



# Bradley, Foster & Sargent, Inc.

## Quarterly Market Commentary

July 2015

### Is the Rally in Biotech Stocks Over?

Valuation metrics in some sectors do appear substantially stretched – particularly those for smaller firms in the social media and biotechnology industries, despite a notable downturn in equity prices for such firms.

Federal Reserve Chairwoman Janet Yellen in prepared remarks before Congress, July 15, 2014

I don't think the party is over in the biotech space, but it may be getting late in the evening. These stocks are not cheap anymore.

Bill Stone, Chief Investment Strategist,  
PNC Financial Group, March 26, 2015

Stocks in the biotechnology industry have been on a tear over the past three-and-a-half years. From 2000 through 2011, biotech stocks went nowhere. From the beginning of 2000 through 2011, the S&P 500 achieved a cumulative total return of only 6.81%. This twelve-year period encompassed the “lost decade” of 2000 through 2009, when the stock market suffered the two crushing bear markets of 2000-2002 and 2007-2009. During this same twelve-year period, the NASDAQ Biotechnology Index turned in a somewhat better cumulative total return of 23.01%. But, starting in 2012, stocks in the biotechnology industry have been on fire. The chart below shows the fourfold price increase in the index over the past 3½ years:

**NASDAQ Biotechnology Index  
2000-2015**



Source: Bloomberg

In this investment commentary, we seek to give a primer on the biotechnology industry: defining what a biologic medicine is and describing the difference between biologic medications and conventional pharmaceutical drugs, the origins and the growth of the industry, the current universe of biotech stocks, and how investors might wish to invest or speculate in this dynamic universe of stocks. Finally, we will seek to demonstrate how the valuations of the large-capitalization biotech stocks are very different from valuations of the small and mid-capitalization biotech stocks.

### **A Brief Introduction to Biotechnology\***

The first medicinal drugs came from natural sources that existed in the form of herbs, plants, roots, vines, and fungi. It was not until the late 19th century that chemical drugs were created. These chemically synthesized remedies (also referred to as small molecule drugs) are traditional pharmaceutical drugs. The most well-known drug developed in the late 19th century was acetylsalicylic acid, branded aspirin by its manufacturer, Bayer AG. The term “biotechnology” was initially coined to describe the interaction between biology and human technology for the conversion of raw materials into socially valuable drugs. One of the first biotechnology drugs was the antibiotic, penicillin, which was discovered in the late 1920s and ultimately manufactured commercially during World War II. The breakthrough that laid the groundwork for modern biotechnology came when the structure of DNA was discovered in the early 1950s. It was only in 1992 that the United Nations and the World Health Organization arrived at a standard definition of biotechnology as “any technological application that uses biological systems, living organisms, or derivatives thereof, to make or modify products or processes for specific use.” Drugs produced using any of these applications are known as biologic medicines.

What exactly, then, is a biologic medicine? A biologic medicine is typically derived from living cells and used in the treatment, diagnosis, or prevention of disease. Biologic medicines generally include therapeutic proteins, DNA vaccines, monoclonal antibodies, and fusion proteins. Biologic medicines are often 200 to 1,000 times the size of a small molecule drug and are far more complex structurally, which is why they are often called large molecule drugs. For example, the small molecule drug, aspirin, has 21 atoms; the IgG1 antibody biologic medicine is made up of 20,000 atoms. Biologic medicines are also highly sensitive to their manufacturing and handling conditions, making them more difficult to produce than small molecule drugs. Due to their size and sensitivity, biologic medicines are almost always administered by injection into a patient’s body.

### **How Biologic Medicines are Used and Manufactured**

Biologic medicines are made in living organisms to produce proteins to treat diseases, often by genetically modifying cells. DNA is often used to insert desirable genes or remove undesirable ones within a living cell. Biotechnology has been used to develop many of today’s most

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\* Borrowed generously from an Amgen Corporation brochure

important medicines including monoclonal antibodies for the treatment of cancer, human insulin for the treatment of diabetes, and the cloning of erythropoietin to stimulate the production of red blood cells in the treatment of chronic anemia. Other illnesses treated by biologics are rheumatoid arthritis, psoriasis, and multiple sclerosis. In the manufacturing of these medicines, there are often thousands of intricate and sensitive steps, requiring robust quality systems, significant expertise, and major financial investment. Even minor alterations in manufacturing can adversely affect a patient's safety and the efficacy of the drug and increase the risk of an undesirable immune response. Worldwide, nearly 200 biologic medicines have been used to improve the lives of over 800 million patients, according to Amgen. The completion of the Human Genome Project in 2006 has led to an escalation in biotechnology research. More than 900 biologic medicines are being studied worldwide to treat serious illnesses such as HIV/AIDS, Alzheimer's disease, cancer, and cardiovascular and autoimmune diseases.

### Early U.S. Pioneers in the Biotechnology Industry

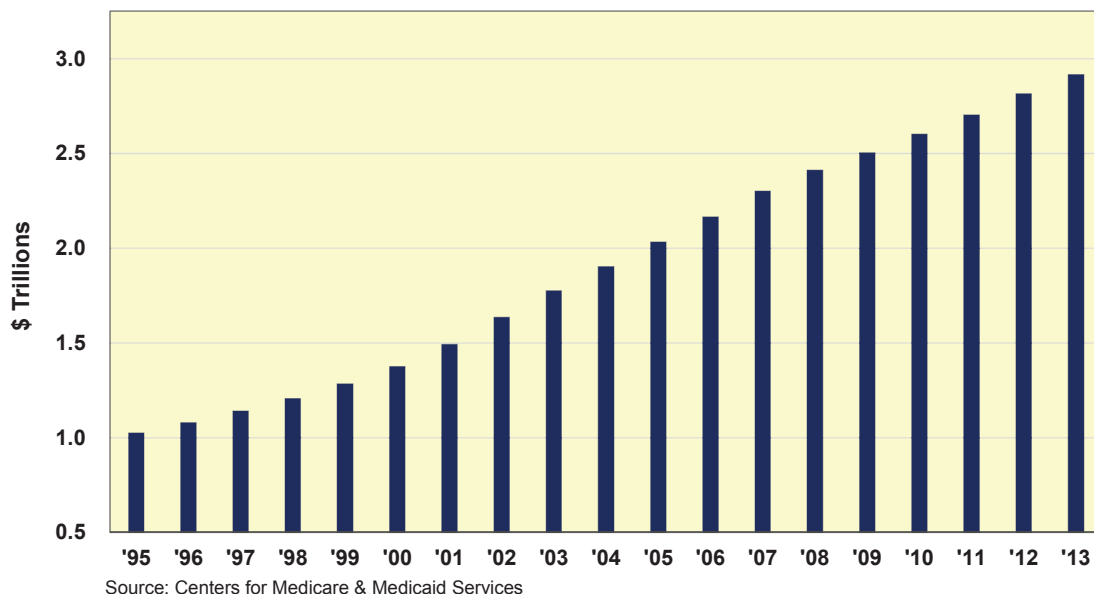
The strong rally in biotechnology stocks since 2012 has led some investors to believe that the industry is relatively new, but the first U.S. biotechnology company was founded in 1976 in California by venture capitalist Robert Swanson and biochemist Dr. Herbert Boyer. Dr. Boyer and geneticist Stanley Cohen pioneered a new scientific field called recombinant DNA technology. The company they founded was called Genentech. The following is a table of leading U.S. large-capitalization biotechnology companies, the year of their founding, and the date of their first Food and Drug Administration (FDA) approved drug:

Company	Year Founded	First FDA-Approved Drug
Genentech (now 100% owned by Roche)	1976	1987
Biogen	1978	1989
Amgen	1980	1989
Celgene	1986	1995
Gilead	1987	1999
Regeneron	1988	2008
Alexion	1992	2007

It is important to note that for all these companies, the research and development process took a long time to develop a drug which received approval from the FDA. The shortest period was nine years in the case of Amgen and Celgene, and the longest period was 20 years in the case of Regeneron. Even now, it takes an average of 10 years for a new medicine to gain approval from the FDA, and less than 15% of investigative medicines that enter Phase I clinical trials achieve FDA approval. Before a drug is reviewed and potentially approved by the FDA, it must go through preclinical testing, and three phases of clinical testing, known as clinical trials.

In preclinical testing, researchers conduct a series of laboratory and animal studies to test how the medicine works and determine if the compound is suitable for clinical (human) testing. In Phase I trials, the candidate medicine is tested in a small group, which can number 20-80 healthy volunteers, to determine the safety of the compound and how it is best processed in the body. Phase II trials are conducted in a larger group of patient volunteers (usually a few hundred) who have the disease or condition that the medicine is designed to treat. Phase III trials test the compound in a much larger group which is generally numbered in the thousands. These trials are designed to generate statistically significant information about safety and efficacy. The average cost to develop a new medicine is estimated to be \$2.6 billion. Since 2000, Pharmaceutical Research and Manufacturers of America (PhRMA) members have spent more than half a trillion dollars on R&D. In 1995, total R&D spending by PhRMA members was \$15.2 billion; in 2014, PhRMA invested approximately \$51.2 billion in R&D. The growth in R&D expenditures over the past 19 years mirrors the enormous growth in overall U.S. health care expenditures, as the chart demonstrates:

**U.S. National Health Care Expenditures  
1995-2013**



During this 19-year period, U.S. health care expenditures nearly tripled. Health care expenditures also increased from 13.4% of total U.S. GDP in 1995 to 17.4% in 2013. While numbers are not available for 2014, the Affordable Care Act will surely cause the percentage of dollars spent on health care in the U.S., relative to GDP, to continue to increase.

### **Biotechnology Company Initial Public Offerings since 2012**

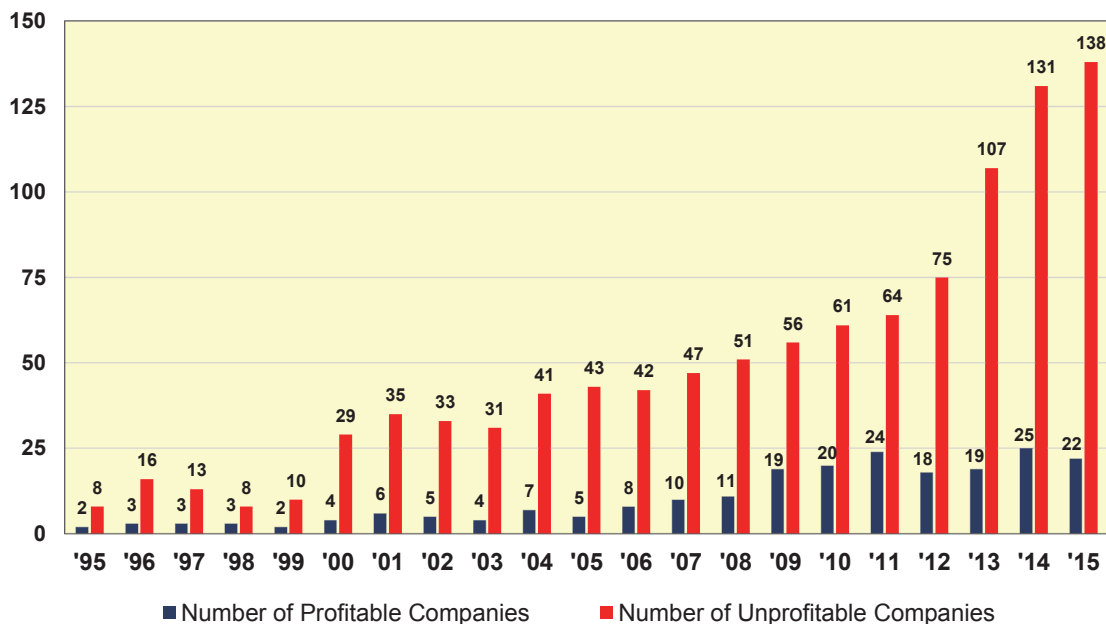
With biotechnology stocks enjoying a strong and continuing rally since January, 2012, the number of initial public offerings (IPOs) of biotechnology companies has exploded. Since early 2012, there have been 149 biotech IPOs. The market value of these 149 companies has now

reached \$89 billion. There have also been a number of secondary offerings from these IPOs, and these secondary offerings have raised over \$3 billion since 2012. The majority of these IPOs during the last 3½ years have a market capitalization below \$500 million; only a handful have a market cap over \$1.5 billion. Most of these IPOs were in the early approval stages (Phase I and Phase II) when they came to market, and less than 5% had an approved drug. The primary focus of these newly public companies is oncology, metabolic diseases, and orphan drugs. As defined in the U.S. Orphan Drug Act of 1983, an orphan drug is a pharmaceutical agent that has been developed specifically to treat a rare medical condition, the condition itself being referred to as an orphan disease. The FDA has created a truncated approval process for orphan drugs, resulting in clinical testing that can be less rigorous and costly. This has led a considerable number of biotech companies to focus their R&D and drug development on orphan drugs. In some cases, the number of patients in the U.S. who have an orphan disease is less than 5,000. The cost per patient for orphan drugs in the U.S. is six times that of non-orphan drugs. An example of the high cost per patient of an orphan drug is the recent approval of Vertex’s drug, Orkambi, which could be used to treat approximately 15,000 of the 30,000 Americans who suffer from cystic fibrosis. The drug is being priced at \$259,000 per patient annually.

### The Universe of Biotechnology Stocks

The chart below is a snapshot of the 160 companies in the biotechnology sector of the Russell 3000. The Russell 3000 includes 1,000 U.S. large-capitalization companies as well as 2,000 small and mid-capitalization companies, encompassing 98% of the investable U.S. equity markets. As can be seen below, less than 14% of the 160 biotechnology companies are profitable:

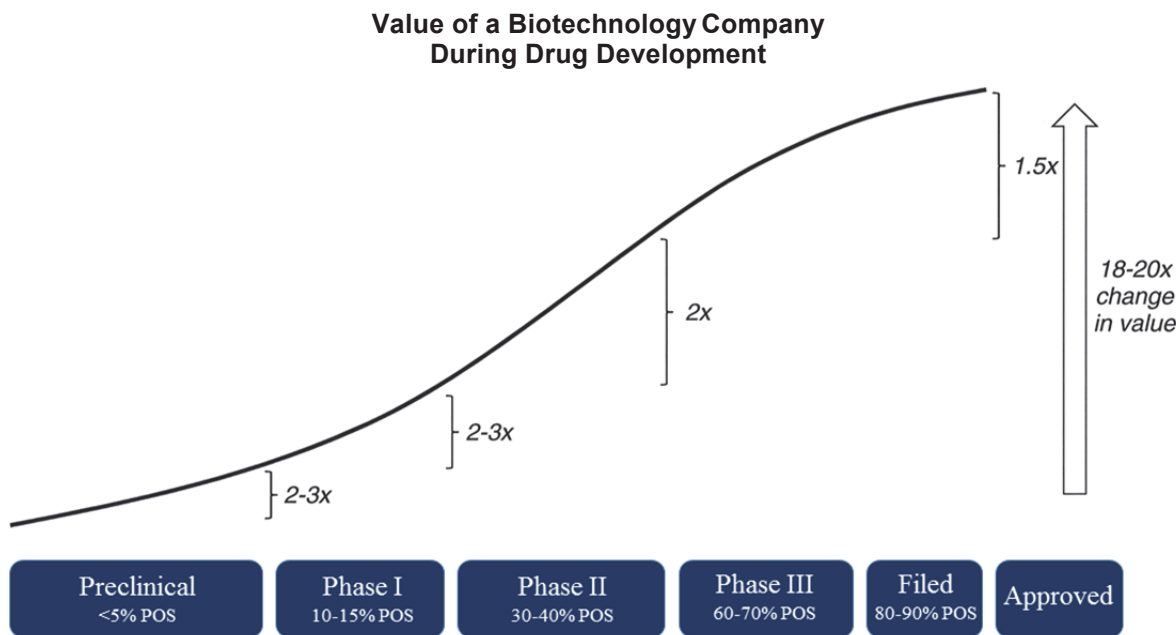
**U.S. Biotechnology Companies in the Russell 3000  
1995-2015**



Source: Bloomberg

## Biotechnology Stock Valuations

Federal Reserve Chairwoman Janet Yellen commented before Congress a year ago that she believed the valuations of small and mid-cap biotechnology companies were “substantially stretched.” Since then, the iShares NASDAQ Biotechnology Index (IBB) has risen 42%. While this might seem to indicate that these small and mid-cap stocks are even more overvalued now, approximately two-thirds of the index weighting is made up of 14 large-cap biotechnology stocks, each of whose market capitalization is greater than \$10 billion. The remaining 131 small and mid-cap stocks in the ETF are extremely difficult to value – especially as many of them do not have any drugs approved by the FDA and are still in FDA Phase I or Phase II clinical trials. The chart below seeks to show how small and mid-cap biotechnology stocks appreciate in value as a drug goes through the developmental process. The ultimate value of a drug is estimated by the probability of its gaining FDA approval (also known in the industry as Probability of Success or POS) and by multiplying the addressable patient population by the drug’s price:



Source: Bernstein Research

Making a judgment that the stocks of more than 100 small and mid-cap biotech companies are overvalued is problematic. However, what is clear is that less than 15% of biotech drugs are ultimately approved by the FDA, so picking individual winners in this space is highly speculative. Furthermore, the number of biotechnology firm IPOs since 2012 (149) and the rapid appreciation in the value of many of these stocks give the appearance of a bubble in this space.

### Large-Capitalization Biotechnology Stock Valuations Appear Reasonable

Valuations of many large-cap biotech stocks present a very different picture. As can be seen from the table on the next page, the four largest companies by market capitalization exhibit valuations which are very similar to old-line pharmaceutical companies such as Merck, Pfizer,

Johnson & Johnson, and AbbVie, whose P/E ratios on 2016 earnings range from 13.6 to 15.3. Other old-line pharmaceutical companies such as Bristol-Myers and Eli Lilly, which have very promising drugs in the pipeline, trade at 29 and 24 times earnings respectively. The biotechnology companies with more robust projected earnings growth trade at higher P/E ratios, as the table below shows:

**Large-Cap Biotechnology Stock Valuations  
July 2, 2015**

	Market Capitalization (\$ Billions)	2016E EPS	2016E P/E	2016E P/Sales
Gilead	169	\$11.00	10.4	5.5
Amgen	117	\$10.54	14.5	5.3
Biogen	95	\$19.41	20.8	7.7
Celgene	95	\$ 6.19	19.3	8.5
Regeneron	53	\$13.15	38.9	11.7
Alexion	42	\$ 6.29	29.5	12.3
Vertex	32	\$ 3.71	35.4	11.8

Source: FactSet

Parenthetically, it is important to note that biologic medicines are no longer exclusively developed by biotechnology companies. Currently, eight of the twelve best-selling biologics are manufactured and sold by traditional large-capitalization pharmaceutical companies, and Gilead's two blockbuster drugs are not even biologic medicines.

**Different Investment Approaches in the Biotechnology Sector**

In seeking to profit from stocks in the biotechnology sector, investors might utilize one or more of the following investment approaches:

- Invest in best-of-breed, top-quality biotechnology firms with proven track records, FDA-approved drugs, quality management teams, strong revenues, and robust earnings. The least risky of these names are the first four companies in the table above. The last three companies also merit a close look; they have faster projected revenue and earnings growth but the valuations are correspondingly richer.
- Invest in the biotechnology space through the use of an ETF such as IBB, the iShares NASDAQ Biotechnology Index, which has a preponderance of its weighting in large-capitalization companies but also has approximately one-third of its weighting in small and mid-cap biotech companies. This ETF has considerable liquidity (\$8 billion +), but investors should expect considerable volatility and downside risk if this sector loses favor with investors.

- Invest in a diversified portfolio of individual small and mid-cap biotechnology stocks. Diversification is paramount, as the path to FDA approval is long and expensive, and many drugs fail in the clinical tests. The rewards can be great – twentyfold appreciation or more – but the risks are daunting. This approach is only appropriate for investors with significant assets so that the biotechnology portfolio does not represent too large a percentage of overall investments.

The title of this investment commentary poses the question: Is the Rally in Biotech Stocks Over? The answer to this question depends on which segment of the biotechnology stock market one addresses. We believe that the small and mid-cap biotech space has many elements of a bubble: a plethora of IPOs since 2012, huge gains in many of these stocks since the IPO, large amounts of money invested by momentum-type investors, and valuations based on hope rather than proven drugs, revenues, and positive cash flow. On the other hand, a majority of large-capitalization biotechnology stocks have reasonable and even inexpensive valuations, which mirror the valuations of traditional, old-line pharmaceutical names. Investing in these high-quality, profitable large-capitalization biotechnology companies is the approach which we, at Bradley, Foster & Sargent, have taken, and we believe it will serve us well in the years to come.

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