million in Series A and B rounds, recruited senior management and now leads the Company's efforts in strategy, business development and M&A from the U.S. office. NewBridge’s current portfolio includes more than 21 therapeutic areas, diagnostics and medical devices acquired through in-licensing and company acquisitions.

Vygantas currently serves on the board of NewBridge as an observer, and previously served on the boards of Nora Therapeutics, Ikano Therapeutics, ProteoGenix, and NanoVasc – Burrill portfolio companies in which he led investments.

Before joining Burrill, Vygantas was with Genentech’s Market Planning Group where he focused on commercialization and launch of Lucentis for the treatment of age-related macular degeneration. He previously worked with the Health Care Investment Banking group at Cowen and in Business Development at EntreMed.

Vygantas is a co-instructor at UCSF’s Center for BioEntrepreneurship’s Idea to IPO course and has actively advised in the formation of numerous biotech and medtech start-ups. He completed his Transitional Residency at the University of Pennsylvania and holds M.D. & M.B.A. degrees from Georgetown University as well as a B.S. in Biochemistry from Boston College. He is a member of Kauffman Fellows Class 13 and serves on a number of non-profit healthcare related boards.

JANOS REDEI  
ENTREPRENEUR-IN-RESIDENCE

Janos Redei, M.D., Ph.D. is an Entrepreneur-in-Residence in the venture capital group with two decades of experience in healthcare technology, the pharmaceutical industry, and academia. He is a former University of California, San Francisco faculty member and holds an M.D. and Ph.D. in Applied Neuroinformatics.

Redei comes to Burrill & Company from Roche/Genentech, a leader in personalized healthcare, where he headed clinical and imaging informatics for all six therapeutic areas globally, including CNS. At Roche, he was instrumental in developing a number of group-wide emerging IT strategies and implemented the company’s first forays into on-demand/cloud computing for clinical applications and digital health. He also led the informatics effort of a consortium of five Pharma companies to enable disease understanding, incorporating biosample, imaging, and clinical data sources from around the globe.

SIMON WADDINGTON  
ENTREPRENEUR-IN-RESIDENCE

Simon Waddington, Ph.D. serves as Entrepreneur-in-Residence where he is involved in building startup companies across the spectrum of the life sciences. Simon serves as the CEO of Evolva Nutrition. He previously served as the President and CEO of Abunda, a company developing next generation ingredients which was acquired by Evolva SA in 2011.

Previously, Waddington spent more than a decade as a venture capitalist. He was a Managing Partner at PolyTechnos Venture-Partners based in Munich, Germany where he led and supported investments in numerous life science and materials-related companies across Europe, Israel, and the United States. Prior to that, he started and ran Monsanto’s European corporate venturing activities from Brussels, Belgium. He was Product Development Manager in the UK for Zeneca’s biopolymers business, which pioneered the fermentation-based production of biodegradable polymers from renewable feedstocks. He also served as a Senior Research Scientist for ICI specializing in surface and interface science; his work on the development and advancement of surface analysis methods led to a long-standing interest in nanoscience. Waddington was a co-founder of the European NanoBusiness Association and served on its Advisory Board.

He holds a Ph.D. in physics and an M.B.A. from Harvard Business School. He is a former board member of the German HBS Alumni Association and currently serves as an International Alumni Ambassador for Liverpool University.

CHEN YEE LIAW  
ASSOCIATE

Chen Yee Liaw joined Burrill & Company in June of 2011 as Business Analyst, and has been working with the Malaysian Life Sciences Capital Fund (MLSCF) since 2009. She is instrumental in evaluating biotechnology companies in the cleantech sectors, where she develops insights and investment strategy through market, technical, competitive and financial analyses. Liaw also served as Business Analyst at Abunda Nutrition, a portfolio company of MLSCF, where she helped identify potential molecules for pipeline expansion, developed insights to guide manufacturing and commercialization strategies, as well as performed financial modeling. Prior to Burrill and MLSCF, Liaw interned at Deloitte Consulting, in Strategy & Operations and did research at Caltech, elucidating the molecular basis of early T-cell development defects that may impact autoimmunity in a Type 1 diabetes mouse model. She holds a B.S. (Honors) in Biology and Business Economics from the California Institute of Technology, and was a recipient of the prestigious Upper Class Merit Award.

Stephen M. Sammut is a venture partner focused on special projects for Burrill & Company (Latin America, the Middle East, Japan and emerging markets). During his career he has been involved in the creation of nearly 40 biotechnology, Internet, and information technology companies. His experience includes Vice President of SR One (the venture fund of Glaxo SmithKline); Vice President of Corporate Development at Telereflex Incorporated, Managing Director of Technology Transfer at the University of Pennsylvania, and Founder and CEO of one of the first and largest transplant organ banks in the U.S. He is on numerous boards of directors and advisory boards, including Mitsubishi International, Combinent Biomedical Systems, Gentis, and Dynamics Therapeutics. In addition, he is on the boards of the Cornell University Research Foundation, the Massachusetts General Hospital Technology Transfer Committee, and the American Type Culture Collection. Sammut is a Senior Fellow in Entrepreneurship and Health Care Systems at the Wharton School of the University of Pennsylvania, where he teaches courses on venture capital, private equity in emerging markets, intellectual property strategy, biotech entrepreneurship, and private sector participation in global health. He is also an advisor to the joint M.B.A./Masters in Biotechnology Program.

He holds graduate and undergraduate degrees in biological sciences and humanities from Villanova University, attended Hahnemann Medical College for two years, and holds an M.B.A from the Wharton School of the University of Pennsylvania.
Merchant Bank/Investment Bank

Stephen A. Hurly joined Burrill Securities as its CEO and head of investment banking in June 2011. He brings an expertise in assisting public and private firms with strategic transactions, difficult financings, product licensing, joint ventures and restructurings. He has experience at both bulge bracket firms as well as specialized boutiques. Through extensive industry relationships and global transaction experience in China, Japan, Australia, the European Union, and North America, Hurly and his team provide tailored solutions and insight to assist clients in reaching their strategic goals.

Hurly was previously with Boenning & Scattergood as a Managing Director and Global Head of the firm’s Health Care Investment Banking Practice. Prior to that appointment, Hurly was the Managing Director and Head of the Life Sciences Group at Janney Montgomery Scott. His earlier investment banking experience was with Hambrecht & Quist in San Francisco, where he closed more than 30 public and private financings as well as M&A transactions, eventually becoming a member of the executive office.

Hurly is also an expert in strategic transactions and associated capital raising, and has completed more than 100 deals with an aggregate value over $10 billion and more than $400 million in capital. He has an M.B.A. from the University of Chicago and a B.S. in Engineering from Swarthmore College.

René Benjamin, Ph.D., joins Burrill from Rodman & Renshaw, where he served as a Managing Director and Senior Biotechnology Equity Research Analyst beginning in 2003. He has expertise in small- and mid-cap companies in the oncology and stem cell sectors and has previously been ranked among the top analysts by StarMine for recommendation performance and earnings estimate accuracy.

Prior to that, he served as an associate analyst in Needham & Company’s biotechnology equity research department. He earned a Ph.D. in Biochemistry and Molecular Genetics at the University of Alabama at Birmingham and a B.S. in Biology from Allegheny College.

Mike Carpenter has more than 20 years of institutional sales and trading experience in both domestic and international equity markets. He started his career at Morgan Stanley, where he became an executive director in the institutional equity division. He spent 19 years at the firm trading for institutional clients primarily based on the West Coast. During his time there he was also responsible for developing new client relationships in U.S. equity sales in London, Paris, Geneva, and Frankfurt. He also served as a member of the firm’s M.B.A. recruitment team at Stanford and UCLA.

During his career, Carpenter also worked as an institutional buy side trader at Dodge and Cox. In 2004, he became a partner at Pacific Growth Equities in San Francisco where he provided research and trading coverage of emerging growth companies in healthcare and technology. Most recently, he served as managing director and head of the San Francisco office of Summer Street Research Partners, a healthcare-focused investment bank. Carpenter holds a B.A. from the University of California, Santa Cruz.

Andrew Daniels joined Burrill Securities as Managing Director in the Equity Capital Markets Group in early 2013. Daniels has almost 20 years of investment banking experience, and has been exclusively focused on life sciences companies since 1999. Prior to Burrill Securities, Daniels was with Merriman Capital and held positions with Janney Securities, Deutsche Bank Securities, Cowen and Company, Marwood Group and Paramount Capital. He began his career at Morgan Stanley. Daniels brings to Burrill deep experience raising capital for life sciences companies through CMPOs, PIPEs, registered direct offerings, and other instruments. His past work has included engagements with companies such as Cougar, Medivation, Kosan, Micromet, and Genelabs.

Daniels earned an M.B.A. from Columbia Business School, and a B.B.A. from the University of Michigan, Ann Arbor.

David Parke joined Burrill & Company in June 2011 as a Managing Director of Burrill Securities. Parke specializes in public offerings, private placements, fairness opinions, and mergers and acquisitions for emerging growth companies. His experience delivers a strong background in capital markets with an in-depth understanding of the issues particular to life sciences and healthcare companies.

Parke joined Burrill & Company from Boenning & Scattergood. Prior to that, he was with Mufson Howe Hunter & Company, where he was instrumental in launching and developing the firm’s emerging growth practice and the corporate finance department of Invesco, and its predecessor, Pennsylvania Merchant Group. Parke has managed or participated in 40 public offerings and private placements, raising more than $1 billion supplied European institutions with custom modeling solutions for their global healthcare investments utilizing a joint venture created with an analytical firm in India.

Laub joined Leerinck, Swann & Co. in 1999 as a director of institutional sales charged with the development and introduction of a new concept in healthcare proficiency and created an entire product line by melding the knowledge of a medical consultant force with a brokerage firm. He went on in 2002 to become a founding partner of Summer Street Research Partners, an equity research broker dealer focused on Healthcare and Life Sciences. He was also Head of Institutional Sales & U.S. Managing Director of Clear Capital Ltd./Noble in London, where he was responsible for an international team.

He has served as the Chairman of the Portfolio Committee for the Massachusetts Maritime Academy Foundation and has been a trustee there since 1994. He graduated the maritime academy with a B.S. in Marine Engineering.
for emerging growth clients. Parke has managed mergers and acquisitions assignments ranging from $5 million to $500 million. Prior to joining Investec in 1992, he was in the corporate finance departments of Wheat First Butcher & Singer, now Wachovia Securities, and Legg Mason.

He has been a director of Petroleum Development Corporation, a publicly-traded natural gas exploration and production company, since 2003. He chairs the board’s Finance and Planning Committee, and is a member of its Compensation and Audit Committees.

Parke received his M.B.A. with honors from The Wharton School of the University of Pennsylvania, and graduated summa cum laude and Phi Beta Kappa from Lehigh University with a B.S. in Finance.

Elemer Piros, Ph.D. joins Burrill from Rodman & Renshaw, where he served as a Managing Director and Senior Biotechnology Analyst since 2002. He has ranked among the top biotechnology analysts in various surveys, including ranking as the top biotechnology analyst in the 2006 Wall Street Journal and 2010 Financial Times surveys, based on stock portfolio performance. Prior to that, he served as a senior biotechnology analyst at Ladenburg Thalmann and a biotechnology research analyst with Spear, Leeds & Kellogg/Goldman Sachs.

Before serving as an analyst, Piros spent eight years conducting research in biophysics, biochemistry, and molecular biology at Cornell University and the University of California, Los Angeles. He holds a Ph.D. in Neurosciences from Mount Sinai School of Medicine for her work on molecular mechanisms of Alzheimer’s disease. Sheinerman also holds an M.B.A. from the Honors program at Baruch College, CUNY.

Elemer Piros
MANAGING DIRECTOR, SENIOR
EQUITY RESEARCH ANALYST

Kira Sheinerman, Ph.D. joined Burrill & Company as a Managing Director, Securities, in October 2012 to focus on structuring and closing private placement financing transactions and public offerings for Burrill & Company clients. Prior to joining Burrill & Company, Sheinerman was a Managing Director, Healthcare Investment Banking at Rodman & Renshaw. She joined Rodman in 2005 and worked on financial and strategic transactions for growth biotech companies with the focus on oncology, CNS, infectious diseases, and molecular diagnostics. Prior to her position at Rodman, she worked at The Atria Group, specializing in analysis of market opportunities for early to late stage biotech products and in investment and acquisition opportunities in the fields of oncology and critical care. Sheinerman is a board member of Boyce Thompson Institute, an affiliate of Cornell University. She received a Ph.D. in Biomedical Sciences from The University of Pennsylvania, her B.S. in biochemistry, and molecular biology at Cornell University, and the University of California, Los Angeles. She holds a Ph.D. in Organic Chemistry from the University of Pennsylvania, his M.B.A. from Penn State, and his B.S. from Shandong University.

Kira Sheinerman
MANAGING DIRECTOR

Wenyong Wang, Ph.D. joined Burrill & Company in 2011 and has more than 18 years experience in the healthcare industry. Prior to joining Burrill Securities, Wang was a senior executive member of Boening & Scattered Global Healthcare Investment Banking practice, where he initiated and led M&A, licensing & partnering, capital raising, fairness opinions, as well as other financial and scientific advisory activities in public and private life sciences companies. He has managed more than 25 public offerings and private placements, as well as M&A assignments ranging from $5 million to $500 million, for an aggregated value of more than two billion dollars. Wang’s prior investment banking experience was with Janney Montgomery Scott in Philadelphia as a vice president, where he and his team provided investment banking services to public and private healthcare clients throughout Asia, Pacific, Europe and North America. Prior to Janney, he worked on drug research and development at GlaxoSmithKline for more than six years. At GSK, he oversaw two drug candidates selected for clinical trials. Wang received his Ph.D. in Organic Chemistry from the University of Pennsylvania, his M.B.A. from Penn State, and his B.S. from Shandong University.

Wenyong Wang
MANAGING DIRECTOR

Neal Fischer joined Burrill & Company’s Securities Division in 2011 as a Senior Associate. Previously, Fischer worked at BNY Mellon for a subsidiary focused on portfolio performance analytics for numerous financial institutions and broker/dealers. Prior to BNY Mellon, Fischer worked in the Healthcare Investment Banking group at Janney Montgomery Scott, where he focused on capital raising, M&A, and strategic advisory. Fischer earned a Master of Finance at Pennsylvania State University, and graduated Cum Laude from Dickinson College with a dual degree in International Business & Management, and East Asian Studies. He has completed certificate programs at Peking University and Beijing Language & Culture University in China.

Neal Fischer
SENIOR ASSOCIATE

Suy Anne R. Martins, M.D., Ph.D. joined Burrill & Company’s Securities Division in September 2012 as a Senior Associate Equity Analyst. Previously, Martins worked at Rodman & Renshaw, performing equity analysis for emerging growth biotech companies. Before joining the investment community, Martins was a practicing ophthalmologist and a corneal transplant surgeon with seven years of clinical practice. She started her investment research career as an analyst at WBB Securities, focusing on small- and mid-cap biotech and medical device companies.

She earned her Medical degree Magna Cum Laude at Federal University of Ceara–School of Medicine, Brazil. Martins completed her Ophthalmology residency, Corneal Transplant and Refractive Surgery fellowship at Paulista School of Medicine, Brazil. She received her Doctorate in Ophthalmology from Paulista School of Medicine, and completed postdoctoral research in Ophthalmology at The Wilmer Eye Institute, Johns Hopkins University School of Medicine. She earned her Master in Finance degree from The Johns Hopkins University Carey Business School. Martins writes and reviews for key ophthalmology journals and texts.

Suy Anne R. Martins
SENIOR ASSOCIATE, EQUITY RESEARCH ANALYST

Vinay Singh joined Burrill & Company in 2012 as a researcher and staff writer in the Media Group. In 2013, he moved to Burrill Securities where he currently works as an Analyst. Prior to joining Burrill & Company, Singh interned at the University of California, San Francisco Hospital with pediatric cancer patients. Singh also served as a summer intern Research Associate at Exelixis in the new drug discovery group, focusing on high-throughput compound screening. He is a graduate of Lehigh University with a B.S. in Biology.

Vinay Singh
ANALYST
John McLaughlin joined Burrill & Company in 2011 and works as a sales trader in the Securities Division. He has more than 20 years of experience in both the domestic and international equity markets. He began his career at Cantor Fitzgerald in New York and then moved on to Furman Selz LLC, where he became a Senior Vice President in the equity trading division. McLaughlin worked at Bank of America securities in San Francisco until 2003. He spent the eight years prior to joining Burrill & Company at BTIG LLC in San Francisco as a Senior Vice President. There he developed a business servicing small- to medium-sized hedge funds. During his career, McLaughlin has traded a variety of products including equity options, futures, bonds, and currency transactions.

He holds a B.A. in History from Boston College.

Lisa Mays is Chief Compliance Officer for Burrill Securities, LLC. Mays has more than 25 years experience in the financial services industry assisting broker-dealers and registered investment advisers in the design and implementation of compliance systems. Prior to joining Burrill Securities in late 2012, Mays was Chief Compliance Officer for a firm with 420 registered representatives.

Mays specializes in crafting operational and compliance procedures to meet Financial Industry Regulatory Authority and Securities Exchange Commission regulations.

Mays began her career at the Pacific Stock Exchange Options Floor in San Francisco. Previously she worked for Smith Barney as an Operations Manager, was the Sales Supervisor on the Robertson Stephens Institutional Sales Floor, and managed the Compliance Department at Essex National Securities. Mays holds the Financial Industry Regulatory Authority Series 7, 10, 24, 63, 65, and 79 licenses.

Prior to joining Burrill & Company, Ron Ree, D.V.M. worked at Roth Capital Partners where he focused on corporate access, institutional sales and investment banking. Previously to Roth he held positions in sales and investment banking with firms including Rodman & Renshaw, Adams, Harkness & Hill, Paine Webber, Kidder Peabody, Hambrecht & Quist, and White Weld. Prior to the investment business, Ree practiced veterinary medicine in Minnesota and North Dakota for six years. Ree obtained his B.A. in the pre-med program at St. Olaf College, his B.S. from the University of Minnesota and his D.V.M. from the University of Minnesota College of Veterinary Medicine.

Deidre Swagerty joined Burrill & Company in February 2013 as an Executive Assistant with Mary Tanner and Fred Frank in their work for both Burrill Securities and Life Science Partners. Swagerty was most recently an Executive Assistant in the Life Sciences Team at Peter J. Solomon for 2+ years, and prior to that gained more than eight years of related experience in various roles at Zubatkin Owner Representation and Forest City Ratner Companies as a marketing coordinator, project coordinator and executive assistant. Swagerty has a Bachelor of Science Degree in International Business from Northeastern University, and is fluent in Spanish.
Jennifer Gregoire joined the Burrill & Company Events Team in July of 2009. Her focus is on individual event management, venue selection, marketing, and client retention for Burrill & Company’s collection of conferences, meetings, and special events. Prior to joining Burrill & Company, she served as a Convention/Event Manager for two major San Francisco area hotels, Marriott & Hyatt International. Gregoire also worked for Pebble Beach Company where she participated in management of the AT&T Pebble Beach Pro-Am Golf Tournament. Gregoire earned a B.A. in English from Vassar College and a Masters in Journalism from the University of California, Berkeley.

Candice Smith joined Burrill & Company in November 2012 as Director of Business Development in the company’s Media Group. She is responsible for generating revenue and building partnerships for all of Burrill’s conferences, publications and digital media. Smith has over 20 years of progressive sales and promotion experience in various media outlets consisting of The Boston Herald, WXRV, and industry-leading outdoor magazines both in the private and non-profit sectors. Prior to joining Burrill & Company, Smith was the West Coast Account Manager for Active Interest Media’s Healthy Living Group. Smith earned a B.S. in Marketing from Southern New Hampshire University and a Masters in Management from Lesley University in Cambridge, Massachusetts.

Marie Daghlian joined Burrill & Company in July 2010 as Associate Editor of publications. Prior to that she worked for the company on a contract basis, helping to launch The Burrill Report in 2009 and contributing to it on a monthly basis, as well as working on the company’s annual state-of-the-industry report for the previous eight years. Daghlian started her career in the fashion industry as an owner, designer, and manufacturer of women’s apparel for 28 years. She attended the University of Pennsylvania for four years and holds a B.A. in Communication Studies from Sonoma State University.

Michael Fitzhugh joined Burrill & Company in April 2011 as an Associate Editor after contributing to Burrill Media publications for two years as a freelance writer and editor. Prior to that, he covered biotechnology for American City Business Journals. Fitzhugh received his Masters in Journalism from the University of California, Berkeley Graduate School of Journalism and holds a B.A. from the University of Michigan, Ann Arbor.

Sheryl P. Denker, Ph.D. joined Burrill & Company in February, 2013, and brings with her a breadth of scientific knowledge and expertise helping scientists communicate their work. Denker was previously a Sr. Program Advisor at the BayBio Institute, the entrepreneurship and science education arm of Northern California’s life science trade association, BayBio. In this role she brought 15 years of research, writing, teaching and project management experience to program development, industry outreach and grant writing efforts for the Institute and its science education program. Denker has a broad perspective from positions in both academia and industry, as Assistant Research Cell Biologist at the University of California, San Francisco, and Senior Scientist at Xenogen.

Prior to Xenogen, she completed post-doctoral research on the cytoskeleton and cell motility at the University of California, San Francisco, where her research efforts on cell shape and motility resulted in an Innovation in Basic Sciences Award to her sponsoring advisor and publications in top cell biology journals. Denker received a B.S. in Physiology from the University of California, Berkeley and a Ph.D. in Biomedical Sciences (focus in Cell Biology and Pharmacology) from the University of California, San Diego, for her work on membrane trafficking and signal transduction.
Vic Hebert, J.D. joined Burrill & Company in October 2008 after serving as its principal outside counsel through Heller Ehrman LLP, since Burrill & Company’s founding. Hebert is a business lawyer with extensive experience in M&As, corporate finance, corporate governance, fund formation and venture capital.

During his legal career, Hebert performed services for Heller Ehrman and clients in numerous industries, including biotechnology, healthcare, financial services, aluminum, steel, telecommunications, semiconductor equipment and services, analytical instruments, computer software and hardware, forest products, solid waste disposal, food and beverages.

Hebert has a long history of serving on the boards of or as an officer of numerous public and private corporations and non-profit organizations. At Heller Ehrman LLP, Hebert served as Chairman of the Management Committee from 1981 to 1993 and as Co-Chairman from 1987 to 1993. Hebert is a member of the State Bar of California, the American Bar Association, and the Bar Association of San Francisco. He holds undergraduate and law degrees from the University of California, Berkeley.

Sen obtained her C.P.A. while an Audit Supervisor at Laventhol & Horwath, where she was responsible for a diverse range of audit engagements. Sen received a B.S. in Accounting from the University of San Francisco.

Herman Ip manages Burrill & Company’s Information Technology infrastructure security and day-to-day operations. Prior to joining Burrill, Ip spent 11 out of his 14 years in the industry as an IT consultant, eight of which were with Burrill through Langtech. As a Senior Systems Consultant at Langtech, he was responsible for helpdesk support, project management and implementation, office moves, network architecture planning, managing information technology departments, and creating internal support procedures and policies.

Jan Hayashi joined Burrill & Company in 2013 as Director, Human Resources. She has more than ten years experience in HR development and leadership functions with start-ups in the high tech industry. Previously Hayashi was Director of HR at VirtuOz, a provider of intelligent virtual agents for online marketing, sales, and support, and at Sabrix, an enterprise tax management software company acquired by Thomson Reuters in 2009. She previously worked at and continues to consult for McMorgan & Company, a registered investment advisory firm. Hayashi has a B.A. from the University of Michigan and an M.B.A. from Boston University.
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Akermin develops energy-efficient and cost-effective systems for carbon dioxide management from a variety of industrial processes. Akermin’s technology leverages the carbonic anhydrase enzyme to accelerate absorption of carbon dioxide.

Chromatin, Inc.
Chromatin develops sorghum varieties for feedstock, biofuels, and biomaterials precursors. Its mini-chromosome technology enables introduction of new genes, stacks of genes and whole metabolic pathways without disrupting the plant’s own genome.

Cobalt Technologies
Cobalt Technologies develops novel technologies for the production of biobutanol, a drop-in replacement for petroleum-derived products. Their bioscience and engineering innovations allow production of sustainable chemicals from cellulosic feedstock.

Codexis
Codexis uses a directed evolution platform to build efficient enzymes for production of renewable bio-based products. It creates sustainable chemicals, clean fuels, pharmaceutical processes, and renewable ingredients that make industry more efficient, productive and profitable.

Glori Energy
Glori Energy’s AERO (Activated Environment for Recovery of Oil) System enhances production from oil fields by stimulating a reservoir’s natural microbes to improve water and oil mobility. Its mission is to sustainably and efficiently recover billions of barrels of oil trapped in reservoirs using existing oil wells.

Virdia
Virdia develops extraction and separation technologies for the conversion of cellulosic biomass to refined fermentable sugars and lignin. The company’s Cold Acid Solvent Extraction (CASE) produces sugar and lignin intermediate supply chain products. The company serves various markets, including renewable fuels and fuel intermediates, renewable chemicals/materials, nutrition, pelletized energy sources, carbon fibers, and flame retardants.

LanzaTech
LanzaTech develops and commercializes proprietary technologies for the production of low-carbon fuels that do not compromise food or land resources. Its process converts carbon-monoxide-containing gases from industrial and agricultural waste into valuable fuel and chemical products.

Mascoma
Mascoma is a renewable fuels company that has developed innovative technology for the low-cost conversion of abundant biomass to renewable fuels and chemicals. Its genetically modified yeast and other microorganisms streamline biofuels production and reduce reliance on enzymes.

Segetis
Segetis develops proprietary biologically based monomers that can be used as substitutes for petrochemicals in plasticizers, solvents, and polyols. Its expertise in levulinic ketal chemistry reduces fossil fuel demand and plastic solvent product toxicity.

Medical Technology and Diagnostics

AliveCor
AliveCor is a mobile health company developing innovative wireless biosensors and cardiac monitors that work with a variety of mobile platforms, including iPhones, iPads, and Android devices.

Adlyfe
Adlyfe develops screening and monitoring products for neurogenerative diseases based upon its misfolded-protein detection (MPD) platform. The company uses small peptides as ligands in its tests for amyloid and prion proteins for the blood screening, human diagnostics, and animal testing markets.

Acusphere
Acusphere develops new drugs and improved formulations of existing drugs using its proprietary porous microsphere technology with a focus on drugs that can offer significant benefits such as improved safety and efficacy, increased patient compliance, greater ease of use, expanded indications, or reduced cost.

BioMimetic Therapeutics
BioMimetic Therapeutics specializes in the development and commercialization of clinically proven products to promote the healing of musculoskeletal injuries and diseases, including therapies for orthopedic and sports medicine applications.

Continued on next page
Flexible Stenting Solutions

Flexible Stenting Solutions is a privately-held medical device company focused on the development and commercialization of flexible stents built on a proprietary design platform.

HyperMed

HyperMed uses Medical Hyperspectral Imaging, an advanced form of spectroscopy that provides a two-dimensional tissue oxygenation map, to analyze tissue health for medical applications.

i2dx

i2dx is developing a multi-modal, cloud-based diagnostic platform for the assessment of prodromal Alzheimer’s Disease.

Spectral Image

Spectral Image is a privately-held, early-stage medical device company focused on the development of imaging technology for biomedical use.

Strand Life Sciences

Strand Life Sciences provides bioinformatics solutions with advanced visualization, predictive systems modeling, data integration, and scientific context management components to transform raw data into actionable insights.

PrimeraDx

Primera Dx uses a combination of advanced PCR and capillary electrophoresis techniques for next-generation, real-time quantitative PCR. The company sells the system and offers collaborations with pharmaceutical companies to develop companion and enabling diagnostic products.

WaveTec Vision

WaveTec Vision provides innovative wavefront measurement technology to the cataract surgeon. Their diagnostic device with precise optics, live display of the eye, and optimized algorithms guide decisions to improve refractive surgery.

XDx

XDx is a molecular diagnostics company focused on the discovery, development and commercialization of non-invasive gene expression testing in the areas of transplant medicine and autoimmunity.

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Lonza

XCaT Biosciences is developing the next generation of biopharmaceuticals that harness the catalytic power of engineered proteases. Its technology is applied to either improve existing protease-based drugs or redirect them to cleave disease-promoting proteins.

Strand Life Sciences

Strand Life Sciences provides bioinformatics solutions with advanced visualization, predictive systems modeling, data integration, and scientific context management components to transform raw data into actionable insights.

MabVax

MabVax is a clinical stage biopharmaceutical company focused on the commercialization of proprietary anti-cancer immunotherapies resulting from two integrated and successful technology platforms: the first is a series of vaccines and the second is a human antibody discovery platform.

ADMA Biologics, Inc.

ADMA Biologics is a clinical stage biotechnology company focused on the development and commercialization of human plasma and plasma-derived therapeutics.

Endocyte

Endocyte is developing targeted therapies for the treatment of cancer and other serious diseases. The company uses a proprietary technology to create novel small molecule drug conjugates and companion imaging diagnostics.

Evolva

Evolva Nutrition is building a pipeline of products with potential utility in consumer health, nutrition, and the food chain. The company uses biosynthetic and evolutionary technologies to create and optimize novel small molecule compounds and their production routes.

Lentigen

Lentigen is a diversified biologics company focused on the development and commercialization of breakthrough treatments for human disease. Lentiviral vectors (LV), the company’s technology platform, are widely recognized as the most efficient method for delivery of genetic sequence information into cells to reprogram their function.

Celtix Diagnostics

Celtix Diagnostics is developing diagnostic products.

Quantum Health

Quantum Health delivers health and wellness services through a proprietary platform that leverages advanced data integration, and scientific context management components to transform raw data into actionable insights.

Therapeutics and Wellness

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Neurotech develops sight-saving therapeutics for chronic retinal diseases. Its core technology platform is a genetically engineered implant that allows continuous delivery of protein drugs directly into the eye.

Neos Therapeutics is a privately owned drug delivery and full-service contract manufacturing company serving prescription pharmaceutical and consumer healthcare markets.

Nora Therapeutics is an early-stage specialty biopharmaceutical company focused on development of therapeutics to address clinical needs in reproductive medicine.

Odyssey Therapeutics is pioneering a pathway-based approach to drug discovery. The company has created a comprehensive strategy for cellular systems biology and drug discovery, and is utilizing this capability both for the benefit of its pharmaceutical partners and to identify small molecules that block key cancer pathways.

OncoGenex Pharmaceuticals is uniquely focused on cancer treatment resistance. The company develops and commercializes new cancer therapies that target mechanisms of resistance.

Sentinext Therapeutics develops safe and efficacious vaccines and therapeutics for tropical infectious diseases. The Malaysian company is targeting vaccines for dengue, enterovirus, and Japanese encephalitis.

Scynexis is a chemistry-focused drug discovery and development company with its headquarters located in Research Triangle Park, North Carolina. Its goal, from concept to clinic, is to deliver effective and innovative drug pipeline solutions to its pharmaceutical partners.

Taiwan Liposome Company is focused on the research, development, and commercialization of innovative pharmaceutical products based on its proprietary drug delivery technologies using micelles and nanoparticles to improve drug efficacy and lower toxicity.

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BetterDoctor is a digital health marketplace startup revolutionizing the way consumers search for and discover highly qualified doctors. BetterDoctor’s mobile and web apps provide consumers personalized recommendations of the best doctors in a matter of minutes and with just a handful of clicks, eliminating the need to spend hours manually searching through web directories.

Cerca Insights specializes in behavioral pharmacology and is dedicated to helping customers discover the next generation of CNS drugs by providing validated assays and delivering world-class services.

JHL Biotech is a best-in-class management team for Asia-based biosimilar manufacturing.

NewBridge Pharmaceuticals is a specialty therapeutics company positioned to become the leading provider of innovative healthcare products to the Middle East, North Africa, and Turkey. It specializes in in-licensing, acquiring, registering and commercializing FDA, EMA, European, and Japanese PDMA-approved therapeutics.

Waterstone Pharmaceuticals is an Indiana-based company with its main manufacturing operations in China. It aspires to be a leading developer and manufacturer of active pharmaceutical ingredients and finished pharmaceutical products. Waterstone’s business focus is to take advantage of the high-quality and lost-cost value proposition and to capture the rapidly growing China pharmaceutical market opportunity.

Wellpartner is a nationally recognized provider of pharmacy distribution solutions for health plans, Medicaid programs, and safety-net providers nationwide. Dedicated to lowering the cost of medications using home delivery and contract pharmacy services, Wellpartner offers innovative solutions that improve pharmacy care for individuals.