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CURRENT ENVIRONMENT

Biotech stocks outpacing broader market performance since 2011

Biotechnology stocks have substantially outperformed the broader equity markets over the past two years, following two years of underperformance in 2009 and 2010. In 2008, despite a widening recession, large-cap biotechnology companies thrived, benefiting from stable patient demand and sustained pricing power, which resulted in robust operating cash flows that insulated them from needing to access tightened credit markets. However, as economic growth resumed in 2009 and 2010, the biotech industry underperformed, which S&P Capital IQ (S&P) attributes to several factors, including signs of slowing industry growth, increased regulatory risk due to a more cautious US Food and Drug Administration (FDA), and uncertainty over the impact of US healthcare reform legislation.

We believe several positive trends emerged that spurred the industry's resurgence in 2011 and 2012. First, the FDA picked up its pace of new drug approvals, giving the nod to 30 new drugs in 2011, and then bettering this result by approving 39 in 2012. (The FDA approved only 21 new drugs in 2010.) Further, nearly half of the new drugs approved in 2012 had been granted the orphan drug designation by the FDA, which is reserved for drugs that treat rare diseases and often represent areas of significant unmet medical needs. The 2012 output followed a productive 2011 that saw several novel drug approvals for diseases in need of new treatment options, including the Hepatitis C virus and the autoimmune disorder lupus.

A second factor in biotech's resurgence over the past two years has been the acquisition of several notable biotech companies by large-cap pharmaceutical companies ("Big Pharma"), which, we believe, renewed investor interest in the biotech sub-industry after a relatively quiet 2010 for M&A. We note that Big Pharma, in making these acquisitions, has had to compete increasingly with large-cap biotechs and even with generic drugmakers looking to diversify into branded medicines. Still, S&P expects Big Pharma to remain at the forefront of the M&A landscape, as it addresses the challenge of replacing revenues that will be lost following a wave of key patent expirations in the coming years.

In 2012, the S&P Biotechnology index increased by 40.5%, versus a 13.7% advance for the S&P 1500 SuperComposite stock index. In 2011, the S&P Biotechnology index increased by 20.0%, versus a 0.3% decline for the S&P 1500. In contrast, in 2010, the S&P Biotechnology index declined 2.9% versus a 14.2% rise for the S&P 1500. In 2009, the S&P Biotechnology index fell 5.4%, while the S&P 1500 rose 24.3%.

The industry's recent performance notwithstanding, we see multiple issues that are likely to keep it volatile. These include the need to reverse a declining trend in research and development (R&D) productivity in the biopharmaceutical pipeline. The industry also has to deal with the changing dynamics in the partnering landscape, as Big Pharma becomes more selective in establishing new alliances (and on terms that seek to balance their risk) and increasingly terminates older partnering deals with smaller biotechs. As a result, we expect smaller biotechs to remain vigilant in protecting their cash positions and raising capital when possible on favorable terms, or selling themselves outright. S&P is also wary of those companies with premium valuations that may show signs of maturing and facing slowing growth prospects following this sustained period of industry outperformance.

POSITIVE CATALYSTS SUSTAIN SECTOR OUTPERFORMANCE

S&P Capital IQ (S&P) believes that biotech company valuations have been significantly compressing in recent years compared with historical premiums. On a price/earnings-to-growth (PEG) basis, the core group of profitable, established biotech companies—Amgen Inc., Biogen Idec Inc., Celgene Corp., and Gilead Sciences Inc.—were recently trading at valuations around an average PEG of 1.0X our 2013 expected earnings. However, we note a wide disparity among these companies, with Amgen and Biogen trading well above this average, and Celgene trading well below. In the past, profitable and growing biotech companies typically warranted a PEG range between 1.3X and 1.5X current year earnings expectations.

Price-to-earning (PE) ratios have also declined. In the 2011 edition of its annual *Beyond Borders: Global Biotechnology Report,* Ernst & Young noted that the average biotech P/E ratio was 55X in 2005. However, slowing earnings growth among these large-cap players amid a maturing industry has led to the large-cap biotech company average in our coverage universe to trade at a forward P/E ratio of around 20X as of March 2013.

While we expect future industry valuations to remain closer to recent levels rather than reverting to 2005 levels, we believe that the sector still holds above-average growth prospects compared with the broader market over the next several years, boosted by several catalysts.

New drug approvals on the upswing

As mentioned earlier, the FDA approved 39 new drugs in 2012—the highest total in 16 years. Of the 39 medicines approved, 11 were cancer drugs, and nearly half of the approved drugs had been granted the orphan drug designation. S&P attributes this enhanced output, in part, to improved operations at the agency, following several years of inconsistent practices. We think that this trend will continue as the FDA becomes more focused on the timely approval of new drugs, particularly for those treating rare diseases and life-extending treatments for cancer.

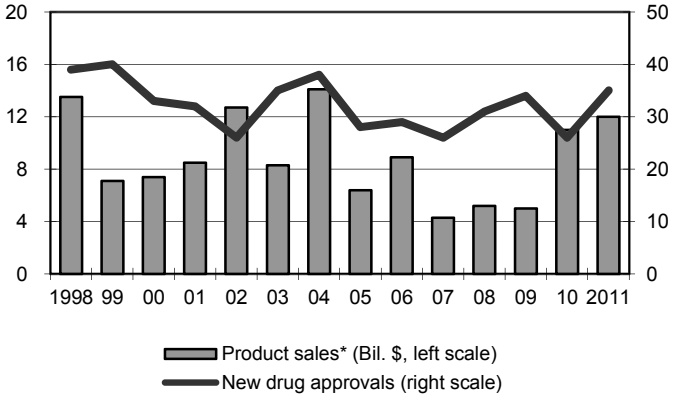
New high-profile compounds nearing market

◆ **Tecfidera (BG-12).** This oral treatment for multiple sclerosis (MS), developed by Biogen Idec, is currently under FDA review, with a review date scheduled for March 2013. The drug has also been filed in Europe. Tecfidera's approval would represent the second oral MS treatment to reach the market. However, its efficacy and safety profile appear to be superior to Gilenya, which is marketed by Novartis AG. Although we expect the multiple sclerosis market to remain fiercely competitive, we see potential for BG-12 to generate peak annual sales of over $3 billion.

◆ **Sofosbuvir (GS-7977).** This oral treatment, being developed by Gilead Sciences via its January 2012 acquisition of Pharmasset Inc., is in Phase III study for treatment of the Hepatitis C virus. The drug has emerged as a leading candidate to enable treatment of Hepatitis C in an all-oral regimen, without injected interferon. The drug began Phase III study during the first half of 2012, and we see potential for its approval as early as 2014.

However, we expect the competitive landscape for Hepatitis C to remain fierce over the long term, with AbbVie Inc. (which was spun off from Abbott Laboratories in January 2013) emerging as a formidable challenger with a combination therapy that has shown robust cure rates—albeit with a more cumbersome regimen, in our view. Other companies that we expect to maintain a presence in this attractive market include Roche Holding AG, Johnson & Johnson, and Vertex Pharmaceuticals. We expect the Hepatitis C market to increase significantly once these new treatments come to market, and we see potential for the US market for Hepatitis C drugs to expand from the current $2 billion (where sales have essentially plateaued while patients wait for improved regimens to come to market) to over $10 billion over the next decade. We think that next-generation treatments such as sofosbuvir could be approved for wide use as early as 2014.

FDA APPROVALS VS. US PRODUCT SALES*



*In fifth year after launch.
Source: EvaluatePharma.

Despite spotty commercial performance, outlook for newly approved drugs surpasses recent years

S&P is encouraged by the higher rate of approvals in the last two years, with 2012's output representing the greatest number of approvals since 1997, according to the FDA. We also think that drugs approved since

2010 show significant commercial promise and hold the potential to lead a recovery from declining R&D productivity trends across the industry in recent years (discussed later in this section). In contrast, few drugs approved between 2004 and 2009 represented novel treatments with the potential to change prevailing treatment paradigms.

According to healthcare market research firm EvaluatePharma, in its annual *World Preview 2018* report released in June 2012, fifth-year US sales of drugs approved in 2011 could reach $12.0 billion, an increase from its forecast of $11.0 billion fifth-year sales for drugs approved in 2010. Both of these figures would represent the best results since the actual sales of $14.1 billion recorded in 2004, when cancer drug Avastin was first approved. Average fifth-year US sales estimates for drugs approved in 2007–09 was $4.8 billion (lowered from $5.4 billion in its prior-year forecast), and well below the industry's longer-term 10-year average of $8.1 billion between 2000 and 2009. We note that the 2007, 2008, and 2009 periods comprise the lowest individual totals over the 10-year period. S&P believes that a continued flow of new drug approvals that represent major advances over existing treatments will be key to maintaining investor confidence in the biotechnology industry.

FDA OVERCOMES PERIOD OF LIMITED FUNDING AND FEWER APPROVALS

After the FDA approved 36 new drugs in 2004, it came under fire in 2005 for its failure to address the safety issues raised about Vioxx, Merck & Co.'s painkiller. S&P thinks that the backlash from this situation sparked a period of conservatism at the agency, which led to a slowing environment for new drug approvals. In subsequent years, the FDA struggled to fulfill its public mandate due to inadequate funding and staffing. A November 2007 study by a subcommittee of the Science Board, an independent advisory group, criticized the agency's scientific deficiencies, insufficient personnel resources and information technology infrastructure, as well as its reactive regulatory environment, among other concerns. The already overburdened agency was further stressed when, in September 2007, the Prescription Drug User Fee Act (PDUFA) was reauthorized, which expanded the FDA's powers to require drug companies to further study the safety of medicines and to mandate new label warnings when safety issues arise.

Despite these new responsibilities, the FDA's 2008 budget was $2.1 billion, just $105 million (5%) above 2007. The agency continued to miss target review deadlines, even though biopharmaceutical companies were paying into the system in exchange for timely reviews. However, in 2009, operations at the agency began to improve and the FDA was sufficiently funded to be able to aggressively expand its Center for Drug Evaluation and Research (CDER), which reviews and approves new medications and monitors the safety of drugs already on the market. By the end of that year, FDA officials stated that the agency was back on track in terms of meeting its goal of timely drug reviews in 90% of submissions.

Over the past few years, the funding environment for the FDA has been much more stable, and the performance of the agency has followed in step. However, S&P notes that the agency could be subject to mandatory spending cuts as part of a wider movement to curb government spending. A mandatory 2% cut in spending under sequestration, originally scheduled to begin on January 1, 2013, is set to take effect April 1.

Agency taking steps to keep momentum on new approvals

As mentioned earlier, S&P thinks that the trend of increasing new drug approvals is positive and will continue. In our view, the agency continues to evolve through innovative policies designed to foster improved communications with biopharma companies, as well as seeking new mechanisms to bring promising drugs to the market sooner than in the past.

Under the most recent reauthorized PDUFA (referred to as PDUFA V), which took effect on October 1, 2012, standard and priority reviews were extended by two months to 12 months and eight months, respectively. While these extensions could slow the rate of new drug approvals modestly, S&P believes that they will likely result in greater communication between the FDA and a submitting company during the review process, which we think should bolster the rate of first-cycle approvals. This improved interaction should also lead to fewer surprises at the decision stage of a drug approval review, as the agency will advise a company earlier about any problem it sees with an application.

Another promising innovation (introduced in the FDA Safety & Innovation Act of 2012) allows the FDA to designate a drug as a "breakthrough therapy," which permits faster approval of drugs that represent significant advances over existing treatments and in areas of particular need. In early 2013, the FDA granted its first two breakthrough drug designations to two drugs under development by Vertex Pharmaceuticals: its cystic fibrosis (CF) drug Kalydeco, and Kalydeco in combination with investigational agent VX-809. Kalydeco is currently approved for a small subset of CF patients, while the combined therapy began Phase III study in early 2013 for a larger patient subgroup. In February 2013, a third program, cancer drug ibrutinib, which is being co-developed by small biotech Pharmacyclics Inc. and large pharma Johnson & Johnson, was granted this designation. As of February 2013, the FDA cited 18 other drugs that had applied, many of them cancer treatments.

While details of the impact of such designations on the approval timeline have not yet been worked out, the FDA in February 2013 suggested that the designation could result in approvals for drugs that have completed only Phase I study, the earliest stage of clinical development. S&P assumes that such programs would need to be designed to establish their potential benefits over existing therapies earlier in clinical study than is typically seen, and would need to show longer-term benefits in order to maintain such an early approval.

MAJOR RECENT BIOTECH DRUG APPROVALS

COMPANY	TRADE NAME	GENERIC NAME	THERAPEUTIC INDICATION	APPROVAL DATE
Celgene	Pomalyst	pomalidomide	Multiple myeloma	Feb-13
NPS Phamaceuticals	Gattex	teduglutide	Short bow el syndrome	Dec-12
Astellas/Medivation	Xtandi	enzalutamide	Cancer	Sep-12
Gilead Sciences	Stribild	cobicistat; elvitegravir; emtricitabine; tenofovir disoproxil fumarate	HIV	Aug-12
Sanofi/Regeneron	Zaltrap	aflibercept	Cancer	Aug-12
Onyx Pharmaceuticals	Kyprolis	carfilzomib	Multiple myeloma	Jul-12
Vertex Pharma	Kalydeco	ivacaftor	Cystic fibrosis	Jan-12
Amylin/Alkermes	Bydureon	exenatide	Type II diabetes	Jan-12
Regeneron	Eylea	aflibercept	Wet adult macular degeneration	Nov-11
Gilead Sciences/ Johnson & Johnson	Complera	emtricitaine; tenofovir disoproxil fumarate; rilpivirine	HIV	Aug-11
Vertex	Incivek	telaprevir	Chronic hepatitis C	May-11
Merck	Victrelis	boceprevir	Chronic hepatitis C	May-11
GlaxoSmithKline	Benlysta†	belimumab	Lupus	Mar-11
Bristol Myers	Yervoy	ipilimumab	Metastatic melanoma	Feb-11

†Developed by Human Genome Sciences w hich w as acquired by GlaxoSmithKline in August 2012.
Sources: Company reports; US Food and Drug Administration.

Uptick seen in first-cycle approvals

Also encouraging is the FDA's progress in approving drugs on their first cycle. In late 2012, FDA officials pegged first-cycle approvals at approximately 77%, a 20-year high, which compares favorably to roughly 63% in 2011 and 50% in 2010. S&P Capital IQ believes that the FDA is benefitting from hiring initiatives made in 2009 and a more stable, though still challenging, funding environment, despite government spending pressures.

S&P also attributes this trend to improved and more thorough application submissions from pharmaceutical and biotechnology companies. Since 2007, companies have increasingly been asked to submit drug risk evaluation and mitigation strategy (REMS) programs as part of their initial applications. Requesting additional information pertaining to REMS was one of the most common reasons for delay in new drug applications. We believe that the FDA and the biopharma industry are likely getting more comfortable with the REMS process, spurring the uptick in first-cycle approvals

Statistics suggest favorable FDA approval trends over other regions

Despite the overhang of negative sentiment towards the FDA due to its approval practices in recent years, a study published in 2012 offered some evidence that the FDA has performed favorably compared with several peer regions. According to the study, which was conducted by researchers at Yale University and the Mayo Clinic, and published in the *New England Journal of Medicine* in May 2012, the FDA approved new drugs approximately 15% faster than its European and Canadian counterparts between 2001 and 2010. Further, the study found that more new drugs were approved in the US first, compared with the other regions, over the study period. Similarly, a Tufts Center for the Study of Drug Development (CSDD) study, issued in July 2012, noted that new oncology drug approvals in the US outpaced European approvals by 33% between 2000 and 2011 (40 to 33). However, the study noted that oncology drug prices averaged 9% lower in Europe than in the US.

BIOPHARMA INDUSTRY GRAPPLING WITH DECLINING R&D PRODUCTIVITY

As mentioned earlier, the biopharmaceutical industry (comprised of both pharma and biotech firms) has begun to show signs of emerging from a period of declining R&D productivity with its recently approved drugs. This poor performance has been magnified by the industry's consistently higher investment in research and development. Industry trade group Pharmaceutical Research and Manufacturers of America (PhRMA) pegged the 2011 (latest available) R&D spending by its members at $49.5 billion, slightly below the $50.7 billion spent in 2010. Due in part to significant R&D expense cuts announced since 2010 (as many leading pharma companies integrated previous acquisitions and reprioritized their pipelines), S&P expects modest future R&D growth, which would be in stark contrast to annual increases of nearly 10% during the prior decade.

UPCOMING BIOTECH PIPELINE CATALYSTS

COMPANY	TRADE NAME	GENERIC NAME	THERAPEUTIC INDICATION	CLINICAL STAGE	ACTION DATE
Biogen IDEC	BG-12	dimethyl fumarate	Multiple sclerosis	Filed	3/30/13
GlaxoSmithKline/ Theravance	Breo	fluticasone furoate/vilanterol trifenatate	Chronic obstructive pulmonary disease/asthma	Filed	5/7/2013
BioMarin	Vimizim	GALNS	MPS IV	To be filed	…
Celgene	CC-10004	Apremilast	Psoriasis, psoriatic arthritis	To be filed	…
Sanofi	Lemtrada	alemtuzumab	Multiple sclerosis	To be re-filed	…
Gilead Sciences	GS-7977	sofobuvir	Hepatitis C	Phase III	…
Vertex Pharma	Kalydeco/ VX-809	ivacaftor/CFTR corrector	Cystic fibrosis	Phase II/III	…
Abbvie/Neurocrine Biosciences	NBI-56418	Elagolix	Endometriosis	Phase III	…
Regeneron/Sanofi	REGN 727	PCSK9 Inhibitor	Hypercholesterolemia	Phase III	…
Amgen	AMG 145	PCSK9 Inhibitor	Hypercholesterolemia	Phase III	…
Alexion Pharma	ENB-040	asfotase alfa	Hypophasphatasia	Phase II/III	…

Sources: Company reports; US Food & Drug Administration.

Declining R&D productivity has moved to the forefront of industry concerns in recent years. According to a 2011 assessment done by Deloitte and Thomson Reuters, the internal rate of return for R&D expense of 12 top global pharmaceutical companies declined to 7.2% in 2012, from 7.7% in 2011 and 10.5% in 2010. Taking a longer-term view, the trend is clearly in decline as well. According to a report published by the Office of Health Economics (OHE), a UK think tank, the average cost of developing an approved drug has increased tenfold since the 1970s, jumping to $1.9 billion in December 2012, from $199 million. Over the same period, the success rate has declined from one in five to one in 10. Further, the average time to get the data needed for an approval has more than doubled, to 13.5 years from 6.0 years.

Also troubling are recent declines in clinical success rates and in the number of overall biopharmaceutical pipeline candidates. In a 2011 study conducted by the Biotechnology Industry Organization (BIO), an industry trade group, and BioMedTracker, which provides insight on the value of biotech and pharmaceutical

companies' drug pipelines, only 9% of drugs that entered Phase I study between 2004 and 2010 garnered regulatory approval—fewer than one in 10. Previous studies had shown an approval rate between one in five and one in six. However, the study noted that biotech drugs were twice as likely to be approved compared with traditional small molecule drugs (15% versus 7%). Cancer drugs had the lowest probability of success at 4.9%, while those treating infectious diseases (12%), endocrine disorders (10.4%), and autoimmune diseases (9.4%) fared better. S&P believes that increased molecule complexity following the approval of "lower hanging fruit" targets and increased clinical trial demands are partly responsible for the failure trend.

According to another study conducted by the KMR Group, a biopharmaceutical data analysis organization, the rate of success for clinical trials has deteriorated. For instance, the win rate in Phase II declined from 34% in 2003–07 to 25% in 2005–09 and to 22% in 2007–11. In Phase III, win rates fell from 70% in 2003–07 to 67% in 2005–09 and to 65% in 2007–11. The trend in Phase III is surprising and troubling, in our view, given the extensive study already undertaken in most cases to arrive at a decision to start Phase III study. KMR said that the number of preclinical trials needed to get a drug approved has increased from 12 in 2003–07 to 24 in 2005–09 and to 30 in 2007–11. It mentioned that the time span between preclinical development and regulatory approval has increased from 11.4 years in 1999–2001 to 13.7 years in 2009–11.

This lack of R&D productivity and the industry R&D pipeline consolation have resulted in an increase in the rate of termination of many programs previously partnered with smaller biotech companies, and their losses written off by the larger partner. In most cases, licensed rights were returned to the originating company, with the latter forgoing previously negotiated milestone and royalty rights. Most of these smaller companies will need to re-partner their respective programs in order to advance, given their limited operating resources and the burden of funding large late-stage studies. In our view, a smaller company's re-partnering prospects in the current biopharma environment are challenging.

Efforts on clinical trials

Companies are taking a number of measures to halt such productivity declines, according to the Tufts Center for the Study of Drug Development (CSDD), a nonprofit academic research group. Such measures include improving clinical trial designs, expanding the use of biomarkers, and adopting sophisticated statistical analyses. Despite these new measures, the CSDD estimates that as much as $6 billion continues to be wasted annually from unnecessary procedures during clinical trials. One example of the effort to eradicate this problem is shown by Amgen's acquisition in December 2012 of deCODE Genetics. In early 2013, Amgen stated that genetic information provided by deCODE had already influenced several "go or no-go" decisions across its pipeline. S&P thinks such technologies could inform a company's decision to advance one program, while "failing faster" on a less promising candidate, thus boosting overall productivity.

S&P also thinks that enhanced discussions between the agency and drug companies during the development period will be increasingly used as a vehicle to boost R&D productivity. According to the FDA, average clinical development times for drugs that developers discussed with the agency before submitting an Investigational New Drug (IND) application to start clinical study were more than three years shorter than drugs for which no meetings were held. For orphan drugs, the impact was more dramatic at six years shorter, on average. The agency claims that it has been working hard to reduce timelines and approve new drugs more efficiently.

New entities arise from pharma pipeline reviews

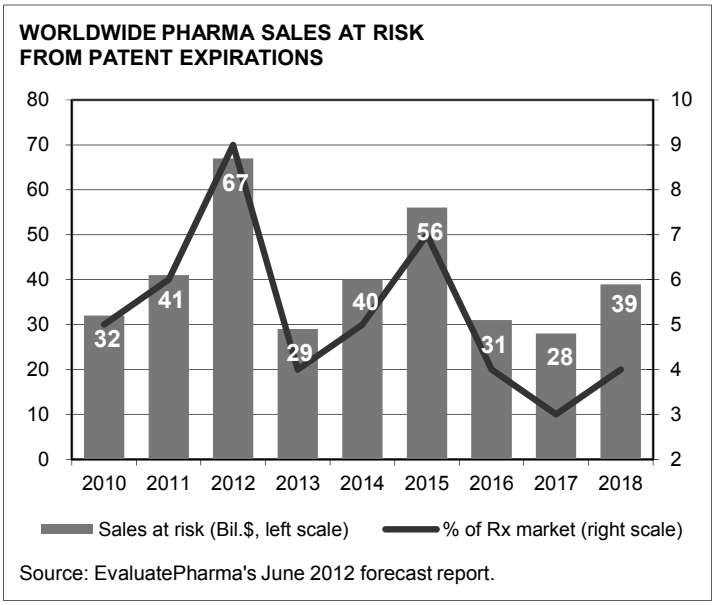
Amid such shrinking returns on investments, many companies have openly spoken of an affinity for "open innovation," which refers to collaborating with others both inside and outside a company to pursue innovation. Such initiatives carry the potential for science and knowledge sharing, which could improve the cost-efficiency of such programs.

One such shift in the biopharmaceutical landscape hastened by declining R&D productivity has been a renewed focus on partnering with academia. Big Pharma companies have recently expanded collaborative relationships with research centers such as universities and hospitals to focus on early-stage drug discovery and translational science, from drug licensing agreements earlier.

Another byproduct of this consolidation has been the formation of new entities to absorb abandoned programs and clinical assets. Such leading biotech figures as former ImClone Systems CEO Sam Waksal and biotech pioneer Sir Christopher Evans have launched new ventures aimed at acquiring discontinued and unwanted assets. Evans' NCPharma plans to develop these assets and then sell the products to pharma firms. In May 2012, Pfizer, AstraZeneca, and Eli Lilly & Co. entered a program with the National Institutes of Health (NIH), a division of the US Department of Health and Human Services (HHS), through which both groups hope to speed the development of new treatments by dusting off two dozen old drugs that failed to treat one disease but might treat another. In addition, the pharmaceutical industry has established the CSTA Pharmaceutical Assets Portal for academic researchers to develop drugs based on compounds previously shelved at the clinical stage. Lastly, the board of the NIH approved the creation of the National Center for Advancing Translational Sciences, which intends to work with drug companies to identify abandoned compounds that may work in other diseases.

M&A ENVIRONMENT REMAINS SOLID, BUT COMPOSITION IS CHANGING

In recent years, merger and acquisition (M&A) activities involving biotechnology companies have driven investor interest in the industry. However, the number and pace of these activities have been variable.



S&P sees a favorable long-term environment for mergers and acquisitions of biotechnology companies. In our view, the major driver of such deals is the "patent cliff" that Big Pharma has been navigating since 2011, which is expected to continue for the next several years. Market intelligence provider EvaluatePharma estimates that global pharmaceutical companies are at risk of losing more than $200 billion in revenues due to patent expirations between 2013 and 2018. Due to these projected losses, along with the challenging R&D productivity trends cited earlier, we expect to see large pharmaceutical companies concentrate on developing drugs for smaller, more targeted patient populations, thus making smaller companies with pipelines focused on rare diseases more attractive.

Fewer blockbuster acquisitions, as pharma's appetite for mega-mergers declines

Over the last few years, deep-pocketed Big Pharma firms have chosen to consolidate, as well as acquire smaller biotech companies. Acquisition deals have ranged from money-losing development companies to full-scale commercial companies valued in the multibillion-dollar range. However, according to a late 2012 report from Ernst & Young, the "patent cliff" crisis and several years of consolidation have resulted in many large pharma companies scaling back their pipeline investments and instead using their financial resources for share buybacks and dividends. In addition, the emerging markets have become more attractive for M&A deals, as pricing pressures have flattened revenues in many developed countries.

According to Ernst & Young, big pharmas accounted for 85% of the total deal-making firepower in 2006, but this figure fell to 75% in 2012, with big biotech, specialty pharmas, and generics companies moving in to fill the gap. Still, according to the Biotechnology Industry Organization (BIO), a trade group, the number of acquisitions of biotechs and specialty pharma companies declined to 39 in 2012, from 51 in 2011.

As a result, typical M&A deals have shifted to a smaller price range (between $5 billion and $20 billion), which can be more easily financed and integrated. In January 2012, Gilead Sciences acquired Pharmasset

Inc. for $11 billion to secure rights to the latter's sofosbuvir, a leading investigational Hepatitis C drug. In August 2012, Bristol-Myers Squibb acquired diabetes drugmaker Amylin Pharmaceuticals for $5.3 billion and the assumption of the latter's debt. Earlier in the year, Bristol-Myers had acquired Inhibitex Inc., a clinical-stage biopharmaceutical company involved in developing treatments for Hepatitis C virus (HCV), for $2.5 billion. However, Bristol-Myers chose to discontinue Inhibitex's Hepatitis C work just months later when safety issues emerged. Prominent acquisitions in 2011 included Sanofi's $20 billion purchase of Genzyme Corp. in April, and generic drugmaker Teva Pharmaceutical's $6.8 billion purchase of diversified specialty pharma/biotech drug company Cephalon Inc. in October.

M&A and licensing deals seek to share clinical risk

New deals are increasingly being structured to ensure that risk is shared among the parties. Typically, licensing pacts consist of upfront cash payments as well as milestones for future program advancement, and sales royalties. In recent years, deals had been shifting more toward clinical and commercial milestones, with lower upfront payments. S&P Capital IQ believes that this structure allowed an acquirer more flexibility to walk away from a transaction if its outlook changes. According to BIO, citing data from medical and scientific publisher Elsevier, 11 deals in 2012 had more than 50% of the total deal value backloaded through the promise of milestones or other mechanisms. This is in contrast to 2011, when the average upfront payment rose, according to Deloitte Recap LLC, a biopharma research firm.

Risk-mitigating measures are also being seen in company acquisitions. For example, Sanofi acquired Genzyme in early 2011 by including a contingent value right (CVR) that would entitle former Genzyme shareholders to cash payments in the future, based on Lemtrada (a multiple sclerosis drug) achieving ultimate regulatory approval and subsequent sales thresholds. The use of CVRs had been dormant for many years in the biopharma industry, as buyers were aggressive in paying for desired targets, despite the high risks. However, the market downturn and decline in R&D productivity have resulted in the increasing use of CVRs as a tool to share risk among the parties in acquisition talks. CVRs were also used in Celgene Corp.'s 2010 acquisition of Abraxis Biosciences. We expect such deal structures to fluctuate over time, depending on market conditions and the scarcity value of the acquired asset reflecting ongoing R&D productivity challenges.

S&P also expects M&A deal flow to vary in scale and structure based on the financial health of the pharmaceutical industry. In our view, Big Pharma made fewer deals in 2010 so that most participants could digest the mega-deals closed in 2009, and realign the size of their research organizations with a more focused number of therapeutic areas. Since 2010, we have seen pharma companies balancing acquisitions and licensing deals, as these firms maintain pipeline alignment and overall corporate headcount levels. According to consulting firm Challenger, Gray & Christmas, pharmaceutical companies laid off 14,150 employees in 2012, compared with more than 21,000 in 2011 and 53,636 in 2010. In our view, Big Pharma's more appropriate staffing levels should foster a more aggressive M&A environment. ■

INDUSTRY PROFILE

Biotech's presence grows, along with its ties to Big Pharma

The US biotechnology industry continues to undergo a major shift, as the number of independent profitable biotech companies has declined due to industry merger and acquisition (M&A) activity. In recent years, global pharmaceutical companies acquired two major biotech companies. In 2009, Roche Holding AG acquired Genentech Inc. (which generated $13.4 billion in 2008 revenues, accounting for roughly 20% of the industry's revenues). In April 2011, France's Sanofi SA acquired Genzyme Corp. (whose revenues peaked at $4.6 billion in 2008 before experiencing manufacturing issues in 2009). We believe that such deals continue to blur the line of distinction between the pharmaceutical and biotech industries.

CONSOLIDATION AT THE "DNA" OF THE INDUSTRY

Most of the industry's market capitalization, and a majority of its revenues and profits are concentrated in a small number of large-cap, independent drug developers. This group includes Amgen Inc., Gilead Sciences Inc., Celgene Corp., and Biogen Idec Inc. S&P Capital IQ expects several companies—including Alexion Pharmaceuticals Inc. and Regeneron Pharmaceuticals Inc.—to move into the industry's upper ranks in the coming years. However, these same companies are also mentioned as prime candidates for acquisition by larger firms.

US BIOTECHNOLOGY INDUSTRY AT A GLANCE*

	2010	2011	% CHG.
Revenues (bil. $)	61.1	58.8	(4)
R&D expenditures (bil. $)	17.2	17.2	0
Net gain (loss) (bil. $)	5.2	3.3	(36)
Market capitalization (bil. $)	292.1	278.0	(5)
Number of employees (thous.)	113.0	98.6	(13)
Capital raised (bil. $)	17.1	25.4	49
Number of IPOs	15	10	(33)

*Public companies. IPO-Initial public offering.
Source: Ernst & Young.

The list of the top revenue-generating US biotech companies has undergone significant change due to M&A activity. Besides the Genentech and Genzyme acquisitions mentioned above, other recent deals include the purchase of Amylin Pharmaceuticals by Bristol-Myers Squibb (August 2012), and the purchase of Cephalon Inc. by Teva Pharmaceutical (October 2011).

Large biotech companies have also played a role in sector consolidation, as evidenced by the merger between Biogen Inc. and Idec Pharmaceuticals, each on the top 10 list when they merged to become Biogen Idec Inc. in 2003. Amgen Inc. acquired Immunex Corp. in 2002.

INDUSTRY TRENDS

In addition to the developments discussed earlier in the "Current Environment" section of this *Survey*, we believe there are several other key trends facing the biotechnology industry. Among these are the convergence of the traditional pharmaceutical model with that of the biotechnological, a rapidly changing regulatory environment hastened by significantly higher drug prices as well as scientific advances, and a rapidly changing competitive landscape among key diseases and treatments. We discuss several of these issues in the following sections.

BIOTECH AND BIG PHARMA CONVERGING

In the 1980s and through much of the 1990s, big pharmaceutical companies (Big Pharma) shunned biotechnology because of its lack of a track record and predictability. However, Big Pharma is now embracing the technology, expecting that it will provide a wealth of new products to drive future growth.

At the same time the pharmaceutical industry is using M&A to gain a presence in developing and marketing biotechnology drugs, several leading biotech companies, led by Gilead Sciences Inc., Celgene Corp., and Vertex Pharmaceuticals Inc., are relying on "small molecule" technologies more traditionally associated with pharmaceutical companies for their marketed products and key pipeline candidates. These compounds

are subject to traditional patent expiration rules and exposure to generic drugs. In contrast, biotech companies such as Amgen, Biogen Idec Inc., and Alexion have built commercial operations and pipelines based on "large molecule" or "biologics," such as monoclonal antibodies and fusion proteins, which are based on living organisms rather than chemicals. However, the blurring lines of distinction are evident in Biogen Idec's planned launch in 2013 of Tecfidera (BG-12), a small molecule pill for the treatment of multiple sclerosis (MS), and Gilead's recent expansion of its pipeline to include its first biologic compound.

Historically, biotech companies have been known for their innovative research-driven activities, a more entrepreneurial focus, and a higher growth trajectory. Firms such as Genentech Inc. and Amgen Inc. pioneered the growth and development of the biotechnology sector, producing drugs based on DNA manipulation of living organisms, and, as a result, enjoyed high returns.

TOP 10 COMPANIES IN GLOBAL PRESCRIPTION DRUG SALES FROM BIOTECHNOLOGY
(Ranked by forecast 2018 global sales)

	SALES (BIL. $)		CAGR (%)
Company	2011	F2018	2011-F18
Roche	25.7	32.6	3
Novo Nordisk	11.4	19.6	8
Sanofi	11.5	17.8	6
Pfizer (Wyeth)	10.1	14.3	5
Amgen	14.4	13.6	(1)
GlaxoSmithKline	4.7	12.5	15
Johnson & Johnson	6.8	8.5	3
Merck	7.7	8.4	1
Eli Lilly	5.3	8.3	7
Abbvie	8.1	7.6	(1)

F-Forecast.
Source: EvaluatePharma.

Of note, in its *World Preview 2018* report, released in June 2012, healthcare intelligence provider EvaluatePharma forecast that nine of the top 10 companies in projected worldwide prescription drug sales from biotechnology in 2018 would be large pharmaceutical companies, with Amgen Inc. (ranked fifth) being the lone exception. Roche Holding AG and Sanofi SA ranked first and third, respectively, on the list, boosted by their respective acquisitions of Genentech and Genzyme.

Further highlighting the growth of biologics across the healthcare industry, EvaluatePharma forecasts that six of the top 10 drugs in 2018, both in the US and globally, would be biotech in origin. (We note, however, that this estimate is down from eight of the top 10 in its prior outlook through 2016.) EvaluatePharma projects that biotech drugs will account for 49% of the top 100 drugs in 2018, up from 17% in 2004 and 34% in 2011.

Big Pharma retools with biotech-like R&D platforms and pipelines

In recent years, many leading pharmaceuticals companies have bolstered their exposure to biologic drugs and technologies focusing on rare diseases, shifting from a prior focus on developing drugs designed to serve large patient groups. According to the Tufts Center for the Study of Drug Development, the share of orphan drugs (typically discovered by smaller biotechnology companies and licensed to larger pharma concerns) receiving priority review in the US was 56% in 2006–08, up from 35% during the comparable period last decade. Further, according to industry trade group Pharmaceutical Research and Manufacturers of America (PhRMA), pharmaceutical and biotech companies are running patient trials for more than 5,400 new medicines, including nearly 1,800 for rare diseases and several hundred for diseases with no available treatment. Many leading pharmaceutical companies, such as Pfizer, GlaxoSmithKline, and Merck & Co., have established new R&D platforms to better replicate the innovative and entrepreneurial structures more prevalent among biotech companies.

Arrival of dividends highlights maturing of biotech industry

In recent years, large-cap biotech companies have expanded their share repurchase programs as a means to boost earnings and deploy excess cash flows, which have grown significantly. The growth rate for the large-cap players in the space has come down significantly during this same period. Biotech firms are now employing such pharmaceutical-like tactics as managing drug lifecycles through enhancing dosing or drug delivery, as well as developing new drugs. As mentioned earlier, several big biotech firms have also entered the biosimilars fray, as they prepare for a market environment in which they will be subject to patent expiration akin to the issues facing pharmaceutical companies.

As growth slowed among large-cap biotech companies, and the impacts of new stock buyback announcements moderated, the issue of instituting a dividend to return excess cash to shareholders entered the biotech discussion. While the industry at large has resisted the notion to date, Amgen Inc. in April 2011

became the first biotech company to announce a regular dividend policy. S&P Capital IQ (S&P) believes that slowing long-term growth is likely to lead to similar announcements, but still expects these companies to reserve ample resources to deploy into research programs.

BIOSIMILARS NEARING MARKET, BUT STILL NEED CLARITY

The pharmaceutical industry has faced competition from generic drugs since the approval of the Hatch-Waxman Act in 1984. In contrast, the biotech industry has not had a formal regulatory pathway for the approval of biosimilar drugs (also referred to as follow-on biologics or biogenerics), which has enabled several first-generation biotech drugs to be sold without competition long after their patents have expired. The 2010 Patient Protection and Affordable Care Act (PPACA), also known as the healthcare reform act, included formal FDA authorization to establish a regulatory pathway for the approval and marketing of biosimilars.

NOTABLE BIOTECH DRUG US PATENT EXPIRATIONS

BRAND NAME	COMPANY	INDICATION	2011 GLOBAL SALES (BIL. $)
2013			
Epogen/Procrit	Amgen/Johnson & Johnson	Red blood cell enhancement	3.73
Humalog	Eli Lilly	Type 1 diabetes	2.37
Neupogen	Amgen	White blood cell enhancement	1.29
Rebif	Pfizer/Merck Serono	Multiple sclerosis	2.35
Remicade	Johnson & Johnson	Rheumatoid arthritis	7.19
2014			
Aranesp	Amgen	Red blood cell enhancement	3.02
Copaxone	Teva	Multiple sclerosis	3.58
2015			
Neulasta	Amgen	White blood cell enhancement	3.95
Rituxan	Roche/Biogen IDEC	Rheumatoid arthritis, blood cancer	6.79
2016			
Humira	Abbvie	Rheumatoid arthritis	8.24
2019			
Avastin	Roche	Oncology	5.98
Herceptin	Roche	Oncology	5.94
2020			
Lucentis	Roche/Novartis	Wet adult macular degeneration	3.77

Sources: EvaluatePharma; company reports.

The exclusivity period granted to originator drugs remains a contentious issue. Despite Congressional and White House leaders seeking a period of five to seven years, the PPACA granted a 12-year exclusivity period for branded companies, on the basis that a shorter period could stifle innovation by preventing drugmakers from recouping drug development costs. While debate over the issue has continued since the law's passage, the US Supreme Court's upholding of the law in June 2012 kept the 12-year exclusivity period intact, which we expect to be maintained.

Another key issue yet to be fully determined is the criteria required to prove similarity, as biologics are typically far more complex to produce than chemical-based small molecule drugs. Biotechnology industry executives are eager to ensure that biosimilar drugmakers be subject to clinical trials (which are not required for traditional pharmaceutical generics), given their view that copies of such complex molecules could never be identical to the originals. Those favoring generics say these trials would be burdensome, and would significantly raise development costs. S&P expects that biosimilar drugs are unlikely to be widely approved with labels indicating that they are "interchangeable" with their branded counterpart until head-to-head comparisons are performed, and we expect this to be reflected in more modest early adoption and market acceptance.

Regulatory framework for biosimilars continues to take shape

The FDA has issued draft guidance proposing that drug developers meet with the FDA to present product development plans and establish a schedule of milestones that would serve as landmarks for future discussions with the agency. From there, companies would use a step-wise approach to show biosimilarity to an FDA-approved biologic drug, including conducting clinical studies comparing the biosimilar drug with the original product, as well as performing safety studies. The FDA intends to use a totality-of-evidence approach to reviewing applications. While these guidelines are not yet finalized, several companies have initiated clinical testing of biosimilar drug candidates.

Initial estimates for the time and cost required to bring a biosimilar to market have ranged from five to eight years and $100 million–$150 million or more. Toward the end of 2011, biotech bellwethers Amgen Inc. and Biogen Idec Inc., entered into deals to develop and market biosimilars, while preparing to protect the sales of their own drugs that are set to face competition. In both cases, the companies stated that their goal was to leverage their manufacturing expertise, while their partners would provide marketing support.

In February 2013, Amgen stated that it expects to launch six biosimilar versions of leading currently marketed cancer and anti-inflammatory drugs in 2017, which is later than we had expected. We partly attribute this lengthening of the timeline to market on challenges in establishing a clear regulatory pathway. In October 2012, Teva suspended a Phase III clinical trial of its biosimilar version of Roche's Rituxan/MabThera in order to consider the best way to meet FDA and European regulatory requirements. In October 2012, Samsung halted clinical development of a similar compound, citing internal reasons. However, this sparked speculation that the halt was a result of changes in regulatory requirements in the US and Europe.

Branded drugmakers are expected to retain significant market share upon the introduction of alternatives, as sizable development and manufacturing costs are likely to deter entrants to many markets. According to a forecast by BioTrends Research Group, sales of biosimilar versions of monoclonal antibodies for cancer are likely to reach $4.9 billion by 2021 in the US, the top five European markets, and the Japanese market, while their branded-version sales are expected to total $6.7 billion. In our view, the need to recoup sizable development, manufacturing, and marketing costs are likely to limit the price discounts of the biosimilar version. However, as more pharma and biotech companies have stated their intentions to compete in the nascent industry, estimates for price discounts have risen from initial levels, but we do not expect any downward pricing pressure to push prices as low as the 80%–90% discount seen among generic versions of traditional chemical-based pharmaceuticals.

In Europe, a regulatory pathway has been in place since March 2006, when the European Medicines Agency issued the world's first guidelines for regulatory pathways for selected groups of biologics. Since then, Sandoz Ltd. (a subsidiary of Novartis AG) received European marketing authorization for Omnitrope, its copy of human growth hormone, and launched the product in Germany at a 20% discount to the branded drug. Omnitrope's sales have been modest to date, as have generic versions of Amgen's erythropoietin (EPO) drugs, which carry similar price concessions. In our view, the modest sales of these drugs have not been overly disruptive to the innovator's market share. With several other countries making progress on defining their biosimilar regulatory frameworks, calls for a consistent, global agreement have increased.

New patent issuances detract from cost savings

Despite the promise of biosimilars to replace older medicines with cheaper alternatives, in recent years, several legacy biologic drugs have been issued new patents that extend product lifecycles and are likely to keep biosimilar competition off the market indefinitely. In 2009, Avonex, a drug for the treatment of multiple sclerosis (2012 sales of more than $2.9 billion), was granted a new patent, taking the drug to 2026, when the drug had previously been facing expiration in the 2012–2013 timeframe. More recently, Enbrel, a leading treatment for rheumatoid arthritis and psoriasis (2012 sales of $4.2 billion), was issued a new patent in November 2011 that could extend the drug's protection to as late as 2028. Enbrel had been expected to be subject to biosimilar competition as early as 2013. Although both of these drugs have seen revenue growth slow amid greater competition in their respective markets, such occurrences threaten to undermine the intent of healthcare reform legislation, which was to introduce more biosimilar drugs and lower the costs to the healthcare system.

Although much money is at stake, opinions differ on biosimilars' likely impact. According to Medco Health Solutions in its *2011 Drug Trend Report*, some 32 biologics with sales of approximately $51 billion in 2009 could go off patent and face biosimilar competition by the end of 2015. The Congressional Budget Office (CBO) has stated that a viable market for biosimilar products may save consumers and health systems as much as $25 billion over 10 years, as newly approved biosimilars drive down the prices of biological drugs. S&P Capital IQ views this amount as very modest in the context of a $2.7 trillion healthcare system.

BIOTECH DRUG COSTS CONTINUE TO RISE DISPROPORTIONATELY TO OVERALL DRUG SPENDING

Concerns about rising health expenses are not new, even though prescription drug prices represent just 10% of healthcare expenditures, according to the Centers for Medicare & Medicaid Services (CMS), a division of the US Department of Health and Human Services. Until recently, payers have generally avoided restrictions on biologics, as the drugs tended to address seriously ill patients with few alternative treatment options and making any efforts to restrict access to them controversial.

According to IMS Institute for Healthcare Informatics, overall pharmaceutical prescription drug sales increased by 3.7% in 2011 (latest available), up from 2.3% in 2010. However, annual growth has been 5% or less since 2007, which we attribute to fewer doctor visits and fewer people starting new therapies, but also to widening use of unbranded generic drugs. According to IMS, US drug sales in 2011 were 80% generics, up from 78% in 2010. In contrast, in 2003, generics accounted for only 47% of such sales. With many leading drugs facing patent expiration in the coming years, we expect this shift to generics to continue. However, the price differential between branded and generics continues to widen. According to the Express Scripts Prescription Price Index, prices on a market basket of the most highly utilized brand-name medications increased 13.3% in the period from September 2011 to September 2012, outpacing the overall 2% rate of inflation over that same time. The prices of generic medications declined 21.9% in the same period.

Specialty drug costs, which include biologic drugs, are growing at a far higher clip. The *2011 Specialty Drug Trend Report* (latest available), published by Express Scripts Holding Co., a pharmacy benefits management (PBM) firm, estimated that specialty drugs accounted for 17.6% of plan costs in 2011, up from 16.3% in 2010 and 14.2% in 2009. However, the rate of specialty trend growth did ease slightly in 2011, to 17.1% compared with 19.6% in 2010. Of note, four specialty classes—inflammatory conditions, multiple sclerosis, cancer, and HIV—accounted for 70% of the specialty drugs covered by pharmacy benefits. Of particular concern was the rising cost of cancer treatments. According to Express Scripts, the cost of oncology drugs is projected to rise by as much as 20% annually through 2020, to $173 billion.

According to a March 2012 survey of US and European pharmaceutical executives conducted by Booz & Company and National Analysts Worldwide, the current biopharmaceutical business model was "broken," with growing healthcare system price/budget pressures, and an increasing need to demonstrate cost-effectiveness and outcomes as key concerns. S&P believes that new approaches to drug pricing will emerge in the coming years to ensure that the cost of drugs reflects the value they provide to patients, and we expect drugmakers and their treatments to face increasing scrutiny from payers in order to maintain coverage decisions. Examples of this may include flexible pricing models, where a drug's price could be raised or lowered after reaching the market should new evidence emerge or a new indication be developed. Such arrangements are becoming more common in countries outside the US, led by the UK.

IMPACT OF PERSONALIZED MEDICINE AND COMPARATIVE EFFECTIVENESS STUDIES

Recent healthcare trends have promoted a shift toward the expanded use of two treatment paradigms, with corollary concerns over whether they can coexist. The first paradigm is personalized medicine, which refers to the development and administration of treatments (based on the presence of genetic biomarkers or mutations) to patients who might best respond to an individually tailored treatment. The second—comparative effectiveness studies—seeks to compare outcomes, such as survival across various therapies, to determine the most efficacious and cost-effective therapies. S&P believes that in order to successfully advance both approaches, comparative effectiveness studies will need to adequately reflect outcomes from particular patient groups that might receive maximum benefit from certain treatments, rather than narrowly defining the criteria used to determine a treatment's effectiveness, and possibly restrict how drugs are prescribed or reimbursed.

Advancement of personalized medicine

The premise of personalized medicine is that developing medicines that are closely matched to a patient's genetic profile is likely to improve the benefits to the patient and minimize adverse reactions. Projects aimed at mapping the human genome have contributed to advances in the use of genetic biomarkers to determine patient response. So far, these scientific advances have not yet made much of a commercial impact, but the

premise is deeply rooted in current drug development, in our view. S&P Capital IQ expects the migration toward personalized medicine to take time as drugs developed using such information advance through the clinical process. Over time, expansion of personalized medicine should lower R&D costs by reducing the length of biotech development timelines and enabling identification of promising targets earlier in the process, while eliminating those less likely to benefit patients.

The pairing of new drugs and companion diagnostics has picked up steam. According to consulting firm PricewaterhouseCoopers, there were 25 in the first nine months of 2012, versus 25 in all of 2010. These figures compare favorably to eight such deals in 2008. In July 2011, the FDA proposed a rule that targeted drugs up for review would have to be reviewed simultaneously, in most cases, with the review of the companion diagnostic on which they rely.

Despite its widespread promise, the advancement of adoption of personalized medicine tools has been slower than anticipated. In its July/August 2011 *Impact Report,* the Tufts Center for the Study of Drug Development (CSDD) estimated that less than 1% of currently marketed drugs in the US have a companion diagnostic. While the rollout of personalized medicine into the drug landscape has been slow, investment in these technologies remains robust. According to estimates from Tufts CSDD, the investment in personalized medicine increased by 80% between 2006 and 2010, and is expected to grow by another 60% between 2011 and 2015.

Comparative effectiveness: how will findings be used?

Included in President Obama's $787 billion stimulus package passed in February 2009 was $1.1 billion for comparative effectiveness studies on currently marketed products, an endeavor that had received only modest funding in the past. According to Congressional Budget Office estimates, up to $2.5 billion could be spent on such studies through 2019. However, absent from this funding was a framework on how to apply the data generated by such studies. The research is expected to draw from sources such as electronic health records, registries, and healthcare claims to derive real-world outcome perspectives rather than relying solely on randomized clinical studies.

Critics have offered a wide range of complaints about comparative effectiveness studies. They suggest that such results may lead to unfavorable reimbursement decisions based on results that could be interpreted differently among physicians; that higher-priced drugs could face a loss of reimbursement at the hands of older drugs, based on price; and that requiring drugmakers to perform comparative studies in order to gain approval will slow an already lengthening industry pipeline. Congress has denied its intention to use comparative effectiveness studies to promote such outcomes, and has admitted that the initiative would be a work in progress and likely to face a "bumpy road." In our view, the Patient-Centered Outcomes Research Institute (PCORI), created as part of the healthcare reform law, has made little progress in finalizing a research agenda, including naming specific diseases or treatments to study.

S&P Capital IQ believes that comparative effectiveness studies are likely to have a profound impact on drug prices over the long term, particularly in cancer research, where progress has been incremental and benefits to survival have been modest, despite an explosion in pricing. We believe that many countries are likely to explore similar forms of health-technology assessments to curb the widespread use of high-priced medicines that offer only modest benefits. However, we expect such reviews to attempt to balance the fact that many drugs perform differently in patient sub-groups based on unique genetic criteria, and their effectiveness should be examined through a personalized medicine viewpoint.

DISEASE TRENDS

Biotechnology is driving innovation and growth in oncology, infectious diseases, autoimmune disorders, and diabetes. In the following section, we review biotech advances in these areas.

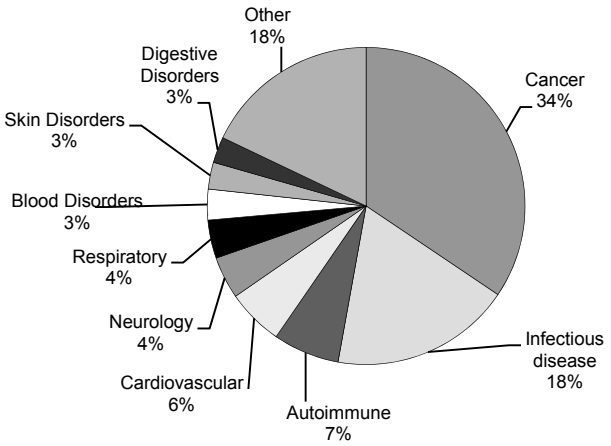
Cancer

Cancer occurs when cells continue to grow and divide, and do not die when they should. Cancer cells damage nearby tissue and can spread to different parts of the body. At the end of the last decade, the World Health Organization noted that cancer was closing in on heart disease as the world's leading killer. In most

leading cancers, progress has been incremental while drug and related medical costs have risen significantly. According to Express Scripts' *2011 Specialty Drug Trend Report*, expenditures for cancer treatments are projected to reach $173 billion in 2020, an increase of more than 20% annually; the NIH said these costs could reach $207 billion if current trends continue.

Cancer treatment is currently one of the most dynamic therapeutic categories in the pharmaceutical sector, and biotechnology companies are at the forefront of many of the ongoing changes. As of May 2012 (latest available), America's biopharmaceutical companies were testing nearly 1,000 medicines and vaccines to fight cancer, according to the Pharmaceutical Research and Manufacturers of America (PhRMA). In its annual *Beyond Borders: Global Biotechnology Report 2012*, Ernst & Young cited that cancer was by far the largest contributor to the overall biopharmaceutical industry pipeline at 44%. Despite the slow progress, cancer treatment has shown signs of improving patient outcomes. According to a combined report by the American Cancer Society, the CDC, the National Cancer Institute, and the North American Association of Central Cancer Registries, cancer mortality has fallen in the US. From 2000 to 2009, overall cancer mortality fell by 1.5% annually for both men and woman, and 1.8% per year among children under age 14. We describe key trends in cancer therapies below.

BIOTECHNOLOGY MEDICINES IN DEVELOPMENT, BY THERAPEUTIC CATEGORY



Source: Pharmaceutical Research and Manufacturers of America.

◆ **Biomarkers are personalizing cancer treatment.** As treatments are increasingly tailored to specific genetic subgroups, drugs will be prescribed for those for whom they are most likely to be effective, with the potential to result in smaller and accelerated clinical trials. Early examples of approved therapies targeted for specific genetic subtypes of cancer include Herceptin, Gleevec, Avastin, and Erbitux.

According to a 2012 analysis by researchers at The Institute of Cancer Research, London, and The Royal Marsden NHS Foundation Trust, treating cancer with targeted therapies appeared to be less toxic than chemotherapy, finding that the overall risk to patients suffering a life-threatening side effect was seven times less than for traditional cytotoxic agents, and response rates of newer-generation, targeted drugs in early human trials were twice that of non-targeted therapies.

◆ **More oncology drugs are being administered orally.** Traditional cancer medications were given intravenously, in doctors' offices, clinics, or hospitals. However, Express Scripts estimates that one-fourth of investigational cancer drugs are taken orally. They consist of small molecules, which can be more easily absorbed into the body than older oncology drugs made up of large proteins that are not easily absorbed.

◆ **Combination therapies are standard.** Most of the oncology drugs in development are likely to be used in combination with other approved oncology drugs, as scientists realize the importance of a multifaceted approach in treating cancer. As a result, nearly all new oncology drugs are being tested in a variety of settings, for multiple indications, including for use with other biologics and/or chemotherapies. New oncology drugs, therefore, have to be judged not only on the initial indication for which they are approved, but also on their potential for use in other areas and with other drugs. The FDA has also encouraged companies to develop combinations in order to boost effectiveness and drive major advances in treatment paradigms, promising consideration for such combinations before each medicine is evaluated on its own.

Infectious diseases

Infectious disease is an area of recent interest, fueled by global concerns about potential epidemics and the rising number of hard-to-treat hospital infections. This field covers a broad range of research on disease-preventing vaccines, new antibiotics to treat drug-resistant infections (a growing problem), and better, cheaper chronic treatments for HIV and AIDS patients. After years without a new alternative for chronic Hepatitis C, several promising treatments are nearing commercialization.

◆ **HIV/AIDS.** According to the United Nations, the number of people infected with HIV worldwide at the end of 2011 was 34 million, about the same number as in the prior year, with the increase attributable to longer survival as a result of anti-retroviral therapy. According to figures released in late 2012, new HIV infections and AIDS-related deaths may have stabilized and started to decline in many regions. Still, while UN-backed programs are helping to get new patients on therapy, slightly more than two-thirds of people with HIV globally are not receiving treatment. In late 2009, the World Health Organization updated treatment guidelines, calling for earlier treatment of HIV, which it estimated could add three million to five million patients to the estimated 9.5 million patients who require HIV therapy. The US represents a fraction of the global HIV epidemic, with more than 1.2 million people infected (of which 20% are unaware that they are infected).

◆ **Hepatitis C.** After years with no new therapies, two new drugs were approved in 2011 for the treatment of Hepatitis C, which has infected an estimated 5.3 million people in the US, according to the CDC, and 170 million worldwide, according to the Hepatitis Foundation International, although the disease remains widely under-diagnosed. In May 2012, the CDC issued draft guidelines proposing that all baby boomers (the generation of Americans born between 1946 and 1964) be tested for Hepatitis C. The competitive landscape for Hepatitis C drugs is intense, with new candidates that seek to reduce or eliminate the use of interferon or ribavirin as components of standard treatment regimens moving toward late-stage study.

The promise of such regimens has driven robust M&A deal flow. In January 2012, Gilead Sciences Inc. acquired Pharmasset Inc. in an $11.2 billion deal to secure rights to sofosbuvir, which is among the most advanced compounds among new candidates. Other companies advancing similarly targeted candidates include AbbVie Inc. (which was spun off from Abbott Laboratories in January 2013) Johnson & Johnson, and Vertex Pharmaceuticals. Currently approved standard of care treatments approved just two years ago have already seen their sales start to wane, as patients await these newer treatment options.

◆ **Drug-resistant infections.** According to the Infectious Diseases Society of America (IDSA), "superbugs" (like methicillin-resistant staphylococcus aureus, or MRSA, one of the most common hospital-acquired antibiotic-resistant bacteria) cost the US healthcare system up to $34 billion per year. MRSA accounts for some 18,000 deaths each year in the US.

According to the IDSA, not enough drugs are being developed to combat agents that are becoming more resistant to current treatments. Due to poor investment returns, only two major drug companies as of 2011 had ongoing antibacterial discovery programs, according to an article published by Reuters. According to the IDSA, there were nearly 20 companies in the field in 1990. Despite this need for novel therapies, we note that the FDA has challenged many recent new applications for drugs aiming to combat infections, and criticisms have been levied towards the FDA due to clinical requirements that the drug industry has called "unrealistic." In March 2012, the Infectious Diseases Society of America (IDSA) offered a plan that would allow the FDA to review certain kinds of antibiotics the way it reviews "orphan" drugs for rare diseases, making it easier for companies to gain approval, which the organization believed could entice drugmakers back to antibiotic research. In September 2012, the FDA formed a task force to try to determine why antibiotic research has waned, and what regulations could change the situation.

Autoimmune diseases

◆ **Rheumatoid arthritis.** Rheumatoid arthritis (RA) is one of the most common and serious forms of arthritis, affecting 1.3 million Americans according to the Arthritis Foundation. RA is mainly characterized by inflammation of the lining (synovium) of the joints, which causes swelling that can result in pain, throbbing, and, ultimately, deformity. Rheumatoid arthritis is most common in women and onset typically

occurs between the ages of 40 and 60. Primary treatments include nonsteroidal anti-inflammatory drugs (NSAIDs) and disease-modifying drugs called DMARDs, particularly methotrexate. Biologics are typically used in combination with DMARDs to modify the immune system by inhibiting proteins called cytokines, which contribute to inflammation. Drugs approved for treating RA are also used for other inflammatory conditions, such as psoriatic arthritis, Crohn's disease, and psoriasis.

According to a January 2013 report by GBI Research, the market for rheumatology therapeutics is expected to climb to $23.8 billion by 2018 from $17.1 billion in 2011, representing a compound annual growth rate (CAGR) of 4.8% (compared with a 9.4% CAGR in 2005–11). We expect new competition over the coming years—ranging from less costly, orally dosed candidates to the introduction of biosimilars over the longer term—to significantly alter the competitive landscape and slow the industry's revenue growth trajectory.

◆ **Multiple sclerosis.** Multiple sclerosis (MS) is a chronic, often disabling disease that attacks the central nervous system (CNS)—the brain, spinal cord, and optic nerves. According to the National Multiple Sclerosis Society, there are approximately 400,000 people with multiple sclerosis in the US and more than 2.5 million people worldwide. There are currently seven approved disease-modifying treatments, six of which require either injection or IV infusion. The first orally dosed drug, Gilenya (fingolimod), marketed by Novartis AG, was approved in September 2010 and launched later that year. In April 2012, the Committee for Medicinal Products for Human Use (CHMP), part of the European Medicines Agency (EMA), the European regulator, allowed Gilenya to remain on the EU market with some additional warnings on cardiovascular effects, after a review following several patient deaths. A second agent, Biogen Idec Inc.'s Tecfidera (BG-12), is under FDA and European review, and we see the possibility of that drug being launched in 2013. However, we expect these drugs' safety to be watched closely.

MS therapies have expanded significantly in both price and use in recent years. With new drugs coming to the market and several more expected in the next few years, S&P sees the potential for the MS market to rise significantly from our recent estimate of nearly $15 billion annually over the next decade, due to new drugs with enhanced efficacy reaching the market and treatment earlier in the course of the disease. However, we note that the category has faced some scrutiny over its cost effectiveness, which we think is likely to increase as many global markets face financial challenges and seek to control spending.

Diabetes

Diabetes is becoming more prevalent, largely as a result of poor nutrition and a lack of physical activity. The American Diabetes Association (ADA) estimated in January 2011 (latest available) the number of people in the US with diabetes as near 26 million, but more than one quarter have not been diagnosed. According to the Centers for Disease Control and Prevention, the number of people in the US with diabetes has grown at an alarming rate. In 42 states, the rates increased by 50% or more between 1995 and 2010, doubling in more than 18 states. Further, another 35% of adults fall into the pre-diabetic category, characterized by rising blood glucose levels, raising one's risk of developing diabetes. Globally, the ADA estimates the number of adults with diabetes at 347 million, more than double the 153 million pegged in 1980. Several studies in recent years have pegged the economic impact of treating diabetes in medical expenditures and lost productivity as high as $200 billion–$300 billion annually.

S&P Capital IQ believes there is ample room for growth in the diabetes treatment area, given the size of the market, and safety concerns over some current treatments. Pharmaceutical trade group PhRMA cited 221 new medicines in development to treat diabetes in a November 2012 report. However, we view the competitive landscape to commercialize next-generation diabetes projects as intense and subject to regulatory scrutiny and delays, given the new guidelines requiring manufacturers to evaluate cardiovascular risks before approval is granted. We expect this trend to increase clinical trial patient sizes and further slow the drug pipeline.

Neurodegenerative diseases

◆ **Alzheimer's disease.** Alzheimer's is a type of dementia that causes problems with memory, thinking, and behavior that worsen over time. According to the Alzheimer's Disease Association, 5.4 million Americans are living with Alzheimer's disease, mostly aged 65 and over, and by 2050, as many as 16 million Americans will have the disease. According to a study conducted by a subsidiary of insurer United HealthCare Group for the

Alzheimer's Disease Association, the total cost to the US economy is projected to be $20 trillion through 2050. Current spending is $130 billion annually.

Alzheimer's has no cure, and several drugmakers in recent years have failed in late-stage studies that could have supported marketing approval for new treatment options. Clearing the brain of beta amyloid plaques has been the primary goal of recent late-stage drugs. However, bapineuzumab, by Johnson & Johnson (via its acquisition of assets from Elan plc) and Pfizer (via its acquisition of Wyeth) failed in Phase III study and was discontinued in August 2012. In May 2012, the National Institutes of Health (NIH) announced plans for a clinical study using a drug developed by Roche's Genentech unit to help prevent Alzheimer's among people who are genetically predisposed to develop the disease, but are not yet showing symptoms. The study is expected to last five years, but some informative data could be available in as little as two years.

◆ **Amyotrophic lateral sclerosis (ALS).** This progressive neurodegenerative disease affects nerve cells in the brain and the spinal cord, and carries an average lifespan of two to five years from diagnosis. It is much rarer than Alzheimer's disease, as only 5,600 in the US are diagnosed each year. ALS has no cure, and success in developing effective treatments in recent studies has been limited. Biogen Idec's dexpramipexole failed in a Phase III study in January 2013 and was discontinued; in October 2012, Neuraltus Pharmaceuticals proceeded with plans for a late-stage study, even though it fell short of Phase II trial goals. Stem cell transplants in mice have shown signs of progress. In a recent study, stem cell transplantation extended the lifespan and improved neuromuscular function in mice, providing hope for improvement in future studies in humans.

Promising technologies

As mentioned earlier in this section, the acceptance of biologic drugs among the pharmaceutical industry has increased dramatically in recent decades. Drug classes that were once shunned, like monoclonal antibodies, now comprise some of the fastest growing segments in the biopharma industry. However, such advancements are rarely achieved without setbacks, both in industry R&D support, as well as market acceptance. Below, we briefly highlight several areas of potential industry growth and recent setbacks they have faced.

◆ **Stem cells**. These cells can be used to repair tissues and grow organs. Although embryonic stem cells are particularly useful because they can transform into any kind of cell in the body, they are also highly controversial because to date, starting a stem cell line has required the destruction of a human embryo and/or therapeutic cloning. In 2001, then-President Bush limited use of embryonic stem cells in scientific research. In 2009, President Obama lifted the ban on their use as one of his first official actions upon taking office. In September 2010, a federal judge issued a temporary injunction barring the federal government from funding research involving the destruction of human embryos. In April 2011, a US appeals court ruled that government funding of embryonic stem cell research could continue, and that ongoing challenges should be dropped. However, in October 2011, the European Union (EU) Court of Justice banned the patents of stem cells when their extraction caused the destruction of a human embryo. The decision could threaten the future of stem cell research in Europe, and hinder the EU's goal of speeding the development of regenerative treatments.

Despite the controversy, the use of stem cells in developing treatments for serious diseases had the support of the general public by a 5-to-1 margin, according to a 2011 study conducted by the University of Nevada, Reno, and published in *Nature Biotechnology* magazine. Stem cells research has also been challenging to drug developers, as a wave of patent applications has slowed industry progress. Universities and private companies have been granted exclusive rights to study certain diseases, blocking advancement of the science. In addition to ethical considerations, the FDA has expressed concern about the potential for health-related issues emerging from stem cell–based treatments, including new cancers or harmful immune system responses, according to *Nature Biotechnology* magazine. We view a commercialized therapy based on stem cell research as remaining years away, but expect the issue to remain controversial.

Uncertainty at the regulatory level has affected progress on the clinical front as well. In late 2011, Geron Corp., a leader in developing stem cell therapies, announced its intention to abandon its stem cell programs, citing that stem cell research still has a long way to go before developing real-world products, and the small company faced considerable cash burn should its research continue. A much larger and well financed company, Roche Holding AG, has taken a lead role in rallying nine other large drugmakers and additional

stakeholders to build a collection of 1,500 induced pluripotent stem (iPS) cell lines for use in early testing of drugs against a range of neurological ailments, as well as diabetes.

◆ **RNA interference (RNAi).** This important new technology involves switching particular genes on or off, and is a natural pathway to control gene expression. Unlike traditional small molecule medicines that target only certain classes of protein, RNAi seeks to design siRNAs (small interfering, or silencing RNA) for every gene/mRNA, to block the production of disease-causing proteins before they are made. This would afford the opportunity to improve disease control and intervention, and focus on disease prevention rather than a standard symptom treatment model.

RNAi was the subject of research by the winners of the 2006 Nobel Prize for Medicine and seems to have tremendous potential for the treatment of cancer and infectious diseases. However, despite significant initial investment from leading pharmaceutical companies, interest has waned in recent years. Most notably, Roche shuttered RNAi research as part of a corporate-wide restructuring, despite initial investments of more than $300 million following a licensing pact with small biotech company Alnylam Pharmaceuticals. Alnylam has made progress advancing its internal pipeline, achieving major drug delivery advances, improving the ability of RNAi therapeutics to enter the cell. Since late 2011, Alnylam has reported positive clinical results for two programs, and we note a revival in partnering interest across 2012 and into 2013 for the technology.

HOW THE INDUSTRY OPERATES

Biotechnology refers to the application of biological and biochemical science to large-scale production of products to modify human health, food supplies, or the environment. Many of biotechnology's basic principles are thousands of years old. Bacteria, fungi, and other living organisms have long been used to stimulate chemical reactions needed to process certain foods and beverages. Decades before the advent of genetic engineering, scientists produced medicines made from living organisms on a large scale—such as penicillin in the 1940s. Since the 1970s, however, scientists have learned how to manipulate organisms at the genetic level and reproduce those changes in massive quantities, facilitating the creation of new medical products.

Current advances in biotechnology are indebted to groundbreaking research in genetics and molecular biology conducted since the mid-twentieth century. In 1953, James D. Watson and Francis Crick first described the structure of deoxyribonucleic acid (DNA)—the molecule that carries the genetic code for virtually all forms of life. Then, in 1967, a team of US researchers, led by Arthur Kornberg, synthesized biologically active DNA in a test tube.

COMMERCIAL MILESTONES

In the early 1980s, the US Supreme Court recognized patent rights on genetically altered life forms. This important ruling enabled US biotech firms to invest in costly research projects, knowing that patents would protect their discoveries and ultimately sustain financial incentives.

In April 2003, the International Human Genome Sequencing Consortium, an international group of scientific centers, completed the sequencing of the human genome. This base of knowledge is enabling medical researchers to run extensive screens of human proteins, giving them the potential to identify thousands of biological targets against which new drugs can be developed.

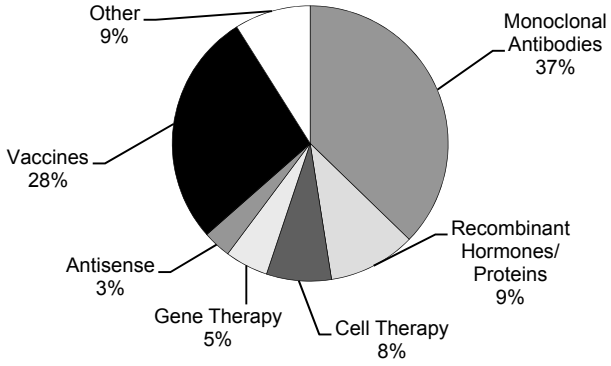
S&P estimates that over 100 recombinant protein-based drugs have been approved to date. According to PhRMA's *2013 Report: Biotechnology Medicines in Development*, more than 900 are currently in development. We estimate that annual global sales of such drugs exceed $100 billion.

Key classes of biotech drugs

In 1986, the US FDA approved the first monoclonal antibody (mAb), Johnson & Johnson's Orthoclone, for the treatment of transplant rejections. Today, mAbs are the key growth driver for the industry, with leading

drugs for the treatment of cancer and inflammatory disease. According to PhRMA's *2013 Report: Biotechnology Medicines in Development*, 338 monoclonal antibodies were in development, accounting for more than one-third of all biotech drugs being developed. Leading mAbs for inflammatory diseases include Johnson & Johnson's Remicade and Abbott Laboratories Humira, with Roche's Avastin a market leader for cancer. Despite these commercial successes, study on the drug class remains at an early stage. The CSDD estimates that most monoclonal antibodies in clinical trials are only in Phase I or Phase II study.

BIOTECHNOLOGY MEDICINES IN DEVELOPMENT, BY PRODUCT CATEGORY



Source: Pharmaceutical Research and Manufacturers of America.

Other leading groups of biologic drugs are vaccines, growth factors, hormones, fusion proteins, cytokines, and therapeutic enzymes. Growth factor stimulants are proteins that can induce tissue development by affecting genetic switches in cells. Notable examples include Amgen's Epogen/Aranesp, which stimulate red blood cell production, and Neulasta/Neupogen, which stimulate white blood cell production. Hormones are chemical messengers that travel through the blood stream to other parts of the body to maintain chemical balance. Key drugs in this group are insulin, human growth hormones, and thyroid stimulating hormones. Fusion proteins are proteins created through the joining of two or more genes originally coded for separate proteins. The leading biologic is this class is Amgen's Enbrel, which treats inflammatory conditions such as rheumatoid arthritis and psoriasis.

Cytokines are small proteins released by cells that have a specific effect on cell interactions. Key cytokine classes include interleukins, lymphokines, and cell signal molecules, such as tumor necrosis factor (TNF), often used for treatment of inflammatory disorders such as rheumatoid arthritis and psoriasis; and interferons, which trigger inflammation and respond to infections, and are prevalent in treating Hepatitis C and multiple sclerosis. Lastly, therapeutic enzymes seek to replace naturally occurring enzymes that are catalysts for complex biological processes. Genzyme Corp. has been a leader in this class, where formulations are used in treating rare disorders with few affected patients and usually sell at premium prices.

TOP 10 BIOTECHNOLOGY DRUGS
(Ranked by 2011 global sales)

				SALES (MIL. $)	
PRODUCT	COMPANY	INDICATED USE	2010	2011	% CHG.
1. Humira	Abbvie	Rheumatoid and other forms of arthritis	6,742	8,236	22.2
2. Enbrel	Amgen/Pfizer/Takeda	Rheumatoid arthritis/psoriatic arthritis	7,257	7,892	8.8
3. Remicade	J&J/Merck	Rheumatoid arthritis/Crohn's disease	6,520	7,187	10.2
4. Rituxan	Roche/Biogen IDEC	B-cell non-Hodgkin's lymphoma/rheumatoid arthritis	6,113	6,790	11.1
5. Avastin	Roche	Oncology	6,214	5,984	(3.7)
6. Herceptin	Roche	Oncology	5,221	5,940	13.8
7. Lantus	Sanofi	Diabetes	4,658	5,451	17.0
8. Neulasta	Amgen	Restoration of white blood cells	3,558	3,952	11.1
9. Lucentis	Novartis/Roche	Wet age-related macular degeneration	2,935	3,772	28.5
10. Epogen/Procrit	Amgen/J&J	Red blood cell enhancement	4,584	3,730	(18.6)
Total, top 10			53,802	58,934	9.5

Source: EvaluatePharma.

SPENDING ON R&D

Companies in the biotech industry range in size from small start-ups to multibillion-dollar firms. Investment in research and development (R&D) is crucial to building a long-term sustainable organization. After years of growth, however, R&D spending growth moderated near the end of the last decade. Industry trade group Pharmaceutical Research and Manufacturers of America (PhRMA) pegged the 2011 (latest available) R&D spending by its members at $49.5 billion, slightly below the $50.7 billion spent in 2010.

LEADING US BIOTECH COMPANIES RESEARCH & DEVELOPMENT EXPENDITURES
(In millions of dollars, ranked by 2011 R&D expenditures)

	R&D EXPENDITURES			REVENUES			R&D AS % OF REVENUES	
COMPANY	2010	2011	% CHG.	2010	2011	% CHG.	2010	2011
Amgen	2,894	3,167	9.4	15,053	15,582	3.5	19.2	20.3
Celgene	1,128	1,600	41.8	3,626	4,842	33.5	31.1	33.0
Gilead Sciences	1,073	1,229	14.6	7,949	8,385	5.5	13.5	14.7
Biogen-Idec	1,494	1,220	(18.3)	4,716	5,049	7.0	31.7	24.2
Vertex Pharmaceuticals	481	562	16.7	143	1,411*	884.2	335.8	39.8
Regeneron Pharmaceuticals	489	530	8.2	459	446	(2.9)	106.6	118.8
Onyx Pharmaceuticals	186	268	44.3	325	447	37.8	57.2	59.9
Biomarin Pharmaceuticals	147	214	45.5	376	441	17.3	39.2	48.6
Human Genome Sciences†	196	196	(0.1)	157	131	(16.8)	124.8	149.8
Cubist Pharmaceuticals	158	185	16.9	636	754	18.5	24.8	24.5

*Vertex launched Incivek for Hepatitis C in May 2011. †Acquired by GlaxoSmithKline in August 2012.
Source: Capital IQ Compustat.

Biotech R&D as a percentage of product sales has traditionally been very high, but has shown signs of decline as industry revenues have grown. Among the profitable, independent companies in the industry, S&P Capital IQ (S&P) estimates this figure at about 15%–25% of sales and expects this trend to shift toward to lower end of the range as more biotech drugs reach the market. We note the potential for negative investor sentiment if levels of research investment drop sharply: innovation is a key differentiator for biotechs and a factor in their valuations.

Access to capital crucial

Given the need to fund R&D, one of the most important issues facing young biotechnology companies is access to capital. New biotech entities are usually funded through seed money from private wealthy investors or small groups of investors, called "angels," and by venture capitalists.

Venture capitalists raise money from wealthy private individuals or institutional investors and create funds that invest in emerging high technology companies (including biotech start-ups), usually with an exit strategy, such as an initial public offering, in mind. Most biotech companies lose money and do not become sustained profitable companies. Until recently, companies rarely faced difficulty in raising capital. As financial markets continue to recover from the significant disruption caused by the global recession, the financing environment has been largely stable. According to *The Burrill Report*, venture investment in US life sciences companies, which include biotechnology therapeutics developers, totaled $9.5 billion in 2012, up 22% from 2011.

Still, macroeconomic challenges have led to a more conservative outlook across the financing industry. According to a December 2012 venture view predictions survey conducted by the National Venture Capital Association (NVCA) and Dow Jones VentureSource, 49% and 53% of respondents, respectively, felt that investment in biopharmaceutical and medical device sectors would decrease in 2013. S&P Capital IQ believes that biotechnology should continue to attract venture interest, albeit more selectively.

The uneven economic recovery has continued to dampen demand for initial public offerings in the life sciences. According to *The Burrill Report*, a total of 16 life sciences companies completed initial public offerings (IPOs) in the US in 2012, the same number as in 2011. We estimate that 11 of these were drug developers. However the total amount raised through the IPOs fell by 21.6% in 2012, compared with 2011. Companies that are already public fared better, as capital raised through follow-on public offerings was 24.5% higher in 2012 compared with 2011.

The recession significantly hurt smaller companies, as many faced limited financing options and were forced to scale back R&D projects and to shelve potentially promising programs due to a lack of resources. However, as the markets stabilized from their March 2009 lows, the pace of announced restructurings slowed and more companies were able to secure financing to extend their cash runway. Typically, S&P looks for a cash balance that could see a biotech firm through at least two years of operations as a benchmark of staying power.

The importance of partnerships

Once a small firm has a promising investigational candidate, it often chooses to team up with a major pharmaceutical or biotech company. The larger company may provide up-front fees, R&D funding, milestone payments, royalties, and possibly co-promotion rights. In addition, the partner often provides needed production facilities and sales organizations for new products.

Many approved biotech products were developed with a collaborative partner, usually a leading pharmaceutical company. Such agreements have become a hallmark of the biopharma industry, and have often led to acquisitions between partnering firms after larger firms gain first-hand insights into a smaller company's management, breadth of research capabilities, and prospects for pipeline advancement. However, as noted earlier in this *Survey*, significant restructuring within the pharmaceutical industry has led to the dissolution of many pharma/small biotech partner deals and the need among biotech companies to seek new transactions in order to advance their clinical assets.

Patents make it happen

Patents are among the most important benchmarks of progress in developing new biotechnology products. When a company obtains a patent for a new process or product, competitors are prohibited from commercial use of that discovery. In the biotech industry, patents are critical to raising the capital for R&D.

Among the different types of patents, a "composition of matter" patent, which describes the product's chemical or biological nature, generally provides the company with the best protection. A "use" patent lets the holder manufacture and market the compound for a specific therapeutic purpose, preventing competitors from using the drug in the same way. A "process" patent describes the manufacturing process of a product.

Since the World Trade Organization (WTO)—the international body that focuses on the rules of trade between nations—established a multilateral trading system on January 1, 1995, many nations that had been lax about protecting patents are changing their laissez-faire approach. WTO regulations include the recognition of pharmaceutical patents, which extend for 20 years from the application date. Still, the ability to obtain and enforce patent protection varies by country, and US pharmaceutical companies have been leery of doing business in countries that fail to recognize international patents. WTO regulations contain an exception known as compulsory licensing, which allows a country to break patents in a national emergency and make copies of an important drug, typically over concerns that their huge, poor populations do not have the money to pay for life-saving, brand-name medications.

Developing nations have become increasingly aggressive in fighting Western brand-name drug patents due to high prices. Recently, the Brazilian government declared Gilead Science Inc.'s core HIV compound Tenofovir to be of public interest, signaling the country's interest in avoiding the drug's patent and planned to issue a compulsory license. In March 2012, India issued a compulsory license for local generics company Natco Pharmaceuticals to sell cancer drug Nexavar, claiming that Bayer had made no effort to make the drug available, accessible, or affordable to the Indian public.

The issue of patents has become increasingly complex as advances in understanding the human genome have been made. Although US patent law states that what occurs in nature cannot be patented, the US Patent and Trademark Office has granted exclusive patent rights for gene sequences isolated from human chromosomes. According to the American Civil Liberties Union (ACLU), up to 20% of human genes have been granted patents. This practice has drawn criticism from multiple groups on the basis of impeding scientific progress. These groups have argued that companies should be able to patent proprietary drugs and tests derived from knowledge gained from gene sequencing, rather than patenting the natural discovery itself. In October 2010, the US Department of Justice opined that unmodified human DNA should not be

eligible for patent. However, in August 2012, a US federal appeals court upheld Myriad Genetics Inc.'s right to patent two genes linked to breast and ovarian cancer. S&P expects protracted legal debate over the issue, but we note that most drugs in development are not directly affected given their manipulation of DNA to form a patentable invention.

INDUSTRY REGULATION

Congress passed the first federal law regulating the drug industry in 1906. Known as the Pure Food and Drug Act, it required that drugs meet official standards of strength and purity, and that drug labels give an accurate list of ingredients. However, in 1937, more than 100 people died after taking elixir sulfanilamide (a sulfa drug mixed with diethylene glycol, which is used in automotive antifreeze). This calamity led to the passage of the Food, Drug, and Cosmetic Act of 1938, which required that drugmakers submit evidence of a product's safety. It also required that a drug's label state its contents, how it should be administered, and its possible side effects. The FDA was created to oversee the law's enforcement.

The law was strengthened in 1962, following an outbreak in Europe of severe birth defects caused by thalidomide. Thalidomide's near-entry to the US market created a clamor for tighter drug regulation, which resulted in legislation requiring manufacturers to demonstrate both the safety and efficacy of new drugs before receiving approval for commercial sale in the United States. In addition, this legislation required that drug manufacturing facilities be subject to FDA approval and periodic inspection.

THE DRUG DEVELOPMENT PROCESS

The biopharmaceutical approval process is both costly and lengthy. As of early 2011, the Tufts Center for the Study of Drug Development (CSDD), a nonprofit academic research group, placed the average cost to develop a new biologic at $1.3 billion, up from $1.2 billion in an earlier 2006 study. Tufts plans to update this figure later in 2013. In December 2012, the Office of Health Economics (OHE), a UK think tank, pegged the average cost of developing an approved drug at close to $1.9 billion.

In a 2011 analysis, the Tufts CSDD concluded that it takes 95 months (roughly eight years) to develop a biologic drug and bring it to market, similar to the timeline for a traditional small molecule drug. The study noted that various FDA mechanisms—such as orphan drug designation, fast track status, and accelerated approvals—have not had a major impact on timelines from initiation to approval between 2000 and 2009. According to the OHE, success rates have declined since the 1970s, dropping from one in five to one in 10, while the average time to bring a drug to approval has more than doubled in that time to 13.5 years from six years.

These trends have given rise to attempts to uncover new ways to accelerate the development timeline, while reversing the trend of rising costs. An economic study sponsored by the National Institute of Standards and Technology suggests that an improvement in the R&D technology infrastructure, led by the standardization of data collection and quality control for post-market surveillance, would save 25%–48% of R&D expenses for each new biopharmaceutical drug approved by the FDA and would reduce development time significantly. In October 2011, the National Institutes of Health (NIH) compiled a list of approved drugs or drugs previously abandoned in clinical study that it believed could be repurposed for other uses, in an attempt to help the industry get more drugs to market more quickly, easing discovery bottlenecks. In December 2010, the director of the FDA's Office of Oncology urged companies to design small pivotal, randomized trials powered to show a large cancer survival effect earlier in the process, rather than continuing the recent trend of lengthy programs that show modest and incremental gains over existing treatments. Such advances will be crucial to reverse these alarming trends.

The effort to discover and develop new therapeutics generally consists of several distinct steps: early discovery and preclinical development, clinical trials, and regulatory filing and review.

Early discovery and preclinical development

According to the Tufts CSDD, preclinical work consumes nearly half of the R&D expenditures per biologic. While it is common to focus on a drug company's clinical development pipeline, industry insiders know that

many of the hurdles encountered during drug development occur before the compound enters the clinic. Toxicity has been the most common reason for drug failure in the preclinical phase. Outdated testing methods have proved to be a major bottleneck in the development process. Key steps in the process of developing biological drugs are detailed below.

◆ **Target identification.** Genes are identified that are thought to be responsible for causing a particular disease. The ultimate goal in this step is to find and isolate potential areas for therapeutic intervention.

◆ **Target validation**. Once a prospective disease target is uncovered, its role in the disease must be determined. Researchers use various methods, such as differential gene expression, tissue distribution analysis, and protein pathway studies, to verify the target's significance.

◆ **Assay development**. Assays, or chemical tests, are developed to determine the activity that potential treatments have on the target. Ideally, a drug development screen should be cost effective, fast, accurate, easy to perform, quantitative, and amenable to automation. Some screens can be reused for other drug development studies, while many others must be tailored for the specific target and set of therapeutic compounds that will be tested.

◆ **Screening**. Once the assay is ready for use, tests with a library of chemical compounds are conducted in an attempt to modulate a validated target. Researchers look for a predefined minimum level of activity against the target to advance the compound to secondary screening, which aims to confirm the activity, measuring the potency and assessing the selectivity of hits from the primary screen. This helps the drug developer to identify the most promising drug candidates in terms of their pharmacological characteristics.

◆ **Lead optimization**. Through rescreening, researchers zero in on candidates with the best chance of safety and therapeutic efficacy. These molecules may demonstrate some activity, but they need to be modified to improve their effectiveness and reduce their potential side effects. This process, known as lead optimization, can include up to 10 or more iterations on previously optimized groups of compounds.

◆ **Preclinical studies**. Prospective compounds that exhibit the greatest activity with the least chance of toxicity are called leads. Leads undergo years of FDA-mandated testing, which is necessary before human clinical trials can be initiated. These preclinical tests are done on animals to examine the compound's absorption, metabolism, distribution, and excretion. The preclinical studies must prove a compound's safety in terms of potential carcinogenicity and other toxic consequences and assess preliminary effectiveness of a compound. A sponsoring drug company must submit the results of preclinical testing to the FDA as part of an investigational new drug application (INDA), which is a formal request for permission to begin human clinical testing.

Clinical trials: putting candidates to the test

The US drug approval system is one of the world's most stringent. Biotechnology medications undergo the same lengthy testing process as any other pharmaceutical product, to demonstrate safety and efficacy.

The clinical testing period in humans usually consists of three phases. During Phase I, the drug is administered to a relatively small number of healthy people in order to test its safety in small doses. If this initial test appears successful, the dosage is slowly increased to determine its safety at higher levels. During Phase II, the drug is given to patients suffering from the disease or a condition that the drug is intended to treat. This round of tests is designed to evaluate the drug's effectiveness and safety, and generally includes a larger patient population and a lengthier test period than Phase I.

Drugs that pass these hurdles then undergo Phase III, in which the most complex and rigorous tests are performed on still larger groups of ill patients to verify the drug's safety, effectiveness, and optimum dosage regimens. Physicians closely monitor patients to determine efficacy and identify adverse reactions. Usually, Phase III trials (and often those of Phase II as well) employ randomized, double blind tests with placebo control to remove any chance for bias. This means that one group of patients is given the drug and another is given an inert substance; however, if there is already an approved drug for the indication, it will be used instead of the placebo. Neither the patients nor their doctors are aware of which patients are actually receiving the drug being tested.

After the development work is complete, company scientists analyze the data. If the data is positive, the company compiles it into a biologics license application (BLA) or a new drug application (NDA), which is submitted to the FDA for review. The application contains results of the preclinical and clinical research and includes details of the product's formula, production, labeling, and intended use. The FDA estimates that, of every 20 drugs entering clinical testing, an average of 13 or 14 will successfully complete Phase I. Of those, about nine will finish Phase II, but only one or two are likely to survive the rigorous Phase III trials. Thus, only 5% to 10% of all drugs entering clinical trials are ultimately approved for marketing.

Regulatory filing and review

The FDA's Center for Drug Evaluation and Research is responsible for reviewing therapeutic biological products and chemical-based drugs. The Center for Biologics Evaluation and Research reviews blood products, vaccines, and tissue-based products.

BLAs and NDAs are typically voluminous documents, sometimes exceeding 100,000 pages. Once an NDA or BLA is approved, the FDA determines the drug's official labeling, including a detailed description of the drug and its composition, indications, contraindications, and side effects. This information is included in a drug's package insert.

Following approval, the FDA continues to monitor the drug, because side effects or other unexpected developments sometimes become known after the drug is widely used. The FDA may require additional post-market studies (Phase IV) in order to evaluate long-term effects. Such studies are becoming more common. Often, after marketing has begun, the manufacturer submits supplemental applications requesting approval to use the drug for additional indications. For their initial applications of a new drug, manufacturers tend to seek narrow indications affecting well-defined sets of patients. Added approvals can greatly expand the market size and commercial potential of a biologic.

PDUFA provides funding for, but doesn't speed up, the approval process

In 1992, the FDA passed the first Prescription Drug User Fee Act (PDUFA), which allowed the agency to collect fees from the biopharma industry to fund the review of drug applications. Since the initial act, user fees have grown significantly as a percentage of the agency's review budget.

As discussed earlier in this *Survey*, the FDA has been inconsistent in its timeliness and in the consistency of approving new drugs. While drugmakers pay for the FDA to review their applications, nearly half of industry participants do not feel that user fees have accelerated the review process and were unclear of the purpose of the user fees, according to a survey conducted by PwC in late 2010. The PDUFA, which has to be reauthorized every five years, was reauthorized in July 2012 for fiscal 2013, which began in October 2012. The FDA extended standard reviews to 12 months (from 10) and priority review to eight months (from six) in the hopes that greater communication between the agency and filing companies will result in enhanced first-cycle approvals.

Shortage of clinical trial candidates slows industry pipeline

More than two million people participate in a total of approximately 80,000 clinical trials every year in the US, according to clinical trial listing service CenterWatch. Increasingly, however, drugmakers are struggling to recruit a sufficient number of patients to participate in clinical studies. According to the Michael J. Fox Foundation for Parkinson's Research, 85% of clinical trials face delays due to limited participation. S&P attributes this situation to several factors. First, the number of drugs under development has risen significantly. However, as discussed earlier in this *Survey*, the industry pipeline has been pared somewhat as a result of industry consolidation and pharmaceutical focus on novel medicines and, increasingly, rare diseases with smaller patient populations. Second, demands to show efficacy and safety over existing treatments have been growing. As more drugs are on the market for a given indication, new drugs face larger and more expensive studies to reach statistically significant results.

Cancer research has been particularly challenged by trial enrollment concerns. According to the American Association for Cancer Research (AACR), the majority of patients don't know about the cancer clinical trials available to them. In recent years, various industry sources, including the AACR and National Cancer Institute (NCI), have pegged participation among cancer patients at around 5%. However, an AACR study

reported in early 2012 suggested that 75% of cancer patients would be willing to participate if they were better informed. The American Society of Clinical Oncologists (ASCO) has identified a lack of engagement among oncologists as a significant factor in the patient shortfall.

According to a January 2013 *Impact Report* released by the Tufts CSDD, 89% of all clinical trials ultimately meet enrollment goals, though these rates of enrollment vary widely across geographies. However, the study found that 11% of sites in a given trial typically fail to enroll a single patient and 37% under-enroll, accounting for nearly half of the total number. On the encouraging side, 13% exceeded enrollment targets.

Expedited processes for life-and-death treatments

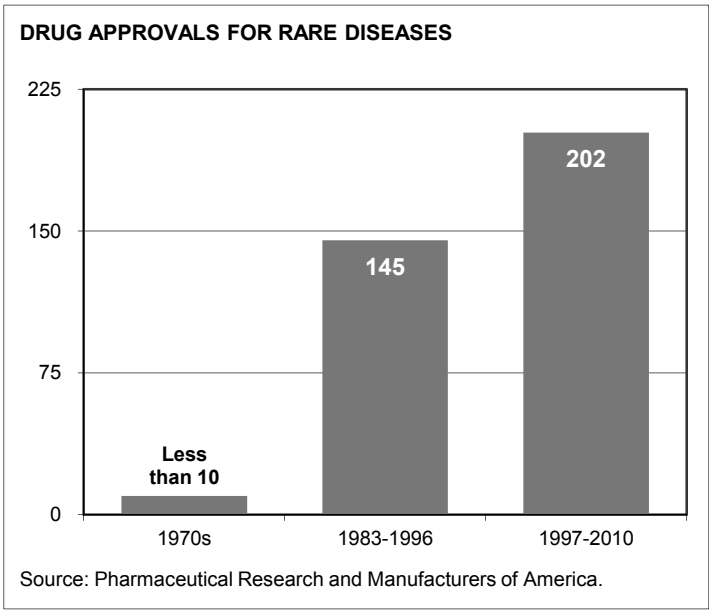
The FDA can allow for experimental drugs to be made available to seriously ill patients through its investigational new drug (IND) treatment policy. This provision lets manufacturers sell drugs (on a cost-recovery basis), provided that Phase I trials for the drug have been successfully completed. This policy was enacted in 1987.

Since 1997, drugs targeting life-threatening diseases that are not effectively treated by existing drugs can receive "fast-track" or expedited review by the FDA. Use of this designation has had a significant effect on speeding access to drugs that treat AIDS and various cancers. Another mechanism available is an accelerated approval pathway, initiated in 1992, in which a drug can be approved on clinical data that suggests that a drug has a meaningful benefit, with the promise of confirmatory data to support a full approval designation. In a May 2012 report by the California Healthcare Institute and Boston Consulting Group, the FDA's accelerated approval process has most benefitted AIDS and cancer drugs, with 32 and 29 approvals, respectively, among a total 81 approvals.

However, accelerated approval does not always result in the granting of full approval. In November 2011, the FDA revoked accelerated approval status granted to Roche (via its acquisition of Genentech) in 2008 for advanced breast cancer. The approval was based on mid-stage studies that showed a progression-free survival benefit. However, late-stage studies ultimately showed a more modest average PFS benefit, while exposing patients to side-effect risks that the FDA determined outweighed the benefit.

Orphan drugs

Enacted in 1983, the Orphan Drug Act was designed to encourage companies to develop drugs to treat rare diseases afflicting fewer than 200,000 Americans by providing research grants, tax breaks, and seven years of exclusive marketing rights to manufacturers of drugs aimed at patient markets that would otherwise be too small to justify commercial development.



An estimated 25 million Americans have one of the 6,000 rare conditions that have been identified by the National Institutes of Health. S&P believes that momentum has been building for drugmakers to increase study of rare diseases. According to a study sponsored by trade group Pharmaceutical Research and Manufacturers of America (PhRMA), pharmaceutical and biotech companies are running patient tests of more than 5,400 potential new medicines, including nearly 1,800 research projects for rare diseases, and hundreds for disorders for which there has been no new medicine in a decade or more. Further, the findings indicated that thousands of the treatments could be first-in-class medicines, including at least 577 medicines that use new

technologies and at least 155 personalized therapies. Apart from the experimental drugs being tested in patients, another 6,551 are being evaluated in preclinical research projects. In addition, nearly half of the 39 new molecular entities approved in 2012 were orphan drugs, the highest percentage on record since the FDA launched the Orphan Drug Act, according to the Associated Press. Additionally, nearly half of the approved drugs fell under the FDA's "fast track" program. S&P expects that the favorable regulatory climate for rare disease drugs is likely to continue.

Historically, the FDA had struggled to entice drugmakers to research many neglected diseases. In June 2010, the FDA established a database for rare disease repurposing, listing currently approved treatments that have received orphan drug designation for an unapproved indication, in the hopes that it would spark interest among drug developers due to a potentially less onerous development path than studying an untested therapy compound. Past efforts that offered priority review vouchers were met with little response. Still, in early 2011, the US Senate introduced the Creating Hope Act, which would offer vouchers promising fast FDA review for companies studying rare diseases that disproportionately affect children. In December 2011, the US Senate introduced another measure, the Unlocking Lifesaving Treatments for Rare-Diseases Act (ULTRA), which would allow the FDA to grant fast-track approval using a surrogate endpoint, without mandating the use of clinical treatment data or other historical clinical data.

Despite these efforts, patient advocate groups have pushed for additional policies that allow greater flexibility in how the agency reviews these drugs. The agency has been called upon to accelerate development timelines for conditions of serious unmet needs as well as to raise the exclusivity period to ten years, to match levels set in Europe, from the current seven.

PRICING CONSIDERATIONS

To date, US biotechnology drug pricing has minimal regulatory scrutiny, as most approved treatments are used for hard-to-treat, potentially fatal diseases, where the cost–benefit equation has been supported by the high value that society places on human life. As such, new biopharmaceuticals are typically very lucrative, and manufacturers have had wide discretion in pricing them. Many factors go into the pricing decision, including the relative efficacy of a given drug versus its rivals, the size of the target market(s), the price of competing therapeutics, and costs incurred in development.

In addition, a lack of alternative therapies for some conditions can leave doctors little choice in making prescription decisions. However, the exemption from cost pressures is eroding, as pharmaceutical costs rise, new biotech products come to market, and the biotechnology field grows increasingly competitive.

Although most drugs are priced near other established drugs in their class, breakthrough therapies for life-threatening conditions are usually priced exceptionally high. For example, in 2007, Alexion Pharmaceuticals Inc. launched Soliris for the treatment of paroxysmal nocturnal hemoglobinuria (PNH), a rare blood disorder; the cost of a year's treatment with Soliris is more than $400,000. Specialty drugs now account for 15% of US drug spending despite representing only 0.5% of prescriptions, according to BioCentury, a leading provider of information, analysis, and data on the biotechnology and pharmaceutical industries.

Europe has taken a leading position on judging a drug's cost effectiveness. A growing number of drugs, particularly cancer drugs, have been approved by the European Medicines Agency (EMEA) but have not been made available because they have been deemed as not cost-effective by local governments. Such rulings can be made in each European Union (EU) member country because the EU's regulatory system is not harmonized. The UK's National Institute for Health and Clinical Excellence (NICE) has led the way.

KEY INDUSTRY RATIOS AND STATISTICS

◆ **R&D as a percentage of sales.** New drugs represent the lifeblood of the biotechnology industry, so changes in this industrywide statistic can have an important impact on future trends in sales and earnings. According to Ernst & Young, research and development (R&D) expenditures as a percentage of total revenues were 29.3% for publicly held biotech companies in 2011 (latest available), up from 28.2% in 2010, but down

from 30% in 2009. For most money-losing operations, R&D expense typically far outpaces revenues. We believe an appropriate barometer when analyzing the more mature, profitable biotechs is approximately 15%–25% of revenues.

At present, the biotech industry devotes a higher percentage of its sales to R&D than any other major US industry. This ratio should decline as the industry matures and more products are commercialized, leading to ratios more comparable to those of the pharmaceutical industry.

◆ **Annual budget of the National Institutes of Health (NIH).** The NIH, a division of the US Department of Health and Human Services (HHS), plays a vital role in drug discovery by funding basic research on the fundamental mechanisms of disease. The budget is usually disclosed in the early part of the year as part of the president's total proposed federal budget for the fiscal year beginning October 1. The first and largest NIH institute is the National Cancer Institute, established in 1937.

About 40% of the NIH's budget supports basic research, 40% is for transitional research, and 20% is for high-risk projects. The NIH receives approximately 50,000 research and training applications per year. From these applications, the division uses a peer review system to select the most qualified proposals for funding. For fiscal 2012, the NIH budget was finalized at $30.7 billion, up $299 million over the previous year. For fiscal 2013, NIH will be operating under a continuing resolution until March 27, 2013. The continuing resolution provides for a budget of 0.6% above the fiscal 2012 level. The budget also included funds to establish the National Center for Advancing Translational Sciences (NCATS) to speed up the process of drug development.

◆ **National healthcare expenditures.** The Centers for Medicare & Medicaid Services (CMS) a division of HHS, releases annual estimates of all healthcare spending in the United States. The data have a full-year lag and are structured according to type of expenditure, such as hospital care, physician care, and drugs and other medical nondurables.

The CMS's annual report, *Health, United States*, includes detailed information on the sources and the amount of funds for each segment. Changes in funding sources are important to recognize, as margins are higher in the private sector than they are in government-financed sales (such as Medicaid and Medicare). Spending changes in specific illness segments can have an important bearing on pharmaceutical sales and demand for biotechnology products. *Health, United States* also provides figures on rates of change in total healthcare spending by segment. Proportional changes in pharmaceutical spending can be measured against other healthcare sectors to determine the industry's relative growth.

The CMS estimates that national health expenditures rose slightly to $2.7 trillion in 2011, representing 17.9% of US gross domestic product (GDP), the same percentage as in 2010. Further, the CMS has projected that costs would account for 19.6% of the national economy by 2021 and increase annually by an average of 6.2%, driven by expected robust Medicare enrollment growth, Medicaid coverage expansions, and exchange plan premium and cost-sharing subsidies.

◆ **Medicare and Medicaid spending.** Changes in spending and in reimbursement rates in these important government healthcare entitlement programs can have a significant impact on biotechnology business.

Medicare is a federally funded national health insurance program for people aged 65 and older, as well as for disabled persons. Historically, it has not covered the cost of drugs dispensed through retail pharmacies, which constitute the bulk of drugs sold in the US. However, it did reimburse for drugs administered in hospitals, clinics, or doctors' offices—a benefit directed disproportionately at biotechnology products, which often are given by infusions or injections. In June 2012 (latest available), CMS projected Medicare spending growth of 5.7% annually from 2011–21, nearly one percent faster than US gross domestic product (GDP). In addition, CMS estimated the healthcare share of GDP rising to 19.6% in 2021, up from 17.9% in 2010. CMS also estimated that the implementation of healthcare reform in 2014 would likely represent a high watermark to these estimates, with 7.4% spending growth expected in that year.

Medicaid is a health benefits program for low-income US residents who are aged, blind, and disabled, or for members of families with dependent children. Federal and state governments jointly fund the program, though each state sets eligibility standards. Medicaid has traditionally covered the cost of pharmaceuticals for members. As of January 1, 2006, however, those eligible for Medicare received their prescription drug benefits through Medicare, and several million Medicaid recipients were moved to Medicare Part D for their drug coverage. The 2010 Patient Protection and Affordable Care Act also promised to expand Medicaid and Children's Healthcare Insurance Program (CHIP) eligibility, beginning in 2014. As such, enrollment in these programs are expected to increase significantly in 2014, although we think the number of new enrollees could be hindered by states that have the right to opt out of this expansion, a right that was granted by the US Supreme Court in June 2012.

◆ **Interest rates.** Like most corporations, biotechnology companies closely monitor changes in interest rates, as those rates affect management decisions on new capital expansion projects, acquisitions, and investment of idle cash. High interest rates increase the cost of borrowing and tend to make acquisitions financed by debt less attractive. In addition, increases in the rate at which future earnings are valued tend to push down biotechnology valuations.

As of February 2013, Standard & Poor's Economics (which operates separately from S&P Capital IQ) was projecting that the yield on the three-month Treasury bill (a proxy for short-term interest rates) would be about 0.1% for 2013. The average yield on 10-year notes (a proxy for long-term interest rates) was projected at 2.1% for 2013.

While lower interest rates make debt financing more attractive, challenging credit conditions across the global economy dim the prospects of smaller companies qualifying for debt financing. For biotech firms that have substantial cash balances, lower interest rates can significantly reduce interest income, while their operating expenditures may not decrease. In September 2007, the federal funds rate was at 5.25%, when the Federal Reserve began cutting rates in order to spur a slowing US economy. As the recession worsened throughout 2008, rates were lowered to an unprecedented fed funds target range of 0.0%–0.25%, where they remain as of early 2013. The Federal Reserve has reiterated that the central bank is prepared for a protracted period of low interest rates, particularly while signs of inflation remain absent.

HOW TO ANALYZE A BIOTECHNOLOGY COMPANY

The analysis of a biotechnology firm, like that of any company, includes a thorough study of both business strategy and financial health. In contrast to companies in more mature industries, many biotech firms do not have commercial track records. Thus, analysts sometimes have to rely more heavily on qualitative rather than quantitative methods of valuation.

RESEARCHING THE BUSINESS

The first step in the analysis is to examine the company's business strategy, core competencies, and market position. Many biotech companies are still in a developmental phase, so this step may rely heavily on qualitative judgments about management skill, technology, and new product potential.

In general, S&P Capital IQ (S&P) does not believe that market capitalization is an overly useful variable for measuring the success or prospects of a biotech entity, since market cap can be artificially inflated or deflated in times when equities are priced irrationally. Furthermore, biotech companies tend to have varying degrees of premiums incorporated into their share prices based on prospects for acquisition by a larger entity, making it more difficult to rely on traditional valuation measures.

Products and pipeline are key

What are the company's key products and features of the company's technology platform? A biotech firm's product portfolio and research pipeline are essential to its success. A company's intrinsic value should be primarily a function of the prospective earnings to be gained from approved products and investigational compounds in development, as well as the probability of successfully developing pipeline candidates.

S&P believes that companies with technologies that are scientifically sound and patentable—with the potential to spawn novel product candidates and applications—generally offer better risk/reward profiles than those that pin their hopes on candidates that may not provide product differentiation.

Look for companies with a number of promising product candidates in later stages of clinical development, preferably targeting diseases with large patient populations for which there is still a need for breakthrough medications. At the same time, be wary of companies with limited resources that may strain their operating capabilities by trying to develop too many marginal (referred to as "me-too" products) products in disease areas that are already well served, which could result in a low likelihood of success or limited market potential, and the possibility of recurring dilutive financing.

Patents provide protection

Do patents adequately protect the firm's products? In assessing a biotech company's product portfolio, it is imperative to determine when the patents on its proprietary drugs and compounds expire. Although this tends to be more of a problem for pharmaceutical companies than for biotech firms, the loss of market exclusivity on key products, without adequate profit potential from other products or pipeline candidates, can lead to financial trouble. The issue of patent protection is poised to become a larger issue in the coming years, as progress toward a regulatory pathway for generic biotech drugs takes shape.

Current patents, meanwhile, can lead to royalties if a company decides to license its technology to other firms. Patents also protect companies by preventing potential competitors from entering certain markets.

Assessing R&D

Have the company's past research and development (R&D) efforts been productive? Most leading biotech companies spend between 15%–25% of operating revenues on R&D, with most development-stage biotechs often spending well over 100%. However, success rates—in terms of developing lucrative new drugs and therapeutics—can differ markedly.

The bigger, better-funded firms tend to have the advantage of being able to afford to hire top scientists and to conduct the larger, more costly clinical trials often required to develop new drugs, particularly as drug safety comes under greater scrutiny. Furthermore, in a healthcare market dominated by managed care, a key factor in future success will be the biotech industry's ability to develop cost-effective new drugs that constitute therapeutic breakthroughs. New products that provide similar results to existing therapies are unlikely to achieve great commercial success.

Look for companies developing drugs for illnesses that are not adequately served by current treatments. Generally, drugs for chronic illnesses (such as asthma and rheumatoid arthritis) that have large patient populations can provide a higher return on R&D expenditures than can one-time treatments, such as vaccines.

Management strength

Does the firm have experienced people? The quality and experience of a company's management and scientific teams are very important in determining long-term success. The industry changes rapidly, so it is crucial for a firm to be led by insightful and quick-thinking individuals who can adapt to volatile circumstances.

Ideally, a biotech company should employ top executives who have helped develop and commercialize pharmaceutical products at large drug companies and successful biotech firms. Look for a demonstrated ability to reach milestones. Management should be credible in terms of historically meeting publicly stated goals and key development milestones. Be wary of a company that consistently misses its own targets.

We like management teams that have operating experience. It is important that the people running the company thoroughly understand and appreciate how expensive the drug development process is, and who have established track records of allocating the company's funds to projects offering the highest returns on investment.

Making the most of alliances

Has the firm entered into any promising collaborations or partnerships? Because of the extraordinarily high costs of drug development, a significant discovery made by a small biotechnology or biopharmaceutical

company may go nowhere unless the firm can find a larger partner to fund clinical trials and help commercialize the product. It is important that biotech firms choose corporate partners that are committed to seeing the product to commercialization, which is increasingly important as many large pharma companies consolidate and streamline their areas of focus, and that have research experience and established sales infrastructure within a targeted market.

Careful attention should be given to the terms of the deal, as they tend to indicate the value the bigger partner places on the biotech company's technology. From the junior partner's perspective, a good deal typically includes a sizable up-front fee from the bigger firm, and may include equity, R&D funding for product development, milestone payments for achieving R&D benchmarks, co-promotion rights, and royalties on sales. Co-promotion rights are usually preferable to royalties, although the smaller firm may be constrained by limited resources, while up-front payments are generally more desirable than those tied to future R&D benchmarks.

Many biotech companies maintain both formal and informal relationships with scientists at leading medical colleges or other organizations, such as the federal government's National Institutes of Health (NIH). Such relationships can be a valuable resource for a company in its quest for new drugs. Companies with connections to the NIH often gain rights to medications or drug targets discovered by the NIH (usually in conjunction with a leading university).

Financial resources

Is the company well financed? A biotech firm must have adequate funding for its development programs, or it may be forced to curtail its R&D efforts. We like to see enough cash on the balance sheet to cover operating expenses for at least two years. Such a position can safeguard a firm from becoming desperate for funding and thus being forced to accept sub-optimal value on its assets.

An ample cash balance will let the firm operate from a position of strength when negotiating collaborative arrangements and gives the firm the ability to carry product development ahead on its own if necessary. The farther along a product is in the development process, the greater the potential future profits the firm should be able to retain in any negotiated deal. Having sufficient cash on hand is also important because access to financing tends to change over time. The biotech sector goes through periods when public equity markets are not particularly receptive to funding risky ventures, and it is important for a company to have sufficient resources to see it through such times.

Regulatory compliance

How effectively does the company work with the US Food and Drug Administration (FDA)? Because all drugs sold in the United States must first be cleared by this agency, it is critical that a firm is able to work closely with the FDA and satisfy the regulatory authority's drug approval requirements.

Size and experience can help. The larger biotech firms are usually adept at working with the agency, while many smaller or newer firms are less proficient and often encounter major snags in obtaining approval for their products. Managers hired from successful biotech or pharmaceutical firms with proven drug development experience, and/or an alliance with a strong corporate partner, can prove to be invaluable. Increasingly, companies are involving the FDA in trial design and protocol throughout the clinical process, in an effort to prevent delays and negative surprises in the later stages.

ANALYZING FINANCIAL STATEMENTS

The usefulness of looking at a biotechnology company's financial statements depends largely on whether the firm has any earnings history. Because most biotech companies (about 90%) are in the developmental stages and have little to no product sale revenues, traditional analytical techniques are of limited value. For these companies, analysts tend to focus on the future earnings potential of products in development, and on whether the company has the resources to fully develop those products.

Conversely, a financial analysis of one of the larger, profitable biotech companies tends to resemble that of a traditional pharmaceutical firm. Key metrics include revenues, costs and expenses, R&D as a percentage of

sales, earnings, margins, growth in earnings per share and sales, and return on equity. When possible, individual company statistics should be compared with those of rival companies and the industry average.

Key elements of the income statement

Central to any analysis is the income statement, which shows a company's operating results over a stated period.

◆ **Sales.** Starting at the top of the income statement, examine the short- and long-term trends in sales or revenues. Ideally, sales in the current period should show increases from the corresponding period in the prior year (year-over-year growth). However, because many biotech companies experience extremely rapid growth following the commercialization of a new drug, a pertinent interim measure for relatively new products is sequential sales growth—that is, increases from the immediately preceding quarter.

Growth rates should be compared with those of direct competitors whenever possible. Also, consider how growth has been achieved. Has it been generated by unit volume gains, price increases, acquisitions, any one-time or nonrecurring gains from asset sales, or some combination of these? Is the company gaining market share, or just riding market growth or price hikes?

◆ **R&D.** Sufficient investment in R&D is critical to the success of any biotechnology company. R&D spending is unusually high for the biotechnology industry in general. For developmental-stage companies that have not yet produced commercial products, R&D typically exceeds revenues by a wide margin. When comparing companies, most analysts look at ratios such as R&D as a percentage of sales, R&D expenditures per employee, or R&D as a percentage of market capitalization.

◆ **Selling, general, and administrative (SG&A) expenses.** Royalty costs and costs related to product co-promotion may be included in SG&A or another line item. Investors should compare royalty obligations and the financial structure of collaborative arrangements between firms in order to assess the potential profitability of a drug.

◆ **Option expense.** Companies were required to expense this item on the income statement beginning in 2006. Investors should be aware of options grants, since a high level of outstanding options could dilute earnings per share (EPS) if these options are eventually exercised. A significant number of options outstanding could also divert company cash to repurchasing shares in order to neutralize the dilutive effect of options. This cash could have otherwise been used for product promotion, drug development, or dividends (assuming that profitable biotech firms eventually pay dividends).

◆ **Gross profit margin.** This is the percentage of revenues left after deducting cost of goods sold. Gross margins generally will be lower for biotech firms than for large pharmaceutical companies, due to the complexity of manufacturing biologic drugs.

◆ **Product profit margin.** S&P uses the percentage of sales remaining after subtracting the cost of goods sold (COGS) and SG&A to ascertain the maximum obtainable profitability per drug. This figure may vary widely because of the costs of co-promotion and royalty arrangements that often are embedded in certain expense line items. Management often does not detail such ongoing costs. In some instances, there are also costs involved for post-marketing clinical trials to support approved products. These costs also should be factored in.

◆ **Operating profit margin.** This is the percentage of sales remaining after subtracting all ongoing operating costs. In the biotechnology industry, expenses (such as the cost of goods sold, R&D, labor, and overhead) tend to be very high. Companies incur substantial costs during a drug's R&D phase; once those costs have been covered, however, a large portion of revenues flows to the bottom line.

◆ **Net profit margin.** Net profit margin equals net income as a percentage of total sales. It reflects a company's additions and subtractions for nonoperating income and expense items (typically interest income and interest expense), as well as taxes. For top-tier firms, net profit margins are usually in the range of 15% to 30%; the rest of the industry remains largely unprofitable.

◆ **Tax rate.** Investors should be aware of a firm's tax rate going forward since many biotech firms will face rising tax rates as they become profitable, which will restrict net earnings and earnings growth in certain years.

◆ **Earnings per share.** This figure—net EPS of outstanding common stock—is important for the more established biotech firms that have achieved profitability. Net earnings are the bottom-line return on a company's business. Investors target growth and expect companies with profitable ongoing operations to meet or exceed EPS expectations.

◆ **Cash flow.** A simplified definition of cash flow is net income (excluding special items) plus depreciation and amortization, less capital expenditures. Projecting this figure over many years is useful for performing discounted cash flow analysis of a firm.

◆ **Return on equity (ROE).** Calculated as net earnings as a percentage of average or ending shareholder's equity, ROE measures the return earned on shareholders' capital.

◆ **Return on assets (ROA).** This ratio (net income divided by average or ending total assets) measures the return on all assets under management's care.

Using the balance sheet to assess liquidity

The balance sheet is a snapshot of a company's financial condition at a specific moment in time, so it should be examined to determine a company's financial health. For biotechnology companies, most balance sheet analysis focuses on liquidity.

◆ **Cash.** Analysts look at a company's level of cash and marketable securities to assess short-term liquidity. The proper level of cash and cash equivalents varies from company to company. For development-stage biotech companies with no earnings, we like to see at least two years' worth of cash on hand to fund operations at the current "burn rate"—the rate at which cash is being consumed by R&D and other expenditures. Investors also must consider the amount of convertible debt outstanding, if any, since a number of biotech firms issue convertible notes. Subtracting outstanding debt from cash balances provides a more stringent measure of a company's actual financial strength.

◆ **Inventory.** Inventory as a percentage of product sales should be analyzed over time. A rising figure can be a warning sign, indicating that sales are falling short of expectations.

◆ **Current ratio.** Another reliable check on liquidity is the ratio of current assets to current liabilities. The current ratio measures a company's ability to pay its bills. A higher-than-average current ratio indicates financial strength, since current assets are readily available to be converted into cash. Given that most biotech companies have relatively large cash positions and low debt (they often rely on equity financings), biotech current ratios tend to be higher than those of other industries. This ratio is generally greater than 2.0 for many biotech firms. Any meaningful degradation in the current ratio from previous reporting periods may signal a liquidity problem.

◆ **Long-term debt to capital.** This ratio is calculated by dividing long-term debt by total capital (the sum of long-term debt and stockholders' equity). Simply put, it shows the percentage of total capital that long-term debt represents. A relatively low percentage indicates that the company may be less burdened than its peers in terms of debt service. Debt leverage varies significantly among biotechnology companies. Most have not tapped the debt markets much because of their lack of cash flow to service interest payments. An appropriate debt load depends largely on a company's product lines and projected new product streams. Any sudden change in the company's attitude toward taking on debt should be thoroughly investigated.

EQUITY VALUATION

S&P Capital IQ believes that there are several relevant valuation methods for valuing biotech companies. For the few profitable and still independent companies, a price-to-earnings (P/E) ratio is widely used to compare a company's valuation versus its peers. Taking this metric a step further, dividing the P/E ratio by a company's long-term growth rate yields a P/E-to-earnings growth (or PEG) ratio, which puts the P/E ratio in

the context of a company's growth prospects rather than on an absolute basis. For companies that are not profitable, but for which profitability is anticipated within a few years, it is not uncommon for a future period's P/E estimate to be used to value that company. Assigning that estimate with a target P/E multiple to reflect its growth prospects, and discounting that total back to the present year at a rate that reflects the risks of the company reaching that target valuation is a widely used technique.

The majority of publicly traded biotech companies remain at the development stage, and without near-term commercial prospects. Valuing these companies can be more difficult. S&P believes it is appropriate in these cases to analyze the revenue potential for the company's pipeline drivers and to discount their expected cash flows back to the present year at a discount rate commensurate with the risks, which typically reflect the stage of development. Determining a net present value of these assets and dividing the totals by the number of company shares can provide an estimate of a company's stock price value. ■

GLOSSARY

Agonist—A drug that promotes certain kinds of cellular activity by binding to a cell's receptor.

Antagonist—A drug that prevents certain types of cellular reactions by blocking other substances from binding to a cell's receptor.

Antibody—A protein produced by certain types of white blood cells to deactivate foreign proteins.

Antigen—Any substance that induces a body's immune response.

Autoimmune disease—A condition, such as multiple sclerosis, where the body produces antibodies against its own tissues.

Bioavailability—The percentage of a drug's active ingredient that reaches a patient's bloodstream and body tissues.

Biochip/microarray—A miniaturized technology that can be used to run hundreds of tests simultaneously. The chips are etched with genetic or proteomic information and used by researchers to analyze DNA sequences, ascertain gene or protein expression, or detect genetic abnormalities known as mutations.

Biologics—Also known as biologic drugs, biologics are medicinal preparations made from living organisms or their byproducts. Vaccines, antigens, serums, and plasmas are examples of biologics.

Biologics license application (BLA)—The formal filing that drugmakers submit to the US Food and Drug Administration (FDA) for approval to market new biologics-based drugs. The application must contain clinical evidence of the compound's safety and efficacy.

Biosimilar/biogeneric—A generic copy of a biological molecule, developed using modern biotechnology techniques. A biosimilar has similar activity and is structurally nearly identical to the biologic that it copies. Unlike generic chemical-based drugs, however, a biosimilar is not truly identical and therefore will require a different regulatory process than pharmaceutical generics.

Breakthrough drug—A compound with a mechanism of action significantly different from that of existing drugs, representing a major therapeutic advance.

Clinical trials—Tests, typically consisting of three stages, in which experimental drugs are administered to humans to determine their safety and efficacy before being submitted for regulatory marketing approval.

Combination therapy—The use of two or more drugs that together have greater therapeutic power in treating illness and diseases than either used alone.

Cytokines—A family of proteins, including interferons, interleukins, and various growth factors, that bind to cellular receptors and are involved in the regulation of cell function.

Deoxyribonucleic acid (DNA)—The basic molecule that contains genetic information for most living systems. The DNA molecule consists of four nucleotide bases (adenine, cytosine, guanine, and thymine) and a sugar-phosphate frame arranged in two connected strands forming a double helix.

Gene sequencing—A scientific technique whereby DNA strands are decoded in order to quantify the exact order of DNA's four nucleotides (A, C, G, and T). This method allows scientists to analyze the sequence of strands and identify specific genes embedded in DNA.

Gene therapy—The introduction of specific genes into a patient's body to replace defective ones or to suppress the action of a harmful one.

Genomics—The study of genes and their functions, including mapping genes within the genome, identifying their nucleic acid structures, and investigating their functions.

Growth factors—Proteins responsible for regulating cell proliferation, function, and differentiation.

Immunomodulator—A drug that attempts to modify the immune system.

Investigational new drug (IND)—Regulatory classification of an experimental new compound that has successfully completed animal studies and has been approved by the FDA to proceed to human trials.

Monoclonal antibodies (mAbs)—Large protein molecules produced by white blood cells, which seek out and destroy harmful foreign substances.

New drug application (NDA)—The formal filing that drugmakers submit to the FDA for approval to market new chemical-based drugs. The application must contain clinical evidence of the compound's safety and efficacy.

Nucleic acid testing (NAT)—A method of biological screening and diagnostic testing that entails amplifying DNA and RNA to identify diseases and infections. NAT is faster and more accurate than more traditional screens and is being used to test blood supplies for HIV and hepatitis infection.

Orphan drug—A drug designed to treat a rare disease afflicting a relatively small patient population (currently fewer than 200,000 cases in the US). The US government provides special incentives to encourage development of such drugs.

Pharmacogenomics—The study of how an individual's genetic composition affects the response to drugs. It combines traditional pharmaceutical sciences, such as biochemistry, with the knowledge of genes, proteins, and single nucleotide polymorphisms.

Polymerase chain reaction (PCR)—A scientific technique that uses special reagents and polymerase enzymes to amplify a specific fragment of DNA into larger quantities. PCR is used in a variety of genetic analysis settings, such as matching a DNA sample with a particular person or detecting infections.

Priority review—An investigational drug receiving this status from the FDA will be reviewed by the agency within eight months of its BLA or NDA submission, rather than the standard 12 months, according to new regulations recently approved for fiscal 2013.

Proteomics—The study of encoded proteins and their function, with an emphasis on the role that proteins may play in the development of disease.

Recombinant DNA technology—The process of creating new DNA by combining components of DNA from different organisms. Usually, the new DNA is then incorporated into therapeutic substances.

Recombinant soluble receptors—Synthetic versions of proteins manufactured using recombinant DNA technology and designed to block unwanted binding of cytokines to their cellular receptors.

Ribosome nucleic acid interference (RNAi)—Ribosomal nucleic acid, or RNA, plays an important role in protein production by carrying instructions from a cell's genes (DNA) to its protein-making apparatus. RNAi is a method that can be used to prevent RNA from delivering its messages—in effect, silencing the gene and blocking production of the protein. Scientists believe RNAi may have tremendous potential for the development of new therapies.

Treatment IND—An FDA program that allows experimental drugs treating life-threatening illnesses to be made commercially available to very sick patients before the drugs obtain formal FDA approval.

Tumor necrosis factors (TNF)—Rare proteins of the immune system that appear to destroy some kinds of tumor cells without affecting healthy cells. ■

INDUSTRY REFERENCES

PERIODICALS

Beyond Borders: Global Biotechnology Report
http://www.ey.com
Annual report on the global biotechnology industry, with information broken down by regions of the world.

BioCentury: The Bernstein Report on BioBusiness
http://www.biocentury.com
Weekly newsletter; analysis, interpretation, and commentary on biotech news and developments.

The Burrill Report
http://www.burrillreport.com
Monthly; actionable market intelligence on the latest global developments and trends in the life sciences industry.

Drug Trend Report
http://www.drugtrendreport.com
Annual publication with detailed analysis of prescription drug costs and utilization; published by Express Scripts, a pharmacy benefit manager.

Genetic Engineering & Biotechnology News
http://www.genengnews.com
Semimonthly; broad coverage of biotech news and analysis of industry trends.

IN VIVO: The Business & Medicine Report
The RPM Report: Regulation, Policy, Market Access
http://www.elsevierbi.com
Monthly trade magazines. The first covers pertinent issues in the healthcare industry (biotech, medical devices, pharmaceuticals), with a focus on company-specific stories. The second covers regulatory and political trends.

The Journal of the American Medical Association
http://www.jama.com
Weekly; peer-reviewed medical journal that publishes research papers on a wide range of topics, as well as commentary from industry experts and physicians.

Nature Biotechnology
http://www.nature.com/nbt
Monthly; encompasses biotech news and trends, opinions, and research articles.

New England Journal of Medicine
http://www.nejm.org
Weekly; professional medical journal containing detailed scientific articles on medical treatments and health issues.

The Scientist
http://www.the-scientist.com
Monthly; covers scientific and business news.

BOOKS

The Merck Manual of Diagnosis and Therapy, 18th Ed.
http://www.merck.com/pubs
Detailed information on various diseases and medical conditions, as well as therapeutics used to treat them.

Stedman's Medical Dictionary, 28th Ed.
http://www.stedmans.com/product.cfm/481/215
Comprehensive medical word reference.

TRADE ASSOCIATIONS

American Society of Clinical Oncology (ASCO)
http://www.asco.org
Professional association of clinical oncologists with up-to-date information on cancer therapies and reimbursement.

The Biotechnology Industry Organization (BIO)
http://www.bio.org
Represents biotech companies, academic institutions, and state biotech centers in legislative and regulatory affairs; publishes industry statistics and information.

Pharmaceutical Research and Manufacturers of America (PhRMA)
http://www.phrma.org
Represents prescription drug firms in legislative and regulatory affairs; publishes industry statistics and information.

GOVERNMENT AGENCIES

Centers for Medicare & Medicaid Services (CMS)
http://cms.hhs.gov
This division of the US Department of Health and Human Services (HHS) administers the Medicare program and works with the states to administer Medicaid and the State Children's Health Insurance Program (SCHIP). CMS also regulates laboratory testing and oversees the certification of nursing homes and continuing care providers.

European Medicines Agency (EMEA)
http://www.emea.europa.eu
Regulatory body responsible for approvals and oversight of medications in the European Union.

Food and Drug Administration (FDA)
http://www.fda.gov
Federal agency charged with supervising the US food, pharmaceutical, and biotechnology industries; part of the Department of Health and Human Services.

National Center for Health Statistics (NCHS)
http://www.cdc.gov/nchs
The US government's principal vital and health statistics agency; part of the Centers for Disease Control and Prevention (CDC).

National Institutes of Health (NIH)
http://www.nih.gov
Part of HHS, the NIH is the primary federal medical research agency. It conducts research in its own laboratories and supports research by scientists in universities, medical schools, hospitals, and research institutions in the United States and abroad. All of its 27 institutes—including the National Cancer Institute, which is a vast source of information on cancer treatments and research trends—can be accessed through the NIH main website.

ONLINE RESOURCES

Biospace.com
http://www.biospace.com
A centralized bioscience-specific "hub" site providing up-to-the-minute biotechnology and pharmaceutical developments, as well as links to other sources of biotech information.

ClinicalTrials.gov
http://www.clinicaltrials.gov
A centralized database operated by the National Institutes of Health, listing information on thousands of public and private clinical drug trials, completed or ongoing, in the United States.

The Pink Sheet
http://www.elsevierbi.com
Weekly newsletter; trade and regulatory coverage of the pharmaceutical and biotech industries.

Health News Daily
http://www.healthnewsdaily.com
Site that provides daily stories on industrywide, regulatory, and company-specific news.

Signals: The Online Magazine of Biotechnology Industry Analysis
http://www.signalsmag.com
Recombinant Capital Inc.'s online magazine covering biotech industry trends.

OTHER SOURCES

IMS Health Inc.
http://www.imshealth.com
Market research firm providing prescription and sales information on pharmaceutical and biotechnology medications.

Tufts Center for the Study of Drug Development
http://csdd.tufts.edu
A nonprofit academic research group (affiliated with Tufts University) that provides strategic information to help drug developers, regulators, and policymakers improve the quality and efficiency of pharmaceutical development, review, and utilization.

COMPARATIVE COMPANY ANALYSIS

Operating Revenues

Ticker		Company	Yr. End	Million $ 2011	2010	2009	2008	2007	2006	2001	CAGR (%) 10-Yr.	5-Yr.	1-Yr.	Index Basis (2001 = 100) 2011	2010	2009	2008	2007
BIOTECHNOLOGY‡																		
ACOR	§	ACORDA THERAPEUTICS INC	DEC	292.2	191.0	54.7	47.8	39.5	23.1	NA	NA	66.1	53.0	**	**	**	**	NA
ALXN	[]	ALEXION PHARMACEUTICALS INC	DEC	783.4 A	541.0	386.8	259.1	72.0	1.6	11.8 A,C	52.1	NM	44.8	6,636	4,582	3,277	2,195	610
AMGN	[]	AMGEN INC	DEC	15,582.0	15,053.0	14,642.0	15,003.0	14,771.0	14,268.0	4,015.7	14.5	1.8	3.5	388	375	365	374	368
ARQL	§	ARQULE INC	DEC	47.3	29.2	25.2	14.1	9.2	6.6 D	58.4 A	(2.1)	48.2	61.9	81	50	43	24	16
BIIB	[]	BIOGEN IDEC INC	DEC	5,048.6	4,716.4 A	4,377.3	4,097.5	3,171.6	2,683.0	272.7	33.9	13.5	7.0	1,852	1,730	1,605	1,503	1,163
CELG	[]	CELGENE CORP	DEC	4,842.1	3,625.7 A	2,689.9	2,254.8 A	1,405.8	898.9	114.2 D	45.5	40.0	33.5	4,238	3,174	2,355	1,974	1,231
CBST	§	CUBIST PHARMACEUTICALS INC	DEC	754.0 A	636.5	562.1 A	433.6	294.6	194.7	14.4	48.6	31.1	18.5	5,240	4,423	3,907	3,014	2,048
EBS	§	EMERGENT BIOSOLUTIONS INC	DEC	273.4	286.2 A	234.8	178.6	182.9	152.7	NA	NA	12.3	(4.5)	**	**	**	**	NA
GILD	[]	GILEAD SCIENCES INC	DEC	8,385.4	7,949.4	7,011.4 A	5,335.8	4,230.0	3,026.1 A	233.8	43.0	22.6	5.5	3,587	3,401	2,999	2,282	1,809
MNTA	§	MOMENTA PHARMACEUTICALS INC	DEC	283.1	116.8	20.2	14.6	21.6	16.0	NA	NA	77.6	142.4	**	**	**	**	NA
REGN	†	REGENERON PHARMACEUT	DEC	445.8	459.1	379.3	238.5	125.0	63.4	22.0	35.1	47.7	(2.9)	2,029	2,089	1,726	1,085	569
SPPI	§	SPECTRUM PHARMACEUTICALS INC	DEC	193.0	74.1	38.0	28.7	7.7	5.7	0.0	NM	102.5	160.4	470,641	180,763	92,744	70,061	18,712
UTHR	†	UNITED THERAPEUTICS CORP	DEC	743.2 A,C	603.8	369.8	281.5	210.9	159.6	5.7	NM	36.0	23.1	12,966	10,534	6,452	4,911	3,680
VRTX	†	VERTEX PHARMACEUTICALS INC	DEC	1,410.6	143.4	101.9	175.5	199.0	216.4	167.5 A,C	23.7	45.5	883.9	842	86	61	105	119
LIFE SCIENCES TOOLS & SERVICES‡																		
AFFX	§	AFFYMETRIX INC	DEC	267.5	305.9	327.1	320.2	371.3	355.3	224.9	1.7	(5.5)	(12.6)	119	136	145	142	165
A	[]	AGILENT TECHNOLOGIES INC	OCT	6,626.0	5,463.0 A	4,481.0	5,774.0	5,420.0	4,973.0 D	8,396.0 C,D	(2.3)	5.9	21.3	79	65	53	69	65
BIO	†	BIO-RAD LABORATORIES INC	DEC	2,073.5	1,927.1	1,784.2 A	1,764.4 A	1,461.1 A	1,262.2	817.5	9.8	10.4	7.6	254	236	218	216	179
CBM	§	CAMBREX CORP	DEC	255.7 F	227.0 F	234.6 F	249.2 F	252.5 D,F	455.5 D,F	498.9 A,F	(6.5)	(10.9)	12.6	51	46	47	50	51
CRL	†	CHARLES RIVER LABS INTL INC	DEC	1,142.6	1,133.4 D	1,202.6 A	1,343.5 A	1,230.6 A	1,058.4 A,C	465.6 A	9.4	1.5	0.8	245	243	258	289	264
CVD	†	COVANCE INC	DEC	2,236.4	2,038.5 A	1,962.6 A	1,827.1	1,631.5	1,406.1 A	855.9	10.1	9.7	9.7	261	238	229	213	191
ENZ	§	ENZO BIOCHEM INC	JUL	102.0	97.1	89.6 A	77.8 A	52.9 A	39.8	58.4	5.7	20.7	5.1	175	166	153	133	91
LIFE	[]	LIFE TECHNOLOGIES CORP	DEC	3,775.7	3,588.1	3,280.3	1,620.3 A	1,281.7 D	1,263.5	629.3	19.6	24.5	5.2	600	570	521	257	204
LMNX	§	LUMINEX CORP	DEC	184.3 A	141.6 A	120.6	104.4	75.0 A	53.0	20.9	24.3	28.3	30.2	880	676	576	499	358
MTD	†	METTLER-TOLEDO INTL INC	DEC	2,309.3	1,968.2	1,728.9 A	1,973.3	1,793.7	1,594.9	1,148.0 A	7.2	7.7	17.3	201	171	151	172	156
PRXL	§	PAREXEL INTERNATIONAL CORP	JUN	1,422.4	1,335.9	1,246.9 A	1,163.0 A	918.1 A	760.0	387.6	13.9	13.4	6.5	367	345	322	300	237
PKI	[]	PERKINELMER INC	DEC	1,921.3 A	1,704.3 D	1,812.2 A,C	1,937.5 D	1,787.3	1,546.4	1,330.1 A,C	3.7	4.4	12.7	144	128	136	146	134
TECH	†	TECHNE CORP	JUN	290.0 A	269.0	264.0	257.4	223.5	202.6	115.4	9.7	7.4	7.8	251	233	229	223	194
TMO	[]	THERMO FISHER SCIENTIFIC INC	DEC	11,725.9 A,C	10,788.7 A	10,109.7 A	10,498.0 A	9,746.4 A	3,791.6 D	2,188.2 A	18.3	25.3	8.7	536	493	462	480	445
WAT	[]	WATERS CORP	DEC	1,851.2	1,643.4	1,498.7	1,575.1 A	1,473.0 A	1,280.2 A	859.2	8.0	7.7	12.6	215	191	174	183	171
OTHER COMPANIES WITH SIGNIFICANT BIOTECHNOLOGY OPERATIONS																		
ALNY		ALNYLAM PHARMACEUTICALS INC	DEC	82.8	100.0	100.5	96.2	50.9	26.9	NA	NA	25.2	(17.3)	**	**	**	**	NA
AMLN		AMYLIN PHARMACEUTICALS INC	DEC	650.7	668.8	758.4	840.1	781.0	510.9	0.0	NM	5.0	(2.7)	NM	NM	NM	NM	NM
ELN		ELAN CORP PLC -ADR	DEC	660.7 D	1,169.7	820.9	761.8	516.4	497.3	1,512.9 A	(8.0)	5.8	(43.5)	44	77	54	50	34
ENZN		ENZON PHARMACEUTICALS INC	DEC	48.1	57.0 D	184.6	196.9	185.6	185.7	31.6	4.3	(23.7)	(15.6)	152	180	584	623	588
HGSI		HUMAN GENOME SCIENCES INC	DEC	131.0	157.4	275.7	48.4	41.9	25.8	12.8	26.2	38.4	(16.8)	1,022	1,228	2,151	378	327
MYGN		MYRIAD GENETICS INC	JUN	402.1 A	362.6	326.5 D	333.6 A	157.1	114.3	45.2	24.4	28.6	10.9	890	803	723	739	348

Note: Data as originally reported. CAGR-Compound annual growth rate. ‡S&P 1500 index group. []Company included in the S&P 500. †Company included in the S&P MidCap 400. §Company included in the S&P SmallCap 600. #Of the following calendar year.
**Not calculated; data for base year or end year not available. A - This year's data reflect an acquisition or merger. B - This year's data reflect a major merger resulting in the formation of a new company. C - This year's data reflect an accounting change.
D - Data exclude discontinued operations. E - Includes excise taxes. F - Includes other (nonoperating) income. G - Includes sale of leased depts. H - Some or all data are not available, due to a fiscal year change.

Net Income

Ticker		Company	Yr. End	Million $ 2011	2010	2009	2008	2007	2006	2001	CAGR (%) 10-Yr.	5-Yr.	1-Yr.	Index Basis (2001 = 100) 2011	2010	2009	2008	2007
BIOTECHNOLOGY‡																		
ACOR	§	ACORDA THERAPEUTICS INC	DEC	30.6	(11.8)	(83.9)	(74.3)	(38.0)	(24.5)	NA	NA	NM	NM	**	**	**	**	NA
ALXN	[]	ALEXION PHARMACEUTICALS INC	DEC	175.3	97.0	295.2	33.1	(92.3)	(131.5)	(47.9)	NM	NM	80.7	NM	NM	NM	NM	NM
AMGN	[]	AMGEN INC	DEC	3,683.0	4,627.0	4,605.0	4,196.0	3,166.0	2,950.0	1,119.7	12.6	4.5	(20.4)	329	413	411	375	283
ARQL	§	ARQULE INC	DEC	(10.8)	(30.1)	(36.1)	(50.9)	(53.4)	(47.2)	(41.0)	NM	NM	NM	NM	NM	NM	NM	NM
BIIB	[]	BIOGEN IDEC INC	DEC	1,234.4	1,005.3	970.1	783.2	638.2	213.7	101.7	28.4	42.0	22.8	1,214	989	954	770	628
CELG	[]	CELGENE CORP	DEC	1,318.2	880.5	776.7	(1,533.7)	226.4	69.0	(2.9)	NM	80.4	49.7	NM	NM	NM	NM	NM
CBST	§	CUBIST PHARMACEUTICALS INC	DEC	33.0	94.3	79.6	169.8	48.1	(0.4)	(69.9)	NM	NM	(65.0)	NM	NM	NM	NM	NM
EBS	§	EMERGENT BIOSOLUTIONS INC	DEC	23.0	51.7	31.1	20.7	22.9	22.8	NA	NA	0.2	(55.5)	**	**	**	**	NA
GILD	[]	GILEAD SCIENCES INC	DEC	2,803.6	2,901.3	2,635.8	2,011.2	1,615.3	(1,190.0)	51.2	49.2	NM	(3.4)	NM	NM	NM	3,929	3,156
MNTA	§	MOMENTA PHARMACEUTICALS INC	DEC	180.4	37.3	(64.0)	(62.6)	(68.9)	(51.9)	NA	NA	NM	383.7	**	**	**	**	NA
REGN	†	REGENERON PHARMACEUT	DEC	(221.8)	(104.5)	(67.8)	(82.7)	(105.6)	(103.2)	(76.2)	NM	NM	NM	NM	NM	NM	NM	NM
SPPI	§	SPECTRUM PHARMACEUTICALS INC	DEC	48.5	(48.8)	(19.0)	(15.5)	(34.0)	(23.3)	(27.8)	NM	NM	NM	NM	NM	NM	NM	NM
UTHR	†	UNITED THERAPEUTICS CORP	DEC	217.2	105.9	19.5	(42.8)	19.9	74.0	(37.3)	NM	24.0	105.1	NM	NM	NM	NM	NM
VRTX	†	VERTEX PHARMACEUTICALS INC	DEC	29.6	(754.6)	(642.2)	(459.9)	(391.3)	(207.9)	(68.4)	NM	NM	NM	NM	NM	NM	NM	NM
LIFE SCIENCES TOOLS & SERVICES‡																		
AFFX	§	AFFYMETRIX INC	DEC	(28.2)	(10.2)	(23.9)	(307.9)	12.6	(13.7)	(34.8)	NM	NM	NM	NM	NM	NM	NM	NM
A	[]	AGILENT TECHNOLOGIES INC	OCT	1,012.0	684.0	(31.0)	693.0	638.0	1,437.0	(406.0)	NM	(6.8)	48.0	NM	NM	NM	NM	NM
BIO	†	BIO-RAD LABORATORIES INC	DEC	178.2	185.5	144.6	89.5	93.0	103.3	44.2	15.0	11.5	(3.9)	403	420	327	203	210
CBM	§	CAMBREX CORP	DEC	13.7	9.3	10.4	7.9	(13.5)	(1.2)	26.6	(6.4)	NM	47.5	52	35	39	30	(51)
CRL	†	CHARLES RIVER LABS INTL INC	DEC	115.1	(328.7)	111.2	(522.3)	157.6	125.2	40.7	11.0	(1.7)	NM	283	(809)	274	(1,285)	388
CVD	†	COVANCE INC	DEC	132.2	68.3	175.9	196.8	175.9	145.0	47.9	10.7	(1.8)	93.7	276	142	367	411	367
ENZ	§	ENZO BIOCHEM INC	JUL	(13.0)	(22.2)	(23.6)	(10.7)	(13.3)	(15.7)	6.8	NM	NM	NM	(190)	(326)	(346)	(156)	(195)
LIFE	[]	LIFE TECHNOLOGIES CORP	DEC	378.5	378.3	144.6	30.0	130.3	(191.0)	(147.7)	NM	NM	0.1	NM	NM	NM	NM	NM
LMNX	§	LUMINEX CORP	DEC	14.5	5.2	17.7	3.1	(2.7)	1.5	(15.7)	NM	57.2	176.7	NM	NM	NM	NM	NM
MTD	†	METTLER-TOLEDO INTL INC	DEC	269.5	232.1	172.6	202.8	178.5	157.5	72.3	14.1	11.3	16.1	373	321	239	281	247
PRXL	§	PAREXEL INTERNATIONAL CORP	JUN	48.8	41.5	39.3	64.6	37.3	23.5	(0.8)	NM	15.7	17.4	NM	NM	NM	NM	NM
PKI	[]	PERKINELMER INC	DEC	1.2	135.9	92.7	126.1	133.8	118.3	(0.6)	NM	(60.3)	(99.1)	NM	NM	NM	NM	NM
TECH	†	TECHNE CORP	JUN	112.3	109.8	105.2	103.6	85.1	73.4	34.0	12.7	8.9	2.3	330	322	309	304	250
TMO	[]	THERMO FISHER SCIENTIFIC INC	DEC	1,019.6	1,033.1	851.3	988.7	779.6	166.3	49.6	35.3	43.7	(1.3)	2,056	2,083	1,717	1,994	1,572
WAT	[]	WATERS CORP	DEC	433.0	381.8	323.3	322.5	268.1	222.2	114.5	14.2	14.3	13.4	378	333	282	282	234
OTHER COMPANIES WITH SIGNIFICANT BIOTECHNOLOGY OPERATIONS																		
ALNY		ALNYLAM PHARMACEUTICALS INC	DEC	(57.6)	(43.5)	(47.6)	(26.2)	(85.5)	(34.6)	NA	NA	NM	NM	**	**	**	**	NA
AMLN		AMYLIN PHARMACEUTICALS INC	DEC	(543.4)	(152.3)	(186.3)	(315.4)	(211.1)	(218.9)	(72.0)	NM	NM	NM	NM	NM	NM	NM	NM
ELN		ELAN CORP PLC -ADR	DEC	(230.3)	(324.7)	(162.3)	(35.2)	(665.9)	(408.7)	(887.2)	NM	NM	NM	NM	NM	NM	NM	NM
ENZN		ENZON PHARMACEUTICALS INC	DEC	(20.8)	(2.8)	0.7	(2.7)	83.1	21.3	11.5	NM	NM	NM	(180)	(24)	6	(24)	721
HGSI		HUMAN GENOME SCIENCES INC	DEC	(381.1)	(233.2)	5.7	(244.9)	(262.4)	(251.2)	(117.2)	NM	NM	NM	NM	NM	NM	NM	NM
MYGN		MYRIAD GENETICS INC	JUN	100.7	152.3	136.3	47.8	(35.0)	(38.2)	(7.2)	NM	NM	(33.9)	NM	NM	NM	NM	NM

Note: Data as originally reported. CAGR-Compound annual growth rate. ‡S&P 1500 index group. []Company included in the S&P 500. †Company included in the S&P MidCap 400. §Company included in the S&P SmallCap 600. #Of the following calendar year. **Not calculated; data for base year or end year not available.

Ticker		Company	Yr. End	Return on Revenues (%) 2011	2010	2009	2008	2007	Return on Assets (%) 2011	2010	2009	2008	2007	Return on Equity (%) 2011	2010	2009	2008	2007
BIOTECHNOLOGY‡																		
ACOR	§	ACORDA THERAPEUTICS INC	DEC	10.5	NM	NM	NM	NM	8.5	NM	NM	NM	NM	17.2	NM	NM	NM	NM
ALXN	[]	ALEXION PHARMACEUTICALS INC	DEC	22.4	17.9	76.3	12.8	NM	14.6	10.8	46.7	8.2	NM	17.6	12.5	63.1	19.0	NM
AMGN	[]	AMGEN INC	DEC	23.6	30.7	31.5	28.0	21.4	8.0	11.1	12.1	11.8	9.3	17.1	19.9	21.4	21.9	17.2
ARQL	§	ARQULE INC	DEC	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NA	NM	NM	NM
BIIB	[]	BIOGEN IDEC INC	DEC	24.5	21.3	22.2	19.1	20.1	14.4	12.1	11.4	9.1	7.4	20.9	17.3	16.1	13.8	10.0
CELG	[]	CELGENE CORP	DEC	27.2	24.3	28.9	NM	16.1	13.1	11.3	15.8	NM	7.1	22.9	17.0	19.7	NM	9.4
CBST	§	CUBIST PHARMACEUTICALS INC	DEC	4.4	14.8	14.2	39.2	16.3	2.0	7.9	9.4	27.1	9.9	4.5	16.6	20.3	82.7	69.1
EBS	§	EMERGENT BIOSOLUTIONS INC	DEC	8.4	18.1	13.3	11.6	12.5	4.4	12.2	9.8	7.3	9.0	5.9	16.9	14.1	11.2	14.8
GILD	[]	GILEAD SCIENCES INC	DEC	33.4	36.5	37.6	37.7	38.2	19.4	27.3	31.5	31.3	32.6	44.5	47.4	50.1	52.8	61.2
MNTA	§	MOMENTA PHARMACEUTICALS INC	DEC	63.7	31.9	NM	NM	NM	55.6	21.6	NM	NM	NM	59.2	24.8	NM	NM	NM
REGN	†	REGENERON PHARMACEUT	DEC	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM
SPPI	§	SPECTRUM PHARMACEUTICALS INC	DEC	25.1	NM	NM	NM	NM	21.8	NM	NM	NM	NM	37.0	NM	NM	NM	NM
UTHR	†	UNITED THERAPEUTICS CORP	DEC	29.2	17.5	5.3	NM	9.4	14.7	8.5	2.0	NM	3.7	23.7	13.8	3.4	NM	7.9
VRTX	†	VERTEX PHARMACEUTICALS INC	DEC	2.1	NM	NM	NM	NM	1.5	NM	NM	NM	NM	4.6	NM	NM	NM	NM
LIFE SCIENCES TOOLS & SERVICES‡																		
AFFX	§	AFFYMETRIX INC	DEC	NM	NM	NM	NM	3.4	NM	NM	NM	NM	1.3	NM	NM	NM	NM	2.2
A	[]	AGILENT TECHNOLOGIES INC	OCT	15.3	12.5	NM	12.0	11.8	10.8	7.9	NM	9.2	8.6	26.9	23.9	NM	23.9	18.5
BIO	†	BIO-RAD LABORATORIES INC	DEC	8.6	9.6	8.1	5.1	6.4	5.8	6.6	6.3	4.5	5.2	10.9	13.3	12.6	8.9	10.4
CBM	§	CAMBREX CORP	DEC	5.4	4.1	4.4	3.2	NM	4.0	2.6	3.0	2.2	NM	13.2	8.8	11.7	9.0	NM
CRL	†	CHARLES RIVER LABS INTL INC	DEC	10.1	NM	9.2	NM	12.8	7.0	NM	5.1	NM	5.9	19.0	NM	8.6	NM	9.1
CVD	†	COVANCE INC	DEC	5.9	3.3	9.0	10.8	10.8	6.5	3.5	9.4	11.9	12.3	9.7	5.1	13.5	17.1	17.3
ENZ	§	ENZO BIOCHEM INC	JUL	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM
LIFE	[]	LIFE TECHNOLOGIES CORP	DEC	10.0	10.5	4.4	1.8	10.2	4.1	4.1	1.6	0.5	4.0	8.4	8.9	3.9	1.2	7.7
LMNX	§	LUMINEX CORP	DEC	7.9	3.7	14.7	2.9	NM	5.3	2.0	7.6	1.8	NM	6.0	2.3	8.6	2.1	NM
MTD	†	METTLER-TOLEDO INTL INC	DEC	11.7	11.8	10.0	10.3	10.0	12.0	11.6	10.2	12.1	10.9	34.7	31.3	28.4	37.4	29.5
PRXL	§	PAREXEL INTERNATIONAL CORP	JUN	3.4	3.1	3.2	5.6	4.1	3.7	3.4	3.6	7.9	6.1	9.7	9.7	9.3	17.4	13.2
PKI	[]	PERKINELMER INC	DEC	0.1	8.0	5.1	6.5	7.5	0.0	4.3	3.1	4.3	4.9	0.1	7.6	5.8	8.0	8.5
TECH	†	TECHNE CORP	JUN	38.7	40.8	39.9	40.2	38.1	19.8	22.2	21.5	21.5	20.6	20.6	22.9	22.3	22.4	21.9
TMO	[]	THERMO FISHER SCIENTIFIC INC	DEC	8.7	9.6	8.4	9.4	8.0	4.2	4.8	4.0	4.7	3.7	6.7	6.7	5.6	6.7	5.5
WAT	[]	WATERS CORP	DEC	23.4	23.2	21.6	20.5	18.2	17.1	18.0	18.3	18.4	15.3	37.7	39.8	42.8	51.7	56.5
OTHER COMPANIES WITH SIGNIFICANT BIOTECHNOLOGY OPERATIONS																		
ALNY		ALNYLAM PHARMACEUTICALS INC	DEC	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM
AMLN		AMYLIN PHARMACEUTICALS INC	DEC	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM
ELN		ELAN CORP PLC -ADR	DEC	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NA	NA
ENZN		ENZON PHARMACEUTICALS INC	DEC	NM	NM	0.4	NM	44.7	NM	NM	0.2	NM	20.2	NM	NM	1.4	NM	NA
HGSI		HUMAN GENOME SCIENCES INC	DEC	NM	NM	2.1	NM	NM	NM	NM	0.5	NM	NM	NM	NM	2.2	NA	NM
MYGN		MYRIAD GENETICS INC	JUN	25.0	42.0	41.7	14.3	NM	16.7	28.7	28.2	11.0	NM	17.9	30.7	31.7	12.5	NM

Note: Data as originally reported. ‡S&P 1500 index group. []Company included in the S&P 500. †Company included in the S&P MidCap 400. §Company included in the S&P SmallCap 600. #Of the following calendar year.

Ticker		Company	Yr. End	Current Ratio					Debt / Capital Ratio (%)					Debt as a % of Net Working Capital				
				2011	2010	2009	2008	2007	2011	2010	2009	2008	2007	2011	2010	2009	2008	2007
BIOTECHNOLOGY‡																		
ACOR	§	ACORDA THERAPEUTICS INC	DEC	4.1	3.3	4.0	4.8	2.8	2.5	3.9	4.9	3.2	9.6	1.9	2.9	3.2	3.3	9.3
ALXN	[]	ALEXION PHARMACEUTICALS INC	DEC	4.1	4.7	4.4	3.3	5.4	0.0	0.5	1.5	36.3	65.7	0.0	0.9	3.6	73.4	116.0
AMGN	[]	AMGEN INC	DEC	4.8	3.5	4.9	3.1	2.1	52.9	31.2	31.6	30.8	33.3	97.7	65.7	70.4	88.8	133.7
ARQL	§	ARQULE INC	DEC	1.5	1.7	1.9	1.7	5.5	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
BIIB	[]	BIOGEN IDEC INC	DEC	3.3	2.4	3.5	2.7	1.1	13.7	16.0	14.3	15.0	0.8	51.4	71.6	61.2	70.7	28.9
CELG	[]	CELGENE CORP	DEC	2.8	4.1	7.8	5.4	7.1	16.9	15.6	0.5	0.6	0.8	45.3	38.7	0.6	1.0	0.9
CBST	§	CUBIST PHARMACEUTICALS INC	DEC	4.1	6.7	3.6	6.5	6.1	33.3	36.9	32.8	49.0	78.0	59.4	50.3	75.8	66.4	102.2
EBS	§	EMERGENT BIOSOLUTIONS INC	DEC	3.6	3.2	3.5	2.8	2.6	11.6	7.6	15.7	15.3	19.9	29.5	18.0	32.3	36.4	48.0
GILD	[]	GILEAD SCIENCES INC	DEC	5.5	2.3	2.6	3.5	4.1	53.0	32.6	15.4	23.0	26.5	66.7	87.5	39.3	42.2	56.7
MNTA	§	MOMENTA PHARMACEUTICALS INC	DEC	24.9	11.5	6.2	5.9	6.6	0.0	0.0	2.1	5.2	5.9	0.0	0.0	2.3	5.8	6.4
REGN	†	REGENERON PHARMACEUT	DEC	4.4	3.3	4.5	6.2	2.8	47.3	23.2	21.6	0.0	0.0	86.4	64.1	32.8	0.0	0.0
SPPI	§	SPECTRUM PHARMACEUTICALS INC	DEC	2.9	1.9	3.2	3.1	7.3	0.0	0.1	0.1	0.2	0.0	0.0	0.1	0.1	0.2	0.0
UTHR	†	UNITED THERAPEUTICS CORP	DEC	2.6	1.8	1.0	5.1	1.3	21.7	7.2	4.4	35.0	0.0	75.9	20.5	NM	116.5	0.0
VRTX	†	VERTEX PHARMACEUTICALS INC	DEC	3.4	2.2	4.6	4.0	2.5	29.9	37.6	8.8	54.6	0.0	48.6	68.7	11.9	44.2	0.0
LIFE SCIENCES TOOLS & SERVICES‡																		
AFFX	§	AFFYMETRIX INC	DEC	5.8	3.9	5.8	6.3	7.9	25.8	24.5	45.4	51.0	42.2	36.7	59.7	71.6	75.2	74.8
A	[]	AGILENT TECHNOLOGIES INC	OCT	3.0	2.0	3.5	2.4	2.2	30.8	39.9	53.8	41.7	37.8	51.8	71.0	102.3	112.9	103.9
BIO	†	BIO-RAD LABORATORIES INC	DEC	3.9	3.0	3.7	2.6	2.5	28.6	31.4	36.2	28.6	29.5	54.6	55.9	64.6	66.0	71.9
CBM	§	CAMBREX CORP	DEC	2.3	2.6	2.7	2.1	1.7	45.7	48.0	50.0	57.7	45.6	126.5	141.1	128.0	166.5	146.9
CRL	†	CHARLES RIVER LABS INTL INC	DEC	2.0	2.1	2.4	2.1	2.0	56.5	48.3	24.4	30.2	20.0	336.4	228.7	132.3	170.5	158.8
CVD	†	COVANCE INC	DEC	2.0	1.9	2.2	1.6	2.2	0.0	6.3	0.0	0.0	0.0	0.0	19.6	0.0	0.0	0.0
ENZ	§	ENZO BIOCHEM INC	JUL	2.9	3.7	5.3	8.0	8.9	0.1	0.0	0.0	0.0	0.0	0.3	0.0	0.0	0.0	0.0
LIFE	[]	LIFE TECHNOLOGIES CORP	DEC	1.4	1.8	1.3	1.6	4.7	31.4	35.3	35.7	46.5	38.1	384.7	303.0	638.4	579.2	134.4
LMNX	§	LUMINEX CORP	DEC	7.2	8.7	7.2	9.8	4.2	1.0	1.4	1.6	1.5	2.8	1.9	2.2	2.9	2.2	7.3
MTD	†	METTLER-TOLEDO INTL INC	DEC	1.7	2.1	1.3	1.6	1.5	34.5	42.8	19.7	46.7	36.1	116.6	111.2	134.4	181.5	163.6
PRXL	§	PAREXEL INTERNATIONAL CORP	JUN	1.6	1.3	1.4	1.3	1.4	28.7	28.0	34.8	0.8	0.1	75.7	115.8	128.9	2.4	0.2
PKI	[]	PERKINELMER INC	DEC	1.4	2.1	1.8	1.6	1.5	33.1	17.6	25.0	24.3	23.9	360.4	74.4	144.0	161.9	174.7
TECH	†	TECHNE CORP	JUN	12.7	11.8	16.5	12.8	12.4	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
TMO	[]	THERMO FISHER SCIENTIFIC INC	DEC	1.5	2.4	2.8	2.8	1.9	25.0	10.6	10.6	10.8	10.9	336.8	83.8	71.4	72.8	116.0
WAT	[]	WATERS CORP	DEC	3.2	4.1	3.0	3.3	1.9	36.3	39.6	37.1	43.1	46.0	52.2	58.3	64.3	75.0	86.4
OTHER COMPANIES WITH SIGNIFICANT BIOTECHNOLOGY OPERATIONS																		
ALNY		ALNYLAM PHARMACEUTICALS INC	DEC	1.9	2.5	2.7	4.4	5.6	0.0	0.0	0.0	0.0	1.5	0.0	0.0	0.0	0.0	0.8
AMLN		AMYLIN PHARMACEUTICALS INC	DEC	1.4	1.7	2.5	3.3	4.7	109.7	57.7	60.4	71.2	61.9	NM	170.6	118.9	120.3	85.8
ELN		ELAN CORP PLC -ADR	DEC	1.8	1.9	4.5	2.3	4.4	42.6	86.7	74.6	114.7	128.8	276.1	289.5	169.9	460.7	246.5
ENZN		ENZON PHARMACEUTICALS INC	DEC	10.8	23.6	5.8	4.9	2.7	39.6	28.8	82.4	86.5	88.3	86.3	32.3	208.0	188.4	156.5
HGSI		HUMAN GENOME SCIENCES INC	DEC	2.0	1.9	4.8	0.6	1.4	57.4	42.6	44.2	146.9	101.6	188.6	173.7	97.1	NM	NM
MYGN		MYRIAD GENETICS INC	JUN	12.2	17.3	11.4	5.1	10.8	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0

Note: Data as originally reported. ‡S&P 1500 index group. []Company included in the S&P 500. †Company included in the S&P MidCap 400. §Company included in the S&P SmallCap 600. #Of the following calendar year.

			Price / Earnings Ratio (High-Low)					Dividend Payout Ratio (%)					Dividend Yield (High-Low, %)				
Ticker	Company	Yr. End	2011	2010	2009	2008	2007	2011	2010	2009	2008	2007	2011	2010	2009	2008	2007
BIOTECHNOLOGY‡																	
ACOR §	ACORDA THERAPEUTICS INC	DEC	43 - 24	NM - NM	NM - NM	NM - NM	NM - NM	0	NM	NM	NM	NM	0.0 - 0.0	0.0 - 0.0	0.0 - 0.0	0.0 - 0.0	0.0 - 0.0
ALXN []	ALEXION PHARMACEUTICALS INC	DEC	75 - 42	77 - 41	14 - 9	NM - 57	NM - NM	0	0	0	0	NM	0.0 - 0.0	0.0 - 0.0	0.0 - 0.0	0.0 - 0.0	0.0 - 0.0
AMGN []	AMGEN INC	DEC	16 - 12	13 - 10	14 - 10	17 - 10	27 - 16	14	0	0	0	0	1.2 - 0.9	0.0 - 0.0	0.0 - 0.0	0.0 - 0.0	0.0 - 0.0
ARQL §	ARQULE INC	DEC	NM - NM	NM - NM	NM - NM	NM - NM	NM - NM	NM	NM	NM	NM	NM	0.0 - 0.0	0.0 - 0.0	0.0 - 0.0	0.0 - 0.0	0.0 - 0.0
BIIB []	BIOGEN IDEC INC	DEC	24 - 13	17 - 12	16 - 12	28 - 14	42 - 21	0	0	0	0	0	0.0 - 0.0	0.0 - 0.0	0.0 - 0.0	0.0 - 0.0	0.0 - 0.0
CELG []	CELGENE CORP	DEC	24 - 17	35 - 25	35 - 22	NM - NM	NM - 70	0	0	0	NM	0	0.0 - 0.0	0.0 - 0.0	0.0 - 0.0	0.0 - 0.0	0.0 - 0.0
CBST §	CUBIST PHARMACEUTICALS INC	DEC	75 - 39	16 - 12	18 - 10	10 - 5	30 - 20	0	0	0	0	0	0.0 - 0.0	0.0 - 0.0	0.0 - 0.0	0.0 - 0.0	0.0 - 0.0
EBS §	EMERGENT BIOSOLUTIONS INC	DEC	41 - 23	15 - 8	26 - 9	38 - 7	22 - 6	0	0	0	0	0	0.0 - 0.0	0.0 - 0.0	0.0 - 0.0	0.0 - 0.0	0.0 - 0.0
GILD []	GILEAD SCIENCES INC	DEC	12 - 10	15 - 9	18 - 14	26 - 16	28 - 18	0	0	0	0	0	0.0 - 0.0	0.0 - 0.0	0.0 - 0.0	0.0 - 0.0	0.0 - 0.0
MNTA §	MOMENTA PHARMACEUTICALS INC	DEC	6 - 3	31 - 13	NM - NM	NM - NM	NM - NM	0	0	NM	NM	NM	0.0 - 0.0	0.0 - 0.0	0.0 - 0.0	0.0 - 0.0	0.0 - 0.0
REGN †	REGENERON PHARMACEUT	DEC	NM - NM	NM - NM	NM - NM	NM - NM	NM - NM	NM	NM	NM	NM	NM	0.0 - 0.0	0.0 - 0.0	0.0 - 0.0	0.0 - 0.0	0.0 - 0.0
SPPI §	SPECTRUM PHARMACEUTICALS INC	DEC	17 - 6	NM - NM	NM - NM	NM - NM	NM - NM	0	NM	NM	NM	NM	0.0 - 0.0	0.0 - 0.0	0.0 - 0.0	0.0 - 0.0	0.0 - 0.0
UTHR †	UNITED THERAPEUTICS CORP	DEC	19 - 10	34 - 24	NM - 74	NM - NM	NM - 51	0	0	0	NM	0	0.0 - 0.0	0.0 - 0.0	0.0 - 0.0	0.0 - 0.0	0.0 - 0.0
VRTX †	VERTEX PHARMACEUTICALS INC	DEC	NM - NM	NM - NM	NM - NM	NM - NM	NM - NM	0	NM	NM	NM	NM	0.0 - 0.0	0.0 - 0.0	0.0 - 0.0	0.0 - 0.0	0.0 - 0.0
LIFE SCIENCES TOOLS & SERVICES‡																	
AFFX §	AFFYMETRIX INC	DEC	NM - NM	NM - NM	NM - NM	NM - NM	NM - NM	NM	NM	NM	NM	0	0.0 - 0.0	0.0 - 0.0	0.0 - 0.0	0.0 - 0.0	0.0 - 0.0
A []	AGILENT TECHNOLOGIES INC	OCT	19 - 10	21 - 14	NM - NM	20 - 8	25 - 19	0	0	NM	0	0	0.0 - 0.0	0.0 - 0.0	0.0 - 0.0	0.0 - 0.0	0.0 - 0.0
BIO †	BIO-RAD LABORATORIES INC	DEC	20 - 13	19 - 12	19 - 10	33 - 18	33 - 19	0	0	0	0	0	0.0 - 0.0	0.0 - 0.0	0.0 - 0.0	0.0 - 0.0	0.0 - 0.0
CBM §	CAMBREX CORP	DEC	17 - 8	19 - 9	20 - 4	41 - 8	NM - NM	0	0	0	0	NM	0.0 - 0.0	0.0 - 0.0	0.0 - 0.0	0.0 - 0.0	190.6 - 53.6
CRL †	CHARLES RIVER LABS INTL INC	DEC	19 - 11	NM - NM	24 - 14	NM - NM	29 - 18	0	NM	0	NM	0	0.0 - 0.0	0.0 - 0.0	0.0 - 0.0	0.0 - 0.0	0.0 - 0.0
CVD †	COVANCE INC	DEC	29 - 19	59 - 35	21 - 12	32 - 10	33 - 21	0	0	0	0	0	0.0 - 0.0	0.0 - 0.0	0.0 - 0.0	0.0 - 0.0	0.0 - 0.0
ENZ §	ENZO BIOCHEM INC	JUL	NM - NM	NM - NM	NM - NM	NM - NM	NM - NM	NM	NM	NM	NM	NM	0.0 - 0.0	0.0 - 0.0	0.0 - 0.0	0.0 - 0.0	0.0 - 0.0
LIFE []	LIFE TECHNOLOGIES CORP	DEC	27 - 17	28 - 20	65 - 28	NM - 63	36 - 20	0	0	0	0	0	0.0 - 0.0	0.0 - 0.0	0.0 - 0.0	0.0 - 0.0	0.0 - 0.0
LMNX §	LUMINEX CORP	DEC	71 - 48	NM - NM	52 - 29	NM - NM	NM - NM	0	0	0	0	NM	0.0 - 0.0	0.0 - 0.0	0.0 - 0.0	0.0 - 0.0	0.0 - 0.0
MTD †	METTLER-TOLEDO INTL INC	DEC	23 - 15	23 - 13	21 - 9	19 - 10	25 - 16	0	0	0	0	0	0.0 - 0.0	0.0 - 0.0	0.0 - 0.0	0.0 - 0.0	0.0 - 0.0
PRXL §	PAREXEL INTERNATIONAL CORP	JUN	34 - 18	36 - 20	24 - 11	31 - 5	38 - 20	0	0	0	0	0	0.0 - 0.0	0.0 - 0.0	0.0 - 0.0	0.0 - 0.0	0.0 - 0.0
PKI []	PERKINELMER INC	DEC	NM - NM	23 - 16	26 - 14	28 - 12	27 - 19	NM	24	35	26	25	1.6 - 1.0	1.5 - 1.1	2.6 - 1.3	2.2 - 0.9	1.3 - 0.9
TECH †	TECHNE CORP	JUN	29 - 20	24 - 19	25 - 16	31 - 22	33 - 25	35	35	27	0	0	1.7 - 1.2	1.9 - 1.5	1.7 - 1.1	0.0 - 0.0	0.0 - 0.0
TMO []	THERMO FISHER SCIENTIFIC INC	DEC	25 - 16	22 - 16	24 - 15	27 - 11	34 - 24	0	0	0	0	0	0.0 - 0.0	0.0 - 0.0	0.0 - 0.0	0.0 - 0.0	0.0 - 0.0
WAT []	WATERS CORP	DEC	21 - 15	20 - 14	19 - 9	25 - 10	31 - 18	0	0	0	0	0	0.0 - 0.0	0.0 - 0.0	0.0 - 0.0	0.0 - 0.0	0.0 - 0.0
OTHER COMPANIES WITH SIGNIFICANT BIOTECHNOLOGY OPERATIONS																	
ALNY	ALNYLAM PHARMACEUTICALS INC	DEC	NM - NM	NM - NM	NM - NM	NM - NM	NM - NM	NM	NM	NM	NM	NM	0.0 - 0.0	0.0 - 0.0	0.0 - 0.0	0.0 - 0.0	0.0 - 0.0
AMLN	AMYLIN PHARMACEUTICALS INC	DEC	NM - NM	NM - NM	NM - NM	NM - NM	NM - NM	NM	NM	NM	NM	NM	0.0 - 0.0	0.0 - 0.0	0.0 - 0.0	0.0 - 0.0	0.0 - 0.0
ELN	ELAN CORP PLC -ADR	DEC	NM - NM	NM - NM	NM - NM	NM - NM	NM - NM	NM	NM	NM	NM	NM	0.0 - 0.0	0.0 - 0.0	0.0 - 0.0	0.0 - 0.0	0.0 - 0.0
ENZN	ENZON PHARMACEUTICALS INC	DEC	NM - NM	NM - NM	NM - NM	NM - NM	5 - 3	NM	NM	0	NM	0	0.0 - 0.0	0.0 - 0.0	0.0 - 0.0	0.0 - 0.0	0.0 - 0.0
HGSI	HUMAN GENOME SCIENCES INC	DEC	NM - NM	NM - NM	NM - 11	NM - NM	NM - NM	NM	NM	0	NM	NM	0.0 - 0.0	0.0 - 0.0	0.0 - 0.0	0.0 - 0.0	0.0 - 0.0
MYGN	MYRIAD GENETICS INC	JUN	23 - 16	17 - 9	32 - 15	67 - 32	NM - NM	0	0	0	0	NM	0.0 - 0.0	0.0 - 0.0	0.0 - 0.0	0.0 - 0.0	0.0 - 0.0

Note: Data as originally reported. ‡S&P 1500 index group. []Company included in the S&P 500. †Company included in the S&P MidCap 400. §Company included in the S&P SmallCap 600. #Of the following calendar year.

Ticker		Company	Yr. End	Earnings per Share ($) 2011	2010	2009	2008	2007	Tangible Book Value per Share ($) 2011	2010	2009	2008	2007	Share Price (High-Low, $) 2011	2010	2009	2008	2007
BIOTECHNOLOGY‡																		
ACOR	§	ACORDA THERAPEUTICS INC	DEC	0.78	(0.31)	(2.22)	(2.19)	(1.45)	5.00	3.35	3.17	5.07	1.73	33.48 - 18.36	40.48 - 24.99	29.27 - 15.52	35.65 - 14.42	26.58 - 15.06
ALXN	[]	ALEXION PHARMACEUTICALS INC	DEC	0.96	0.55	1.73	0.22	(0.63)	5.19	4.46	3.59	1.19	0.54	72.25 - 40.04	41.81 - 22.43	24.76 - 15.39	23.98 - 12.31	20.03 - 8.78
AMGN	[]	AMGEN INC	DEC	4.07	4.82	4.53	3.92	2.83	5.90	11.14	8.81	5.79	3.03	65.00 - 47.66	61.26 - 50.26	64.76 - 44.96	66.51 - 39.16	76.95 - 46.21
ARQL	§	ARQULE INC	DEC	(0.20)	(0.68)	(0.82)	(1.16)	(1.33)	0.55	(0.32)	0.26	0.98	2.01	7.83 - 3.98	7.49 - 2.97	6.38 - 2.62	6.09 - 1.75	10.59 - 5.47
BIIB	[]	BIOGEN IDEC INC	DEC	5.09	3.98	3.37	2.67	2.02	15.16	10.30	11.69	8.70	6.44	120.66 - 64.28	68.60 - 45.96	55.34 - 41.75	73.59 - 37.21	84.75 - 42.86
CELG	[]	CELGENE CORP	DEC	2.89	1.90	1.69	(3.46)	0.59	1.78	1.78	7.55	5.37	6.73	68.25 - 48.92	65.79 - 48.02	58.31 - 36.90	77.39 - 45.44	75.44 - 41.26
CBST	§	CUBIST PHARMACEUTICALS INC	DEC	0.54	1.60	1.38	3.00	0.87	3.05	6.64	3.40	5.09	1.35	40.49 - 20.95	25.48 - 18.66	25.50 - 13.81	28.74 - 16.25	25.72 - 16.97
EBS	§	EMERGENT BIOSOLUTIONS INC	DEC	0.65	1.63	1.02	0.69	0.79	9.93	8.94	7.82	6.61	5.75	26.41 - 14.90	23.93 - 13.22	27.00 - 9.15	26.40 - 4.93	17.75 - 4.40
GILD	[]	GILEAD SCIENCES INC	DEC	1.81	1.70	1.46	1.09	0.87	3.10	2.77	2.69	2.28	1.86	21.75 - 17.23	24.75 - 15.86	26.64 - 20.31	28.82 - 17.80	23.95 - 15.48
MNTA	§	MOMENTA PHARMACEUTICALS INC	DEC	3.62	0.84	(1.60)	(1.74)	(1.93)	7.71	4.09	2.05	2.43	3.40	21.00 - 10.15	26.20 - 10.77	13.17 - 6.94	20.00 - 5.91	21.98 - 4.58
REGN	†	REGENERON PHARMACEUT	DEC	(2.45)	(1.26)	(0.85)	(1.05)	(1.59)	5.23	5.90	4.89	5.24	5.84	79.90 - 32.32	33.94 - 20.45	24.97 - 11.81	25.25 - 12.62	28.74 - 13.55
SPPI	§	SPECTRUM PHARMACEUTICALS INC	DEC	0.91	(0.99)	(0.48)	(0.49)	(1.17)	2.48	0.87	1.52	0.07	1.53	15.22 - 5.76	7.16 - 3.67	10.00 - 1.39	3.35 - 0.46	7.88 - 2.58
UTHR	†	UNITED THERAPEUTICS CORP	DEC	3.80	1.89	0.37	(0.94)	0.47	17.28	15.19	11.70	9.46	6.46	70.74 - 36.55	64.66 - 46.14	53.57 - 27.34	58.91 - 23.82	55.35 - 23.83
VRTX	†	VERTEX PHARMACEUTICALS INC	DEC	0.14	(3.77)	(3.71)	(3.27)	(3.03)	0.44	(0.20)	2.76	1.58	2.04	58.87 - 26.50	44.24 - 31.25	44.04 - 25.94	35.00 - 13.84	41.42 - 22.80
LIFE SCIENCES TOOLS & SERVICES‡																		
AFFX	§	AFFYMETRIX INC	DEC	(0.40)	(0.15)	(0.35)	(4.49)	0.18	3.48	3.61	3.49	3.43	6.16	8.16 - 3.68	8.38 - 3.75	10.06 - 1.78	23.85 - 2.02	31.95 - 20.00
A	[]	AGILENT TECHNOLOGIES INC	OCT	2.92	1.97	(0.09)	1.91	1.62	6.67	3.69	4.86	4.81	6.75	55.33 - 28.67	42.08 - 26.68	31.77 - 12.02	38.00 - 14.76	40.42 - 30.26
BIO	†	BIO-RAD LABORATORIES INC	DEC	6.36	6.70	5.28	3.32	3.49	36.03	34.78	26.42	17.95	16.10	126.98 - 84.02	125.01 - 80.00	100.99 - 51.33	109.50 - 60.51	115.23 - 66.80
CBM	§	CAMBREX CORP	DEC	0.46	0.32	0.36	0.27	(0.47)	2.01	2.22	2.28	1.35	2.29	7.84 - 3.87	6.08 - 2.85	7.22 - 1.48	10.99 - 2.06	26.17 - 7.36
CRL	†	CHARLES RIVER LABS INTL INC	DEC	2.26	(5.25)	1.70	(7.76)	2.35	4.80	6.52	10.73	9.03	8.67	42.84 - 25.52	41.65 - 26.82	40.14 - 23.03	69.19 - 19.92	68.00 - 42.71
CVD	†	COVANCE INC	DEC	2.22	1.08	2.76	3.12	2.76	21.78	19.05	19.93	17.14	15.60	63.86 - 42.79	63.53 - 37.44	58.95 - 32.31	99.08 - 31.43	90.59 - 57.12
ENZ	§	ENZO BIOCHEM INC	JUL	(0.34)	(0.59)	(0.63)	(0.29)	(0.38)	1.09	1.38	1.87	2.70	3.27	5.80 - 1.98	6.78 - 3.33	7.98 - 2.70	14.90 - 3.36	18.98 - 9.70
LIFE	[]	LIFE TECHNOLOGIES CORP	DEC	2.11	2.06	0.82	0.31	1.39	(8.48)	(10.85)	(10.16)	(16.78)	(0.53)	57.25 - 35.30	56.78 - 41.10	52.97 - 22.76	49.00 - 19.56	49.58 - 27.95
LMNX	§	LUMINEX CORP	DEC	0.35	0.13	0.44	0.08	(0.08)	4.27	4.30	4.08	3.84	1.80	24.70 - 16.78	19.86 - 13.25	22.83 - 12.75	27.00 - 12.57	17.77 - 11.44
MTD	†	METTLER-TOLEDO INTL INC	DEC	8.45	6.98	5.12	5.92	4.82	6.71	7.17	4.87	(0.52)	1.14	193.56 - 126.10	159.07 - 93.43	106.99 - 44.01	115.10 - 60.26	119.84 - 77.45
PRXL	§	PAREXEL INTERNATIONAL CORP	JUN	0.83	0.72	0.68	1.16	0.69	3.79	1.78	1.18	4.33	3.60	27.91 - 15.26	25.64 - 14.10	16.62 - 7.20	36.16 - 6.11	26.05 - 14.00
PKI	[]	PERKINELMER INC	DEC	0.01	1.16	0.80	1.07	1.13	(8.07)	(0.03)	(2.55)	(2.40)	(2.21)	28.75 - 17.45	26.24 - 18.69	21.09 - 10.88	29.95 - 12.70	30.00 - 21.28
TECH	†	TECHNE CORP	JUN	3.03	2.95	2.78	2.65	2.16	12.04	12.82	11.50	11.85	10.33	86.43 - 62.04	69.74 - 55.63	69.95 - 45.38	82.92 - 57.10	72.00 - 54.49
TMO	[]	THERMO FISHER SCIENTIFIC INC	DEC	2.68	2.56	2.06	2.36	1.85	(12.83)	0.13	0.27	(0.42)	(3.33)	65.86 - 43.06	57.40 - 41.74	49.70 - 30.83	62.77 - 26.65	62.02 - 43.60
WAT	[]	WATERS CORP	DEC	4.77	4.13	3.37	3.25	2.67	8.50	6.64	4.10	2.60	1.81	100.00 - 70.88	81.00 - 55.97	63.09 - 30.00	81.84 - 32.21	81.53 - 48.55
OTHER COMPANIES WITH SIGNIFICANT BIOTECHNOLOGY OPERATIONS																		
ALNY		ALNYLAM PHARMACEUTICALS INC	DEC	(1.36)	(1.04)	(1.14)	(0.64)	(2.21)	2.76	3.73	4.24	4.86	4.86	12.34 - 5.88	19.29 - 8.79	26.36 - 14.82	36.37 - 16.37	37.35 - 14.87
AMLN		AMYLIN PHARMACEUTICALS INC	DEC	(3.73)	(1.06)	(1.32)	(2.30)	(1.59)	(5.06)	2.36	2.96	2.53	4.08	16.65 - 8.03	24.21 - 9.51	15.69 - 7.89	37.38 - 5.50	53.25 - 35.55
ELN		ELAN CORP PLC -ADR	DEC	(0.39)	(0.56)	(0.32)	(0.07)	(1.42)	1.14	(0.31)	0.43	(1.28)	(1.45)	14.02 - 5.73	8.24 - 4.25	9.13 - 4.61	37.45 - 4.99	24.90 - 11.70
ENZN		ENZON PHARMACEUTICALS INC	DEC	(0.40)	(0.05)	0.02	(0.06)	1.89	4.08	5.64	0.08	(0.42)	(0.71)	12.61 - 6.13	12.71 - 8.86	10.92 - 4.70	9.85 - 2.95	10.36 - 6.31
HGSI		HUMAN GENOME SCIENCES INC	DEC	(1.97)	(1.24)	0.04	(1.81)	(1.95)	2.30	3.10	4.08	(1.78)	(0.09)	30.15 - 6.51	34.49 - 20.56	31.40 - 0.45	11.95 - 1.20	12.87 - 7.04
MYGN		MYRIAD GENETICS INC	JUN	1.12	1.58	1.46	0.54	(0.43)	5.73	5.91	4.53 J	4.76 J	3.92 J	25.89 - 17.51	27.13 - 14.11	47.08 - 22.38	36.22 - 17.17	29.59 - 15.00

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J-This amount includes intangibles that cannot be identified.